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Sepsis Pathophysiology, Chronic Critical Illness and PICS

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Abstract

Objective—To provide an appraisal of the evolving paradigms in the pathophysiology of sepsis, 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.

Results—Sepsis remains one of the most debilitating and expensive illnesses, and its incidence 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 (CCI), rarely fully recover and often experience an indolent death. Patients with CCI often exhibit 'a persistent inflammatory-immunosuppressive and catabolic syndrome' or PICS, and it is proposed here that PICS contributes to many of these adverse clinical outcomes. The underlying cause of PICS 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.

Conclusion—Although newer therapeutic interventions are targeting the inflammatory, the immunosuppressive, and the protein catabolic responses individually, successful treatment of the septic patient with CCI and PICS may require a more complementary approach.

Keywords

inflammation; shock; myeloid derived suppressor cells; immunosuppression; chronic critical illness; persistent inflammation immunosuppression and catabolism syndrome (PICS)

Introduction

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

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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'* (SSC) 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 has 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.* 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%[13]. However, poor compliance with these measures persists[9]. While recent studies report a decrease in *severe sepsis* inhospital 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 measure SEP-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 has 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, increased mortality) characteristic of sepsis, rather than uncomplicated infections. In its support, Seymour *et al.* demonstrate that a positive quick Sepsis-related Organ Failure Assessment (qSOFA) score has an improved predictive validity for in-hospital mortality when compared to the SIRS criteria [19].

While we have made important strides in in-hospital and 28-day mortality, long-term mortality remains prohibitively high, with recent studies reporting two and three-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 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 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 (AF), as they have an increased long-term risk of heart failure, stroke, and death[25] . Ultimately, 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 (MOF), a number of paradigms have been established and discarded over the past three decades[28-31]. The terms, "systemic inflammatory response syndrome" (SIRS) and "compensatory anti-inflammatory response syndrome" (CARS) 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 Intensive Care Unit (ICU) management, most patients now survive their initial traumatic injury or septic insult. Many reestablish physiological 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 seven 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 eight 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 health-care costs[33, 34]. The majority of these patients (>60%) were admitted with a sepsis diagnosis[34]. While 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 years-old), and in the long term, few return home to functional independence (10%) and have a one-year survival estimated to be <50%[37-40]. Most recently, Iwashyna *et al.* showed that while accounting for just 5% of ICU admissions, patients with CCI accounted for >30% of ICU bed-days and

>14% of hospital bed-days, had higher mortality and were less likely to be discharged home than the usual ICU patient[41].

Recently, we proposed a new syndrome for individuals who survive the initial sepsis/injury event but become chronically critically ill, the 'Persistent Inflammation-Immunosuppression Catabolism Syndrome' (PICS)[28]. We *hypothesize* that it is PICS which mechanistically underlies a subset of CCI patients. This new syndrome is not to be confused with "Post-ICU Syndrome" which 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, 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(Figure 1). This in turn leads to poor functional outcomes, poor quality of life, and probable discharge to a 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 neurological deficits which may also be explained by other mechanisms[43, 44]. Rather, its intent was to explain the immunological 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 expansion of hematopoietic stem cells (HSC). These new HSCs preferentially differentiate down myeloid pathways towards mature granulocytes, macrophages and dendritic cells[45-47]. This process occurs at the expense of both lymphopoiesis and erythropoiesis which 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 HSC 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] (Figure 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 can also contribute to the persistent inflammation, through their ability to produce inflammatory mediators, NO 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 Chronic Critical Illness?

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 non-home location, increased in-hospital and long-term mortality, and increased readmission and resource utilization[65-67]. Similarly, long-term cognitive 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], immunosuppressed[74] and have chronic inflammation[75] have lower life expectancies than those that 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 showed to decreased MDSCs while increasing antitumor activity of $CD8^+$ T cells in tumor bearing mice[76-78]. Additionally, blockade of CXR2 mediated MDSC trafficking has been shown to enhance anti-PD1 efficacy in a murine model[79]. In renal cell cancer, patients treated with sunitinib saw a reduction in MDSC and a reversal of type 1 T-cell suppression[80]. Moreover, 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-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 Chronic Critical Illness

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 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 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 PAMPs. The persistent inflammation of hospitalized patients with CCI could be attributed to the increased release of DAMPs or endogenous alarmins from 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].

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 re-infection, and frequently readmission to acute care facilities. Once infection has re-established, 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 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 IL-7 and IL-15, and blockade of checkpoint inhibition (anti-cytotoxic T-lymphocyte-associated protein (CTLA4), or anti-programmed death ligand-1 (PD-L1)/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 pathological 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, 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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References

1. Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YC, Mathison J, Ulevitch R, Cerami A. Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. Nature. 1985; 316(6028):552–554. [PubMed: 2993897]
2. Fischer E, Marano MA, Van Zee KJ, Rock CS, Hawes AS, Thompson WA, DeForge L, Kenney JS, Remick DG, Bloedow DC, et al. Interleukin-1 receptor blockade improves survival and hemodynamic performance in Escherichia coli septic shock, but fails to alter host responses to

sublethal endotoxemia. The Journal of clinical investigation. 1992; 89(5):1551–1557. [PubMed: 1533231]

3. Alexander HR, Doherty GM, Buresh CM, Venzon DJ, Norton JA. A recombinant human receptor antagonist to interleukin 1 improves survival after lethal endotoxemia in mice. The Journal of experimental medicine. 1991; 173(4):1029–1032. [PubMed: 1826127]
4. Giroir BP. Mediators of septic shock: new approaches for interrupting the endogenous inflammatory cascade. Critical care medicine. 1993; 21(5):780–789. [PubMed: 8482101]
5. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. Chest. 1992; 101(6):1644–1655. [PubMed: 1303622]
6. Marshall JC. Why have clinical trials in sepsis failed? Trends Mol Med. 2014; 20(4):195–203. [PubMed: 24581450]
7. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive care medicine. 2004; 30(4):536–555. [PubMed: 14997291]
8. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Critical care medicine. 2013; 41(2):580–637. [PubMed: 23353941]
9. Rhodes A, Phillips G, Beale R, Cecconi M, Chiche JD, De Backer D, Divatia J, Du B, Evans L, Ferrer R, et al. The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). Intensive care medicine. 2015; 41(9): 1620–1628. [PubMed: 26109396]
10. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. Critical care. 2005; 9(6):R764–770. [PubMed: 16356225]
11. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, Holanda MS, Ortiz F, Llorca J, Delgado-Rodriguez M. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. Critical care medicine. 2010; 38(4):1036–1043. [PubMed: 20154597]
12. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Intensive care medicine. 2010; 36(2):222–231. [PubMed: 20069275]
13. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, Osborn T, Lemeshow S, Chiche JD, Artigas A, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Critical care medicine. 2015; 43(1):3–12. [PubMed: 25275252]
14. Stoller J, Halpin L, Weis M, Aplin B, Qu W, Georgescu C, Nazzal M. Epidemiology of severe sepsis: 2008-2012. Journal of critical care. 2015
15. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. Journal of the American Geriatrics Society. 2012; 60(6):1070–1077. [PubMed: 22642542]
16. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. NCHS data brief. 2011; (62):1–8.
17. Dellinger RP. Foreword. The Future of Sepsis Performance Improvement. Critical care medicine. 2015; 43(9):1787–1789. [PubMed: 26274702]
18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama. 2016; 315(8):801–810. [PubMed: 26903338]
19. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama. 2016; 315(8): 762–774. [PubMed: 26903335]

20. Karlsson S, Ruokonen E, Varpula T, Ala-Kokko TI, Pettila V. Finnsepsis Study G. Long-term outcome and quality-adjusted life years after severe sepsis. Critical care medicine. 2009; 37(4): 1268–1274. [PubMed: 19242321]
21. Borges RC, Carvalho CR, Colombo AS, da Silva Borges MP, Soriano FG. Physical activity, muscle strength, and exercise capacity 3 months after severe sepsis and septic shock. Intensive care medicine. 2015; 41(8):1433–1444. [PubMed: 26109398]
22. Widmann CN, Heneka MT. Long-term cerebral consequences of sepsis. The Lancet Neurology. 2014; 13(6):630–636. [PubMed: 24849863]
23. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. Jama. 2010; 304(16):1787–1794. [PubMed: 20978258]
24. Yende S, Linde-Zwirble W, Mayr F, Weissfeld LA, Reis S, Angus DC. Risk of cardiovascular events in survivors of severe sepsis. American journal of respiratory and critical care medicine. 2014; 189(9):1065–1074. [PubMed: 24456535]
25. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. Chest. 2014; 146(5):1187–1195. [PubMed: 24723004]
26. Heyland DK, Hopman W, Coo H, Tranmer J, McColl MA. Long-term health-related quality of life in survivors of sepsis. Short Form 36: a valid and reliable measure of health-related quality of life. Critical care medicine. 2000; 28(11):3599–3605. [PubMed: 11098960]
27. Battle CE, Davies G, Evans PA. Long term health-related quality of life in survivors of sepsis in South West Wales: an epidemiological study. PloS one. 2014; 9(12):e116304. [PubMed: 25549097]
28. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, Moldawer LL, Moore FA. Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical intensive care. The journal of trauma and acute care surgery. 2012; 72(6):1491–1501. [PubMed: 22695412]
29. Robertson CM, Coopersmith CM. The systemic inflammatory response syndrome. Microbes and infection / Institut Pasteur. 2006; 8(5):1382–1389.
30. Ward NS, Casserly B, Ayala A. The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. Clinics in chest medicine. 2008; 29(4):617–625, viii. [PubMed: 18954697]
31. Rosenthal MD, Moore FA. Persistent inflammatory, immunosuppressed, catabolic syndrome (PICS): A new phenotype of multiple organ failure. Journal of advanced nutritional and human metabolism. 2015; 1(1)
32. Marini JJ, Vincent JL, Annane D. Critical care evidence--new directions. Jama. 2015; 313(9):893–894. [PubMed: 25602680]
33. Lamas D. Chronic critical illness. The New England journal of medicine. 2014; 370(2):175–177. [PubMed: 24401058]
34. Kahn JM, Le T, Angus DC, Cox CE, Hough CL, White DB, Yende S, Carson SS. ProVent Study Group I. The epidemiology of chronic critical illness in the United States*. Critical care medicine. 2015; 43(2):282–287. [PubMed: 25377018]
35. Cox CE. Persistent systemic inflammation in chronic critical illness. Respiratory care. 2012; 57(6): 859–864. discussion 864-856. [PubMed: 22663963]
36. Kandilov, AM., I, M., Morley, M., Coomer, NM., Dalton, K., Gage, B., Superina, C., Kennell, D. Chronically Critically Ill Population Payment Recommendations (CCIP-PR). Reasearch Triangle Institute; NC: 2014.
37. Carson SS, Bach PB. The epidemiology and costs of chronic critical illness. Critical care clinics. 2002; 18(3):461–476. [PubMed: 12140908]
38. Marchioni A, Fantini R, Antenora F, Clini E, Fabbri L. Chronic critical illness: the price of survival. European journal of clinical investigation. 2015; 45(12):1341–1349. [PubMed: 26549412]
39. Cox CE, Carson SS, Lindquist JH, Olsen MK, Govert JA, Chelluri L. Quality of Life After Mechanical Ventilation in the Aged I. Differences in one-year health outcomes and resource utilization by definition of prolonged mechanical ventilation: a prospective cohort study. Critical care. 2007; 11(1):R9. [PubMed: 17244364]

40. Scheinhorn DJ, Hassenpflug MS, Votto JJ, Chao DC, Epstein SK, Doig GS, Knight EB, Petrak RA. Ventilation Outcomes Study G. Post-ICU mechanical ventilation at 23 long-term care hospitals: a multicenter outcomes study. Chest. 2007; 131(1):85–93. [PubMed: 17218560]
41. Iwashyna TJ, Hodgson CL, Pilcher D, Bailey M, van Lint A, Chavan S, Bellomo R. Timing of onset and burden of persistent critical illness in Australia and New Zealand: a retrospective, population-based, observational study. The Lancet Respiratory medicine. 2016
42. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, Zawistowski C, Bemis-Dougherty A, Berney SC, Bienvenu OJ, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Critical care medicine. 2012; 40(2): 502–509. [PubMed: 21946660]
43. Deutschman CS, Raj NR, McGuire EO, Kelz MB. Orexinergic activity modulates altered vital signs and pituitary hormone secretion in experimental sepsis. Critical care medicine. 2013; 41(11):e368–375. [PubMed: 24105451]
44. Silverman HA, Dancho M, Regnier-Golanov A, Nasim M, Ochani M, Olofsson PS, Ahmed M, Miller EJ, Chavan SS, Golanov E, et al. Brain region-specific alterations in the gene expression of cytokines, immune cell markers and cholinergic system components during peripheral endotoxin-induced inflammation. Molecular medicine. 2014; 20:601–611.
45. Furze RC, Rankin SM. Neutrophil mobilization and clearance in the bone marrow. Immunology. 2008; 125(3):281–288. [PubMed: 19128361]
46. Scumpia PO, Kelly-Scumpia KM, Delano MJ, Weinstein JS, Cuenca AG, Al-Quran S, Bovio I, Akira S, Kumagai Y, Moldawer LL. Cutting edge: bacterial infection induces hematopoietic stem and progenitor cell expansion in the absence of TLR signaling. Journal of immunology. 2010; 184(5):2247–2251.
47. Ueda Y, Kondo M, Kelsoe G. Inflammation and the reciprocal production of granulocytes and lymphocytes in bone marrow. The Journal of experimental medicine. 2005; 201(11):1771–1780. [PubMed: 15939792]
48. Manz MG, Boettcher S. Emergency granulopoiesis. Nat Rev Immunol. 2014; 14(5):302–314. [PubMed: 24751955]
49. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009; 9(3):162–174. [PubMed: 19197294]
50. Dilek N, Vuillefroy de Silly R, Blancho G, Vanhove B. Myeloid-derived suppressor cells: mechanisms of action and recent advances in their role in transplant tolerance. Front Immunol. 2012; 3:208. [PubMed: 22822406]
51. Bronte V. Myeloid-derived suppressor cells in inflammation: uncovering cell subsets with enhanced immunosuppressive functions. European journal of immunology. 2009; 39(10):2670–2672. [PubMed: 19757440]
52. Talmadge JE, Gabrilovich DI. History of myeloid-derived suppressor cells. Nature reviews Cancer. 2013; 13(10):739–752.
53. Delano MJ, Scumpia PO, Weinstein JS, Coco D, Nagaraj S, Kelly-Scumpia KM, O'Malley KA, Wynn JL, Antonenko S, Al-Quran SZ, et al. MyD88-dependent expansion of an immature GR-1(+)CD11b(+) population induces T cell suppression and Th2 polarization in sepsis. The Journal of experimental medicine. 2007; 204(6):1463–1474. [PubMed: 17548519]
54. Makarenkova VP, Bansal V, Matta BM, Perez LA, Ochoa JB. CD11b+/Gr-1+ myeloid suppressor cells cause T cell dysfunction after traumatic stress. Journal of immunology. 2006; 176(4):2085–2094.
55. Derive M, Bouazza Y, Alauzet C, Gibot S. Myeloid-derived suppressor cells control microbial sepsis. Intensive care medicine. 2012; 38(6):1040–1049. [PubMed: 22552586]
56. Popovic PJ, Zeh HJ 3rd, Ochoa JB. Arginine and immunity. J Nutr. 2007; 137(6 Suppl 2):1681S–1686S. [PubMed: 17513447]
57. Bronte V, Zanovello P. Regulation of immune responses by L-arginine metabolism. Nat Rev Immunol. 2005; 5(8):641–654. [PubMed: 16056256]
58. Heim CE, Vidlak D, Kielian T. Interleukin-10 production by myeloid-derived suppressor cells contributes to bacterial persistence during Staphylococcus aureus orthopedic biofilm infection. J Leukoc Biol. 2015; 98(6):1003–1013. [PubMed: 26232453]

59. Lei GS, Zhang C, Lee CH. Myeloid-derived suppressor cells impair alveolar macrophages through PD-1 receptor ligation during Pneumocystis pneumonia. Infection and immunity. 2015; 83(2):572–582. [PubMed: 25404033]
60. Huang H, Zhang G, Li G, Ma H, Zhang X. Circulating CD14(+)HLA-DR(-/low) myeloid-derived suppressor cell is an indicator of poor prognosis in patients with ESCC. Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine. 2015; 36(10): 7987–7996. [PubMed: 25967454]
61. Cuenca AG, Delano MJ, Kelly-Scumpia KM, Moreno C, Scumpia PO, Laface DM, Heyworth PG, Efron PA, Moldawer LL. A paradoxical role for myeloid-derived suppressor cells in sepsis and trauma. Molecular medicine. 2011; 17(3-4):281–292. [PubMed: 21085745]
62. Noel JG, Osterburg A, Wang Q, Guo X, Byrum D, Schwemberger S, Goetzman H, Caldwell CC, Ogle CK. Thermal injury elevates the inflammatory monocyte subpopulation in multiple compartments. Shock. 2007; 28(6):684–693. [PubMed: 17607156]
63. Janols H, Bergenfelz C, Allaoui R, Larsson AM, Ryden L, Bjornsson S, Janciauskiene S, Wullt M, Bredberg A, Leandersson K. A high frequency of MDSCs in sepsis patients, with the granulocytic subtype dominating in gram-positive cases. J Leukoc Biol. 2014; 96(5):685–693. [PubMed: 24929004]
64. Mathias B, Delmas AL, Ozrazgat-Baslanti T, Vanzant EL, Szpila BE, Mohr AM, Moore FA, Brakenridge SC, Brumback BA, Moldawer LL, et al. Human Myeloid-derived Suppressor Cells are Associated With Chronic Immune Suppression After Severe Sepsis/Septic Shock. Annals of surgery. 2016
65. Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, Bulger E, Kozar RA. Nutrition, Rehabilitation Investigators C. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Critical care. 2013; 17(5):R206. [PubMed: 24050662]
66. Le Maguet P, Roquilly A, Lasocki S, Asehnoune K, Carise E, Saint Martin M, Mimoz O, Le Gac G, Somme D, Cattenoz C, et al. Prevalence and impact of frailty on mortality in elderly ICU patients: a prospective, multicenter, observational study. Intensive care medicine. 2014; 40(5):674–682. [PubMed: 24651884]
67. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, Artiuch B, Ibrahim Q, Stollery DE, Rokosh E, et al. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2014; 186(2):E95–102.
68. Limaye AP, Kirby KA, Rubenfeld GD, Leisenring WM, Bulger EM, Neff MJ, Gibran NS, Huang ML, Santo Hayes TK, Corey L, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. Jama. 2008; 300(4):413–422. [PubMed: 18647984]
69. Kalil AC, Florescu DF. Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. Critical care medicine. 2009; 37(8): 2350–2358. [PubMed: 19531944]
70. Libert N, Bigaillon C, Chargari C, Bensalah M, Muller V, Merat S, de Rudnicki S. Epstein-Barr virus reactivation in critically ill immunocompetent patients. Biomedical journal. 2015; 38(1):70–76. [PubMed: 25179711]
71. Huang A, Zhang B, Wang B, Zhang F, Fan KX, Guo YJ. Increased CD14(+)HLA-DR (-/low) myeloid-derived suppressor cells correlate with extrathoracic metastasis and poor response to chemotherapy in non-small cell lung cancer patients. Cancer immunology, immunotherapy : CII. 2013; 62(9):1439–1451. [PubMed: 23760662]
72. Chen MF, Kuan FC, Yen TC, Lu MS, Lin PY, Chung YH, Chen WC, Lee KD. IL-6-stimulated CD11b+ CD14+ HLA-DR- myeloid-derived suppressor cells, are associated with progression and poor prognosis in squamous cell carcinoma of the esophagus. Oncotarget. 2014; 5(18):8716–8728. [PubMed: 25238263]
73. Blum D, Stene GB, Solheim TS, Fayers P, Hjermstad MJ, Baracos VE, Fearon K, Strasser F, Kaasa S, Euro I. Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model--a study based on data from an international multicentre project (EPCRC-CSA). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2014; 25(8):1635–1642.

74. Chen J, Chen Z. The effect of immune microenvironment on the progression and prognosis of colorectal cancer. Medical oncology. 2014; 31(8):82. [PubMed: 25034363]

75. Meirow Y, Kanterman J, Baniyash M. Paving the Road to Tumor Development and Spreading: Myeloid-Derived Suppressor Cells are Ruling the Fate. Front Immunol. 2015; 6:523. [PubMed: 26528286]

76. Suzuki E, Kapoor V, Jassar AS, Kaiser LR, Albelda SM. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. Clinical cancer research : an official journal of the American Association for Cancer Research. 2005; 11(18):6713–6721. [PubMed: 16166452]

77. Vincent J, Mignot G, Chalmin F, Ladoire S, Bruchard M, Chevriaux A, Martin F, Apetoh L, Rebe C, Ghiringhelli F. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer research. 2010; 70(8): 3052–3061. [PubMed: 20388795]

78. Yuan H, Cai P, Li Q, Wang W, Sun Y, Xu Q, Gu Y. Axitinib augments antitumor activity in renal cell carcinoma via STAT3-dependent reversal of myeloid-derived suppressor cell accumulation. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2014; 68(6):751–756. [PubMed: 25081318]

79. Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, Morse E, Kaplan RN, Mackall CL. Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Science translational medicine. 2014; 6(237):237ra267.

80. Ko JS, Zea AH, Rini BI, Ireland JL, Elson P, Cohen P, Golshayan A, Rayman PA, Wood L, Garcia J, et al. Sunitinib mediates reversal of myeloid-derived suppressor cell accumulation in renal cell carcinoma patients. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009; 15(6):2148–2157. [PubMed: 19276286]

81. Mirza N, Fishman M, Fricke I, Dunn M, Neuger AM, Frost TJ, Lush RM, Antonia S, Gabrilovich DI. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer research. 2006; 66(18):9299–9307. [PubMed: 16982775]

82. Cuenca AG, Cuenca AL, Winfield RD, Joiner DN, Gentile L, Delano MJ, Kelly-Scumpia KM, Scumpia PO, Matheny MK, Scarpace PJ, et al. Novel role for tumor-induced expansion of myeloid-derived cells in cancer cachexia. Journal of immunology. 2014; 192(12):6111–6119.

83. Kang JW, Kim SJ, Cho HI, Lee SM. DAMPs activating innate immune responses in sepsis. Ageing research reviews. 2015; 24(Pt A):54–65. [PubMed: 25816752]

84. Timmermans K, Kox M, Scheffer GJ, Pickkers P. Danger in the Intensive Care Unit: Damps in Critically Ill Patients. Shock. 2016; 45(2):108–116. [PubMed: 26513703]

85. Yamanouchi S, Kudo D, Yamada M, Miyagawa N, Furukawa H, Kushimoto S. Plasma mitochondrial DNA levels in patients with trauma and severe sepsis: time course and the association with clinical status. Journal of critical care. 2013; 28(6):1027–1031. [PubMed: 23787023]

86. Gao S, Yang Y, Fu Y, Guo W, Liu G. Diagnostic and prognostic value of myeloid-related protein complex 8/14 for sepsis. The American journal of emergency medicine. 2015; 33(9):1278–1282. [PubMed: 26206243]

87. White LE, Hassoun HT, Bihorac A, Moore LJ, Sailors RM, McKinley BA, Valdivia A, Moore FA. Acute kidney injury is surprisingly common and a powerful predictor of mortality in surgical sepsis. The journal of trauma and acute care surgery. 2013; 75(3):432–438. [PubMed: 24089113]

88. Korenkevych D, Ozrazgat-Baslanti T, Thottakkara P, Hobson CE, Pardalos P, Momcilovic P, Bihorac A. The Pattern of Longitudinal Change in Serum Creatinine and 90-Day Mortality After Major Surgery. Annals of surgery. 2015

89. Villar J, Blanco J, Zhang H, Slutsky AS. Ventilator-induced lung injury and sepsis: two sides of the same coin? Minerva anestesiologica. 2011; 77(6):647–653. [PubMed: 21617628]

90. Schepens T, Verbrugghe W, Dams K, Corthouts B, Parizel PM, Jorens PG. The course of diaphragm atrophy in ventilated patients assessed with ultrasound: a longitudinal cohort study. Critical care. 2015; 19:422. [PubMed: 26639081]

91. Powers SK, Wiggs MP, Sollanek KJ, Smuder AJ. Ventilator-induced diaphragm dysfunction: cause and effect. American journal of physiology Regulatory, integrative and comparative physiology. 2013; 305(5):R464–477.
92. Hotchkiss RS, Opal S. Immunotherapy for sepsis--a new approach against an ancient foe. The New England journal of medicine. 2010; 363(1):87–89. [PubMed: 20592301]
93. Hotchkiss RS, Moldawer LL. Parallels between cancer and infectious disease. The New England journal of medicine. 2014; 371(4):380–383. [PubMed: 25054723]
94. Oberholzer C, Oberholzer A, Clare-Salzler M, Moldawer LL. Apoptosis in sepsis: a new target for therapeutic exploration. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2001; 15(6):879–892. [PubMed: 11292647]
95. Hotchkiss RS, Tinsley KW, Swanson PE, Chang KC, Cobb JP, Buchman TG, Korsmeyer SJ, Karl IE. Prevention of lymphocyte cell death in sepsis improves survival in mice. Proceedings of the National Academy of Sciences of the United States of America. 1999; 96(25):14541–14546. [PubMed: 10588741]
96. Hotchkiss RS, Chang KC, Swanson PE, Tinsley KW, Hui JJ, Klender P, Xanthoudakis S, Roy S, Black C, Grimm E, et al. Caspase inhibitors improve survival in sepsis: a critical role of the lymphocyte. Nature immunology. 2000; 1(6):496–501. [PubMed: 11101871]
97. Unsinger J, McGlynn M, Kasten KR, Hoekzema AS, Watanabe E, Muenzer JT, McDonough JS, Tschoep J, Ferguson TA, McDunn JE, et al. IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sepsis. Journal of immunology. 2010; 184(7):3768–3779.
98. Inoue S, Unsinger J, Davis CG, Muenzer JT, Ferguson TA, Chang K, Osborne DF, Clark AT, Coopersmith CM, McDunn JE, et al. IL-15 prevents apoptosis, reverses innate and adaptive immune dysfunction, and improves survival in sepsis. Journal of immunology. 2010; 184(3):1401–1409.
99. Chang KC, Burnham CA, Compton SM, Rasche DP, Mazuski RJ, McDonough JS, Unsinger J, Korman AJ, Green JM, Hotchkiss RS. Blockade of the negative co-stimulatory molecules PD-1 and CTLA-4 improves survival in primary and secondary fungal sepsis. Critical care. 2013; 17(3):R85. [PubMed: 23663657]
100. Shindo Y, Unsinger J, Burnham CA, Green JM, Hotchkiss RS. Interleukin-7 and anti-programmed cell death 1 antibody have differing effects to reverse sepsis-induced immunosuppression. Shock. 2015; 43(4):334–343. [PubMed: 25565644]
101. Lee JM, Kim EK, Seo H, Jeon I, Chae MJ, Park YJ, Song B, Kim YS, Kim YJ, Ko HJ, et al. Serum amyloid A3 exacerbates cancer by enhancing the suppressive capacity of myeloid-derived suppressor cells via TLR2-dependent STAT3 activation. European journal of immunology. 2014; 44(6):1672–1684. [PubMed: 24659444]
102. Chun E, Lavoie S, Michaud M, Gallini CA, Kim J, Soucy G, Odze R, Glickman JN, Garrett WS. CCL2 Promotes Colorectal Carcinogenesis by Enhancing Polymorphonuclear Myeloid-Derived Suppressor Cell Population and Function. Cell Rep. 2015; 12(2):244–257. [PubMed: 26146082]
103. Nagaraj S, Gupta K, Pisarev V, Kinarsky L, Sherman S, Kang L, Herber DL, Schneck J, Gabrilovich DI. Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer. Nat Med. 2007; 13(7):828–835. [PubMed: 17603493]
104. Chioda, M., M, I., Mandruzzato, S., Mocellin, S., Bronte, V. Arginase, nitric oxide synthase, and novel inhibitors of L-arginine metabolism in immune modulation. In: Prendergast, GC., J, E., editors. Cancer Immunotherapy. 2. San Diego: Academic Press; 2013. p. 597-634.
105. Zhu J, Huang X, Yang Y. Myeloid-derived suppressor cells regulate natural killer cell response to adenovirus-mediated gene transfer. Journal of virology. 2012; 86(24):13689–13696. [PubMed: 23055553]
106. Pan PY, Ma G, Weber KJ, Ozao-Choy J, Wang G, Yin B, Divino CM, Chen SH. Immune stimulatory receptor CD40 is required for T-cell suppression and T regulatory cell activation mediated by myeloid-derived suppressor cells in cancer. Cancer research. 2010; 70(1):99–108. [PubMed: 19996287]

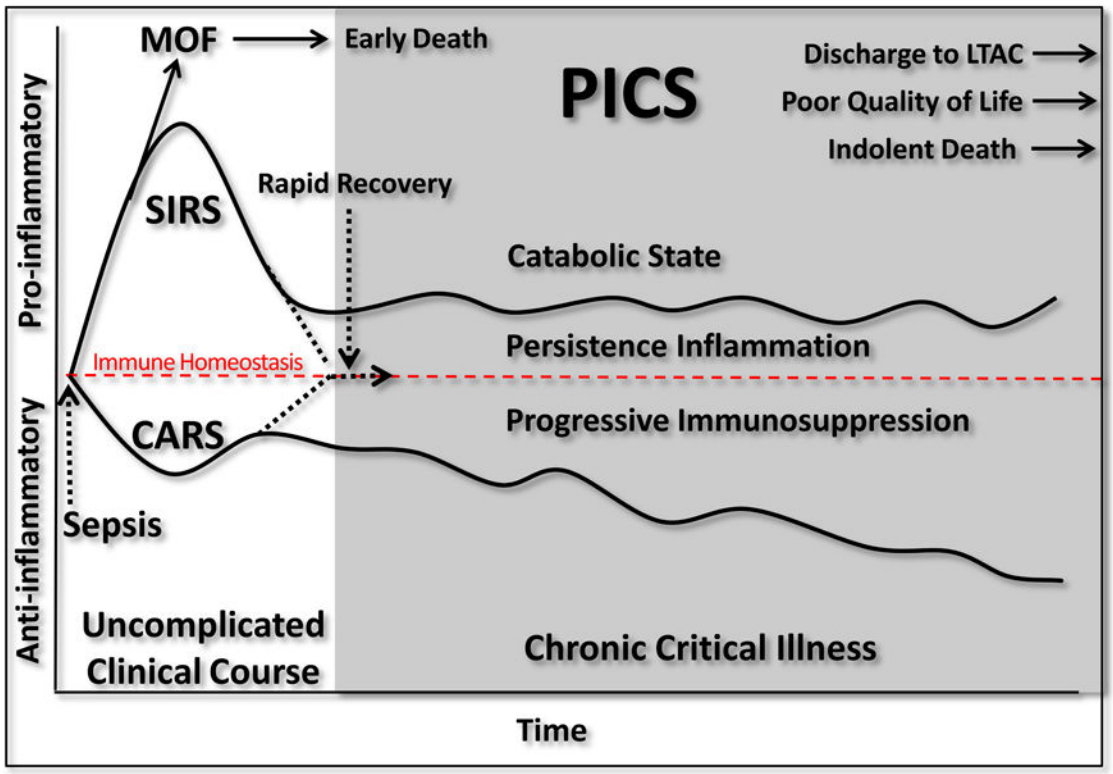

Figure 1. Model of PICS

Early deaths from acute MOF secondary to the acute hyper-inflammatory 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 CCI 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 three-year mortality of 71% [20, 28]. Modified from [28].

Abbreviations: MOF – multiple organ failure; SIRS – systemic inflammatory response syndrome; CARS – compensatory anti-inflammatory response syndrome; PICS – persistent immune suppression inflammation and catabolism syndrome; LTAC – Long term acute care facility.

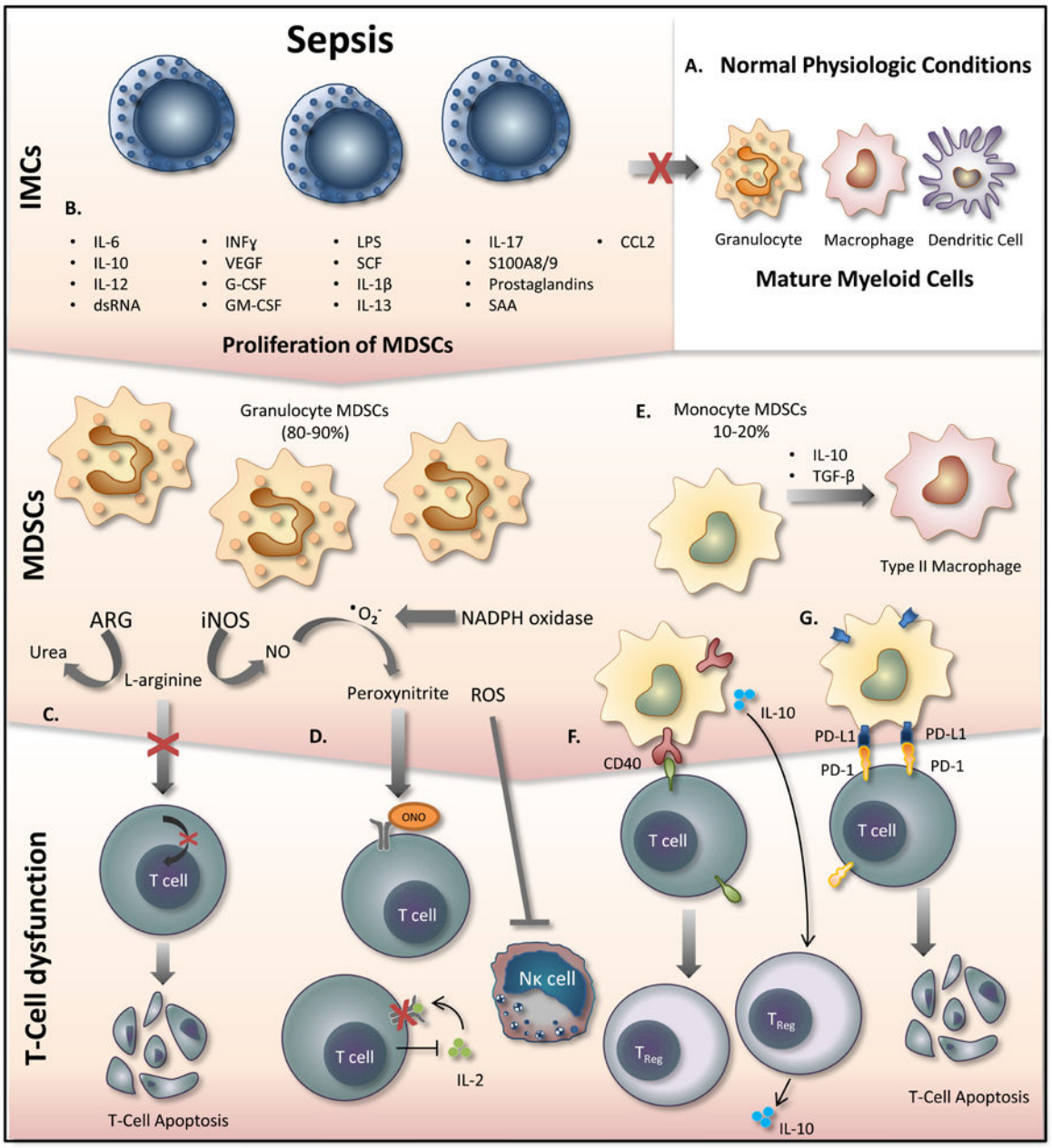

Figure 2. Role of MDSCs in Severe Sepsis/Septic Shock Patients

A. Under normal physiologic conditions, immature myeloid cells (IMC) 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 IL-6, IL-10, IL-12, dsRNA, INF-γ, VEGF, G-CSF, GM-CSF, LPS, SCF, IL-1β, IL-13, IL-17, S100A8/9, prostaglandins, SAA, and CCL2 [49, 50, 101, 102]. As a result, IMCs remain as MDSCs at the expense of differentiation into mature myeloid cell populations. While 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 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 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 towards a type II phenotype via IL-10 and TGF-β production [53]. Additionally, 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 MDSC has been associated with induction of T_{reg} cells that produce IL-10 [58]. G. Upregulation of PD-L1 and other checkpoint inhibitors in MDSC leads to T-cell apoptosis [100].

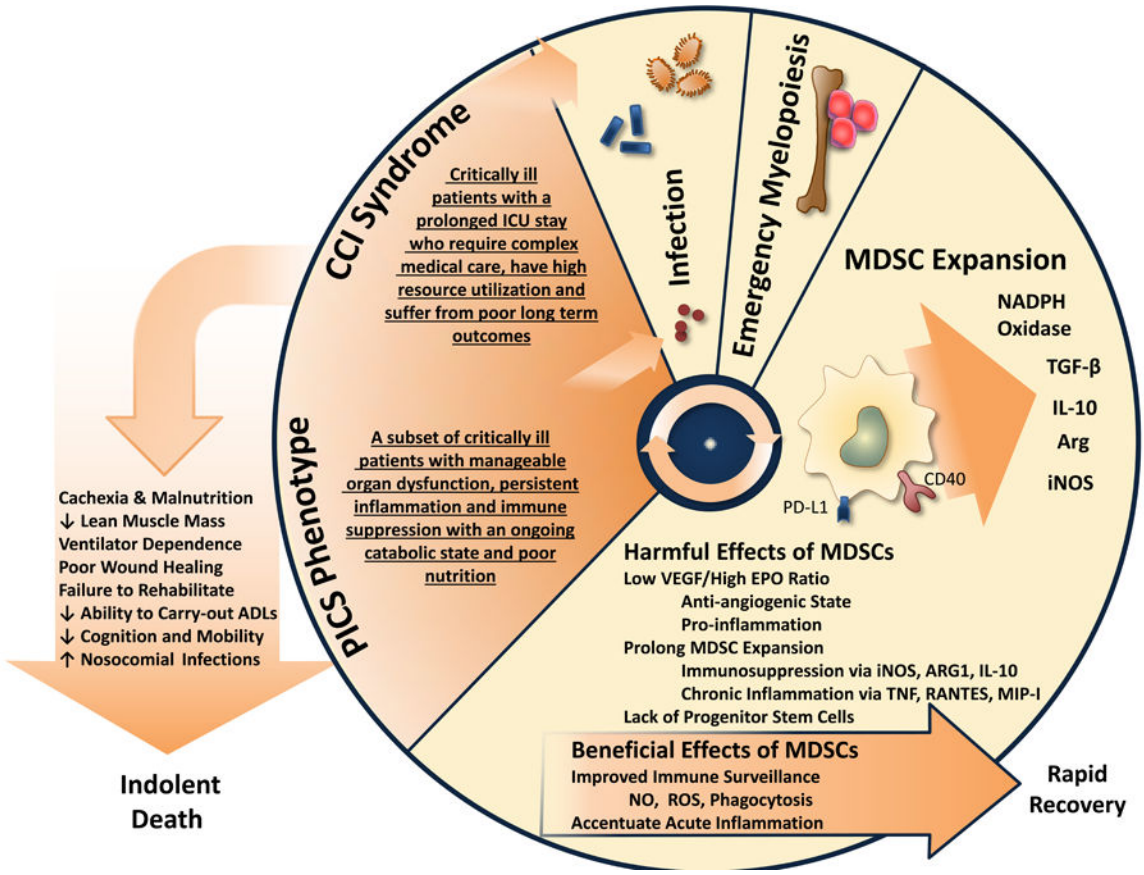

Figure 3. Sepsis, Emergency Myelopoiesis, MDSC expansion and the development of CCI and PICS

Sepsis results in a self-stimulating cycle. Initially, sepsis leads to emergency myelopoiesis and MDSC expansion [52]. While 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, 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.

Table 1

Terminology and Definitions

New consensus criteria for defining sepsis, septic shock [18]. While the SOFA score provides the most robust predictive validity for outcomes, particularly in the ICU, the qSOFA provide a rapid bedside assessment with readily available parameters that promotes further investigation and clinical intervention. Modified from [18]. PICS criteria are also defined here by surrogate markers of inflammation, immunosuppression, and catabolism that are readily available in most clinical settings [28]. Use of these parameters can aid in the identification of patients at risk of PICS.

Term	Definition	
Infection	Interaction between host and pathogen that promulgates a local or systemic host response *	
Sepsis	Life threatening organ disjunction secondary to a dysregulated host response to infection	
Sepsis onset	Evidence of new organ dysfunction remote from site of infection	
Organ dysfunction	Acute change in total SOFA score >2 points remote from infection site **	
Septic Shock	Profound metabolic, cellular, and circulatory derangements in a subset of sepsis associated with increased risk of mortality ***	
Rapid bedside organ dysfunction score – qSOFA ** – at least 2 of the following**	Altered Mental Status – Glasgow Coma Scale ≤ 14	
	Systolic Blood Pressure ≤ 100 mmHg	
	Respiratory Rate 22 breaths per min	
PICS	Critically ill patient →	Admission to the ICU > 14 days
	Persistent inflammation →	CRP > 50 μg/dL
		Retinol binding protein < 1 mg/dL
	Immunosuppression →	Total lymphocyte count < 0.80 $\times 10^9$/L
	Catabolic state →	Serum albumin < 3.0 g/dL
		Creatinine height index < 80%
		Weight loss > 10% ‘or’ BMI < 18 during hospitalization

* Conventional definition, not redefined by the Sepsis-3 Task Force

** Associated with > 10% in-hospital mortality

*** Associated with > 40% in-hospital mortality

**** Quick assessment to prompt further clinical investigation of organ dysfunction

Abbreviations: MAP – mean arterial pressure; SOFA – Sepsis-related Organ Failure Assessment; qSOFA – Quick SOFA; PICS – Persistent Inflammation, Immunosuppression and Catabolism Syndrome; ICU – Intensive Care Unit; CRP – C-reactive protein; BMI – Body mass index;

Table 2

Myeloid Derived Suppressors Cells in Sepsis

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

	12 hrs	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 * (n=72)	37.8 * (n=70)	26.2 * (n=66)	25.6 * (n=51)	32.9 * (n=37)	34.9 * (n=24)	35.6 * (n=16)
Healthy Control – Mean Granulocytic MDSC %	26.6 (n=18)						
Sepsis – Mean Granulocytic MDSC %	71.0 * (n=72)	68.5 * (n=70)	58.6 * (n=66)	60.5 * (n=51)	66.4 * (n=37)	65.5 * (n=24)	67.5 * (n=16)
Septic patient with ICU LOS <14 days – 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 days) – Mean MDSC %	63 ** (n=6)	64.3 ** (n=5)	38.0 (n=4)	25.8 (n=1)			

* p<0.05 when compared to heathy control subjects

** p<0.05 when compared to patients with ICU LOS <14 days

Abbreviations: MDSC – Myeloid Derived Suppressor Cells; ICU – Intensive Care Unit; LOS – Length of Stay