Dysregulated Immunity and Immunotherapy after Sepsis

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Abstract: Implementation of protocolized surveillance, diagnosis, and management of septic patients, and of surgical sepsis patients in particular, is shown to result in significantly increased numbers of patients surviving their initial hospitalization. Currently, most surgical sepsis patients will rapidly recover from sepsis; however, many patients will not rapidly recover, but instead will go on to develop chronic critical illness (CCI) and experience dismal long-term outcomes. The elderly and comorbid patient is highly susceptible to death or CCI after sepsis. Here, we review aspects of the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) endotype to explain the underlying pathobiology of a dysregulated immune system in sepsis survivors who develop CCI; then, we explore targets for immunomodulatory therapy.

Keywords: PICS; CCI; MDSC; inflammation; immunosuppression; sepsis

1. Introduction

Sepsis remains one of the leading causes of death in the United States [1]. Implementation of the 2004 and 2011 Surviving Sepsis Campaign guidelines, as well as of the Centers for Medicare & Medicaid Services guidelines for sepsis management [2], and an increase in systemic and protocolized surveillance, diagnosis, and management of sepsis, all together led to a significant decrease in early death and an increase in hospital survival [3,4]. However, this increased initial survival after sepsis is not yet translated to similarly improved long-term outcomes nor full recovery [5,6]. Specifically, following surgical sepsis, three common clinical trajectories are described: early death, rapid recovery, or development of chronic critical illness (CCI) (Figure 1). Historically, many patients would develop fulminant multiple organ failure from systemic inflammatory response syndrome, leading to early death. Currently, less than 10% of surgical sepsis patients succumb to early death [5]; the majority of patients survive sepsis and either rapidly recover or develop CCI [5,7]. Unfortunately, almost one-third of surgical sepsis patients develop CCI and have dismal long-term outcomes [5].

CCI is defined in several ways, but an accepted definition in the literature is an individual with a prolonged intensive care unit stay (>14 days) and persistent organ dysfunction ranging from low-grade organ insufficiency to chronic organ failure [8,9]. Patients who develop CCI are more likely to be older males with a greater number of medical comorbidities [10,11]. Importantly, patients who develop CCI continue to consume vast resources long after hospital discharge [12]. Additionally, CCI patients have an increased number of secondary infections [13,14] and have poor long-term outcomes that include functional and neurocognitive impairments, increased muscle wasting, and higher 30-day and 1-year mortality [5,9,10,15]. However, the underlying pathobiology of CCI remains unclear.
Figure 1. Proposed hypothesis for Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) in sepsis survivors. Abbreviations: MDSC—myeloid-derived suppressor cell; DAMP—damage-associated molecular protein; LTAC—long-term acute care facility.

In a 2012 review, the University of Florida Sepsis and Critical Illness Research Center, under the leadership of Dr. Frederick Moore, defined the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) as the clinical endotype underlying the CCI phenotype [16]. PICS is not specific to a critical illness and is seen in a number of conditions including sepsis, trauma, advanced cancer, and chronic inflammatory diseases [16,17]. A significant subset of CCI patients progress to PICS, experiencing ongoing inflammation (e.g., neutrophilia) and immunosuppression (e.g., lymphopenia) that are associated with a sustained acute phase response (e.g., high C-reactive protein and low pre-albumin) and persistent whole body protein catabolism [8,18,19]. Clinically, PICS patients (as stated above) suffer from recurrent nosocomial infections and poor wound healing, and frequently develop decubitus ulcers. Despite aggressive nutritional intervention, there is a constant loss of lean body mass accompanied by a proportional reduction in both functional status and wound healing potential [14]. Patients with PICS are commonly discharged to long-term acute care facilities where they face failure to rehabilitate, sepsis recidivism requiring re-hospitalization, and ultimately sufferance of an indolent death [20].

The Persistent Inflammation, Immunosuppression, and Catabolism Syndrome represents a testable hypothesis to elucidate what drives the development of CCI and its morbidities, including persistent immunologic dysfunction, lack of organ recovery, and functional deficit. All of these factors contribute to poor long-term outcomes after severe pro-inflammatory insults such as trauma, sepsis, pancreatitis, or burn injury [21]. Importantly, the PICS endotype offers insight into the dysregulated immunity and dysfunctional emergency myelopoietic response seen in CCI patients after sepsis [7,8,22]. Sepsis is a complex disease process in which outcomes are affected by both the early and late inflammatory response [23,24]. In this review, we will focus on the pathobiologic processes that contribute to the post-sepsis PICS endotype.

2. Persistent Inflammation

During acute sepsis, the progression from sepsis to CCI/PICS is mediated by widespread innate immune activation in the early inflammatory response [25]. In sepsis survivors who develop CCI, there remains a persistent elevation in a number of inflammatory
markers at least 28 days after sepsis onset, and potentially much longer [26]. The body’s response to sepsis or severe injury begins with the recognition of alarmins derived from either microbial products (pathogen-associate molecular patterns; PAMPs) or tissue injury (damage-associated molecular patterns; DAMPs) [23]. Alarmins represent an array of ligands for highly-conserved pattern recognition receptors (PRRs) that detect exogenous microbial components or host danger signals [23]. These alarmins were previously identified as major mediators of persistent inflammation in CCI after sepsis.

Major classes of PRRs include Toll-like receptors (TLRs), C-type lectin receptors, nucleotide-binding oligomerization domain-like receptors, retinoic-acid-inducible gene-I-like receptors, and receptors for advanced glycation end products (RAGE) [27]. PRRs are comprised of both cell membrane and cytoplasmic receptors that can collectively recognize microbial peptidoglycans, lipopolysaccharides, glucans, phospholipids, high mobility group box (HMGB) proteins [28], S100 family of proteins, nucleic acids [29–31], glycoproteins and glycolipids [32], flagellin [33], glycosylated end products [28,34], and oxidation/nitrosylation products associated with cellular injury [27,35–37]. Upon recognition of these molecular patterns, PRRs initiate downstream signaling events that induce a host-protective response [36].

In the case of sepsis, alarmins are mostly derived from foreign pathogen materials or PAMPs [27,36]. Among the critically ill, PAMPs are released during the initial sepsis event and in secondary nosocomial infections or reactivated viral infections. PAMPs from these microbes induce a rapid activation of effector cells [36]. PAMPs initiate dendritic cell maturation to promote antigen processing, MHC expression, and migration to lymph nodes to activate T cells [36,38]. In one study of critically ill patients, viral DNA from either CMV, EBV, HHV-6, or TTV was identified in the blood of nearly 87% of critically ill septic patients, compared with <15% for non-septic critically ill patients and healthy controls [39]. Of note, nearly 43% of the septic patients that were examined tested positive for two or more viruses [39].

The other source of alarmins comes from endogenous nucleic acids, proteins, and metabolites released from cellular stress, death at sites of injury, or active secretion from immune cells [40,41]. DAMPs include HMGB1, heat shock proteins, nuclear and mitochondrial DNA and structural peptides such as hyaluron, cellular intermediates such as adenosine, and the cytokines, interleukin (IL)-1α and IL-33 [41–43]. Multiple DAMPs, including nuclear DNA, RAGE, and S100, are significantly elevated in sepsis survivors throughout their entire hospitalization [44–47]. DAMPs are initially released from acutely inflamed and injured tissue secondary to initial septic insult. It is thought that DAMPs are also chronically released from ongoing oxidant and mitochondrial injury in the kidneys, lungs, and intestines of patients with CCI, contributing to a continued low-grade inflammation in these patients after sepsis [7].

The persistent low-grade inflammation seen in CCI/PICS after sepsis, similar to the chronic low-grade inflammation experienced in cancer and other inflammatory disorders, results in a constant cycle of inflammation-induced organ injury and injury-induced inflammation [17]. The chronic inflammation in PICS induces increased mitochondrial production of reactive oxygen species [48–50]. This oxidative stress leads to mitochondrial dysfunction, oxidative damage, and cellular metabolism energy deficits, which further aggravates inflammation and cell death pathways, contributing to low-grade persistent inflammation and organ injury [51]. Continued kidney and muscle damage from inflammation results in further release of DAMPs from these tissues, which further perpetuates this cycle of inflammation [52]. The sepsis-induced chronic inflammation in the brain, termed sepsis-associated encephalopathy, leads to declines in cognitive function and related reductions in quality of life among survivors of sepsis [53,54]. This is especially detrimental in the older patient who already suffers from “inflammaging”, the gradual deterioration of host-protective immunity associated with natural aging [55]. This vicious cycle of inflammation leads to more organ failure and eventually death (Figure 2).
3. Persistent Immunosuppression

Immunosuppression after sepsis is reflected in a reduced acute lymphocyte count (ALC) and monocyte membrane (m) HLA-DR expression alongside an increase in soluble programmed cell death ligand-1 (PD-L1), which persists for weeks after sepsis [56]. Low ALC remains suppressed in CCI patients, while it returns to baseline in patients that rapidly recover [56]. Additionally, mHLA-DR is decreased in those that developed secondary infections [57] and is an independent predictor of nosocomial infections [58]. Macrophage and T-lymphocyte dysfunction are important contributors to the PICS-associated immunosuppression [59]. In late sepsis, a state of immune “paralysis” develops as bacterial clearance, cytokine release, and capacity for antigen presentation all decline [59,60]. Additionally, there is a relative lymphocyte “exhaustion” characterized by dysfunctional T cell differentiation and decreased ability to respond to new or continued antigen presentation [61–63].

This ongoing immune dysfunction, seen mostly among sepsis-induced CCI survivors, results in increased vulnerability to secondary infections after sepsis. There is a 25–32% readmission rate among all sepsis survivors, with 52–66% of these admissions being for recurrent sepsis [14]. Furthermore, sepsis survivors with CCI experience increased secondary and nosocomial infections at a rate two and a half times greater when compared to patients who rapidly recovered, with a 60% readmission rate for those with CCI [64]. Mortality approaches 40% at six months for patients with CCI, largely due to sepsis recidivism [65–67].

4. Persistent Catabolism

Sepsis is associated with increased protein breakdown and suppressed protein synthesis, resulting in increased muscle catabolism and a release of muscle-derived DAMPs. Patients with CCI experience a prolonged state of this catabolism with muscle wasting and cachexia that contribute to poor long-term functional outcomes. This breakdown occurs despite enteral supplementation and may require increased protein enrichment with specific additives [15].

There is a plethora of evidence that supports prolonged muscle wasting in late sepsis [15,68,69]. Brakenridge et al. [70] demonstrated that glucagon-like peptide 1, a biomarker of catabolism, is elevated at 24 h and remains elevated at 21 days in sepsis survivors with CCI. Unfortunately, the exact mechanism(s) of sepsis-induced catabolism is not known. There is some evidence that the sustained protein catabolism seen in CCI is partially due to the self-perpetuating inflammation and mitochondrial oxidant injury that
leads to the continued release of DAMPs driving inflammation and leading to continued breakdown of skeletal muscle. For example, circulating mitochondrial DNA (mtDNA) present in aging and muscle wasting disorders is also seen in sepsis [71]. DAMPs such as mtDNA, HMGB1, and mitochondrial transcription factor A are increased in systemic circulation during periods of catabolism and continue to drive persistent inflammation [72,73].

5. Dysregulated Myelopoiesis

Infections and sepsis also induce emergency myelopoiesis [74,75]. Acute infection initiates mobilization of mature myeloid cells that leads to depletion of bone marrow stores and subsequent release of more immature populations [74]. Early stem cells and multipotent progenitor cells all express PRRs, respond to alarmins, and undergo expansion in response to sepsis. Preferential myeloid progenitor expansion is mediated by inflammatory cytokines and chemokines, including the granulocyte-macrophage-colony stimulating factor (GM-CSF) and the granulocyte-colony stimulating factor (G-CSF) [74]. In a murine model of chronic sepsis, 95% of murine bone marrow cells were noted to be myeloid cells at seven days, with the majority of these cells being phenotypically immature and functionally immunosuppressive [76].

Myeloid-derived suppressor cells (MDSCs) were extensively studied in chronic critical illness of cancer patients and more recently emerged as important immune cells in early and late sepsis [77–79]. In the early phases of sepsis, strong signals from DAMPs, PAMPs, and various cytokines and chemokines stimulate rapid mobilization of differentiated monocytes and granulocytes from the bone marrow via classic myelopoiesis [80]. However with persistent weak signaling seen in chronic inflammatory states, such as late sepsis or cancer, there is a shift towards the mobilization and pathologic activation of immature myeloid populations [81]. MDSCs are a heterogeneous group of immature myeloid cells that undergo expansion during emergency myelopoiesis in an attempt to preserve host innate immunity in these pathologic conditions [82]. MDSCs consist of two major groups of cells: polymorphnuclear (PMN-MDSC) and monocytic (M-MDSC) [52]. Phenotypically, PMN-MDSCs are defined as CD11b+CD14−CD15+CD66b+LOX-1+ with low side scatter (SSC), and M-MDSCs are defined as CD14+CD15−HLA-DR−/lo with low SSC [83]. Functional characterization of these cells is contingent upon their immunosuppressive functions, i.e., their ability to suppress lymphocyte proliferation and cytokine production [82]. Studies demonstrated that circulating MDSCs are persistently elevated out to 28 days after severe sepsis and septic shock, and are associated with an increase in secondary infections, increased ICU stay, and poor functional status [74,84,85]. In a study of surgical sepsis survivors, MDSCs remained significantly elevated for six weeks post-infection; those same MDSCs only demonstrated suppressive properties at and beyond 14 days post-sepsis [86]. As patients continue to experience unresolved inflammation, there is continued expansion and an eventual pathologic activation of MDSCs [52]. Although the initial expansion of MDSCs may be beneficial by potentiating the early innate immune response and pathogen surveillance, persistent MDSC expansion can be detrimental, as it both propagates persistent inflammation and dampens the adaptive immune response via T cell suppression [82,85,87,88].

6. Immunotherapy

Despite the recent decreases in sepsis mortality thanks to earlier recognition and standardized management, the poor long-term outcomes experienced by sepsis survivors with CCI lend evidence to a continued need to investigate agents for use in preventing undesirable sepsis outcomes. At its core, CCI/PICS is an appropriate early inflammatory response that goes awry when it becomes persistent and unabated. The goal of most interventional studies is to bring about a return to immune homeostasis through leukocyte growth factors that suppress MDSCs, promote restoration of normal lymphocyte numbers and function, and/or restore mature functional myeloid populations (Table 1). Leukocyte growth factors such as GM-CSF and G-CSF are one such focus. In one clinical trial, recombinant GM-CSF
therapy in immunosuppressed pediatric patients with sepsis restored tumor necrosis factor production in lymphocytes and reduced nosocomial infections to zero in the treatment group [89]. Two other randomized clinical trials involving recombinant G-CSF in severe sepsis and community acquired pneumonia demonstrated an increase in total leukocyte counts in patients receiving the experimental therapy; however, there were no significant improvements in 28-day mortality [90,91]. Similarly, a meta-analysis of 12 clinical trials using recombinant G-CSF and GM-CSF as sepsis treatments in humans found a significant improvement in the rate of infection clearance, but failed to demonstrate any significant improvements in mortality [92]. We attribute this to a failure to address the expansion of pathologically activated MDSCs stimulated by these colony-stimulating factors.

Of note, none of these trials focused on long-term outcomes after 28 days. The use of standard 28-day mortality rates as an endpoint can be misleading and fail to capture the delayed and protracted course of sepsis-related deaths after hospital discharge accurately [93,94]. Though further studies are warranted to assess effects on long-term outcomes, their documented role in reducing infections suggests that there may yet be a role for G-CSF/GM-CSF as one element of a multidrug treatment in combination with other immunotherapies.

There also were studies aimed at directly impacting T cell immunity in sepsis [95,96]. IL-7 is a hematopoietic cytokine that promotes B and T cell development, proliferation and enhancement of T-cell activation, and mobilization to sites of injury [97–99]. IL-7 is noted to increase CD4+ and CD8+ T cell numbers in murine sepsis by upregulating the expression of the anti-apoptosis regulator B-cell lymphoma 2 protein, which is associated with improved survival [99,100]. IL-7 improves ex vivo lymphocyte function [97], and administration of IL-7 enhances T cell receptor diversity in humans, which is typically reduced in sepsis [96,101]. Treatment of sepsis with IL-7 is promising—it was shown to be well-tolerated in clinical trials with no severe toxicities [102]. Furthermore, IL-7 administration more than doubles the levels of circulating CD4+ and CD8+ T cells in HIV and cancer patients, and preferentially promotes effector T cells instead of regulatory T cells [103–106]. A follow-up trial is underway to study the effect of IL-7 in restoration of absolute lymphocyte counts in septic patients (NCT03821038).

Interferon gamma (IFN-γ) was also the target of immunomodulatory therapies in inflammatory disease. IFN-γ is important for immune activation against viral, bacterial, and protozoal infections [107]. IFN-γ production is typically suppressed during sepsis in rodents and humans [99,108,109]. However, studies show that the restoration of IFN-γ production improves survival in murine sepsis [99,110]. Treatment with recombinant IFN-γ was associated with increased mHLA-DR expression on monocytes in septic patients and improved monocyte function [111–113]. In one randomized controlled trial, IFN-γ treatment decreased infection-related and overall mortality in severely injured trauma patients [114]. IFN-associate genes were suppressed in trauma patients with complicated outcomes, which highlights a potential subgroup for recombinant IFN-γ therapy or IFN-stimulating agents [115,116]. IFN-γ could be a potential immunomodulatory therapy during sepsis. However, as Patil points out, this benefit may ultimately be limited to those with already downregulated mHLA-DR [117]. A clinical trial is underway to examine the effects of IFN-γ on immune function in septic patients (NCT01649921).

An alternative approach is to target the immunosuppressive properties of mature leukocyte populations. Inhibitors of negative co-stimulatory pathways and immune checkpoint inhibitors emerged as potential targets for immunomodulation in sepsis. PD-1 blockade showed promising results in cancer therapeutics [118]. As a result, the PD-1/PD-L1 pathway is an ongoing target for the treatment of sepsis. PD-L1 and its receptor, PD-1, serve as a checkpoint inhibitor responsible for limiting CD8+ T cell proliferation and accumulation in lymph nodes. PD-1 is upregulated on CD4+ and CD8+ T cells in states of infection and inflammation [119,120]. High levels of PD-1 are associated with elevated secondary infection and mortality rates, and limited T cell proliferation among critically ill patients [119]. PD-1 knockout mice have improved effector T cell proliferation and faster
adenovirus clearance [121]. In vitro PD-1/PD-L1 blockade decreases T cell apoptosis and IL-10 release, and improves the function of neutrophil and monocytes from septic mice and humans [122,123]. In vivo, it appears to restore impaired CD8⁺ T cell function, leading to improved cytokine release and decreased viral loads (even in CD4-deficient models), with this improved functionality persisting for weeks following the transient blockade [124]. In pre-clinical mouse models of sepsis, blockade of other proteins in the PD-1/PD-L1 pathway significantly improved survival as well [110]. Additionally, inhibition of the PD-1/PD-L1 pathway prevented lymphocyte depletion and apoptosis, and improved survival after CLP in mice [125,126]. However, just as with other clinical trials in sepsis, there yet is no study to assess the effects of PD-1/PD-L1 inhibition on long-term outcomes beyond 30 days.

Table 1. Summary of select immunotherapy studies in sepsis or immunodeficiency.

| Intervention            | Result                                                                 | Ref  |
|-------------------------|------------------------------------------------------------------------|------|
| GM-CSF                  | Restoration of monocytic immunocompetence.                             | [89] |
|                         | Shortened time of mechanical ventilation and hospital stay.            |      |
| G-CSF                   | Increased total leukocyte counts. No difference in mortality rates or complications in sepsis patients. | [90] |
| G-CSF & GM-CSF          | Improved infection clearance, but no difference in mortality rates in sepsis patients. | [92] |
| IL-7                    | Improved lymphocyte counts (CD4⁺ and CD8⁺ immune effector cells) in sepsis patients. | [102] |
| IL-7                    | Increased CD4/CDS T cells in HIV patients.                             | [104] |
| IL-7                    | Increased CD4/CDS T cells in patients with lymphopenia.                | [105] |
| IFN-γ                   | Increased HLA-DR expression and decrease in natural killer cells in patients with sepsis. | [111] |
| IFN-γ                   | Decreased infection related mortality and overall mortality in trauma, but no difference in infection rates in trauma patients. | [114] |
| PD-1/PD-L1 blockade     | Ex-vivo restoration of function in neutrophils, monocytes, T cells, and NK cells in whole blood from septic patients. | [122] |
| PD-1/PD-L1 blockade     | In-vitro decreased T-cell apoptosis, potentiated monocyte LPS-induced TNF-α and IL-6 production from sepsis patients. | [123] |

Newly emerging interest in the role of MDSCs in sepsis triggered studies to target these cells for therapy. Although MDSCs were demonstrated to improve bacterial clearance, persistent activation also results in the failure to resolve acute inflammation and immunosuppression, ultimately leading to increased mortality [127]. Attenuating or modifying MDSC activation, expansion, and migration may be another approach to the treatment of sepsis [128]. A multitude of clinical efforts are underway to target MDSCs’ number and function in cancer [129]. The implications of such approaches after sepsis are less clear-cut; however, many immunomodulatory targets to attenuate MDSC immunosuppressive function have already emerged. Studies limiting MDSC expansion and functionality using gemcitabine-treated or CCAAT enhancer binding protein beta-knockout mice yielded conflicting results. After burn injury, gemcitabine treatment successfully resulted in a decrease in MDSCs and increased survival following a lethal dose of LPS, but conferred a decreased survival to Pseudomonas aeruginosa infection [130]. In another study, deficiency in MDSC signaling pathways caused persistent elevation in inflammatory cytokines and worsened survival, which all improved with the reintroduction of MDSCs [131]. Though there are no current clinical trials targeting MDSCs in sepsis, future trials should take into account the timing of MDSC modulatory treatment, as the MDSC immunosuppressive function is not seen until day 14 after sepsis [86].
7. Conclusions

Thanks in no small part to concerted efforts and global campaigns over the last two decades, patients with sepsis are surviving in greater numbers early in their hospitalization. Unfortunately, many of those who survive do not rapidly recover and instead experience prolonged intensive care unit stays and persistent organ dysfunction. CCI after sepsis is associated with long-term dismal outcomes out to one year from onset, including poor functional status, recurrent infection, failure to rehabilitate, and increased mortality [5]. The pathobiology of CCI is likely multifactorial but can be partially explained as being driven by the constellation of inflammatory, immunologic, and metabolic dysregulation, collectively defined as PICS. Single therapies that target aspects of PICS have yet to be successful, but long-term adverse outcomes after sepsis may be best attenuated with multimodal therapy. It is clear from clinical trials that a “one-size-fits-all” treatment strategy does not, in fact, fit all. Therefore, the multimodal therapy may require a precise, personalized strategy to be successful in helping patients not only survive sepsis, but also offering them a better chance for good functional recovery.

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References
1. Rhee, C.; Dantes, R.; Epstein, L.; Murphy, D.J.; Seymour, C.W.; Iwashyna, T.J.; Kadri, S.S.; Angus, D.C.; Danner, R.L.; Fiore, A.E.; et al. Incidence and trends of sepsis in us hospitals using clinical vs claims data, 2009–2014. J. Am. Med.Assoc. 2017, 318, 1241–1249. [CrossRef]
2. Levy, M.M.; Rhodes, A.; Phillips, G.S.; Townsend, S.R.; Schorr, C.A.; Beale, R.; Osborn, T.; Lemeshow, S.; Chiche, J.-D.; Artigas, A.; et al. surviving sepsis campaign: Association between performance metrics and outcomes in a 7.5-year study. Intensive Care Med. 2014, 40, 1623–1633. [CrossRef] [PubMed]
3. Croft, C.A.; Moore, F.A.; Efron, P.A.; Marker, P.S.; Gabrielli, A.; Westhoff, L.S.; Lottenberg, L.; Jordan, J.; Klink, V.; Sailors, R.M.; et al. Computer versus paper system for recognition and management of sepsis in surgical in-tensive care. J. Trauma Acute Care Surg. 2014, 76, 311–317. [CrossRef]
4. McKinley, B.A.; Moore, L.J.; Sucher, J.F.; Todd, S.R.; Turner, K.L.; Valdivia, A.; Sailors, R.M.; Moore, F.A. Computer protocol facilitates evidence-based care of sepsis in the surgical intensive care unit. J. Trauma Inj. Infect. Crit. Care 2011, 70, 1153–1167. [CrossRef]
5. Brakenridge, S.C.; Efron, P.A.; Cox, M.C.; Stortz, J.A.; Hawkins, R.B.; Ghita, G.; Gardner, A.; Mohr, A.M.; Anton, S.D.; Moldawer, L.L.; et al. Current epidemiology of surgical sepsis: Discordance between inpatient mortality and 1-year outcomes. Ann. Surg. 2019, 270, 502–510. [CrossRef] [PubMed]
6. Moore, L.J.; McKinley, B.A.; Turner, K.L.; Todd, S.R.; Sucher, J.F.; Valdivia, A.; Sailors, R.M.; Kao, L.S.; Moore, F.A. The epidemiology of sepsis in general surgery patients. J. Trauma: Inj. Infect. Crit. Care 2011, 70, 672–680. [CrossRef] [PubMed]
7. Mira, J.C.; Gentile, L.F.; Mathia, B.J.; Efron, P.A.; Brakenridge, S.C.; Mohr, A.M.; Moore, F.A.; Moldawer, L.L. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit. Care Med. 2017, 45, 253–262. [CrossRef] [PubMed]
8. Hawkins, R.B.; Raymond, S.L.; Stortz, J.A.; Horiguchi, H.; Brakenridge, S.C.; Gardner, A.; Efron, P.A.; Bihorac, A.; Segal, M.; Moore, F.A.; et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. Front. Immunol. 2018, 9, 1511. [CrossRef]
9. Iwashyna, T.J.; Hodgson, C.L.; 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. Lancet Respir. Med. 2016, 4, 566–573. [CrossRef]
10. Cox, M.C.; Brakenridge, S.C.; Stortz, J.A.; Hawkins, R.B.; Darden, D.B.; Ghita, G.L.; Mohr, A.M.; Moldawer, L.L.; Efron, P.A.; Moore, F.A. Abdominal sepsis patients have a high incidence of chronic critical illness with dismal long-term outcomes. Am. J. Surg. 2020, 220, 1467–1474. [CrossRef]
11. Mankowski, R.T.; Anton, S.D.; Ghita, G.; Brumback, B.; Cox, M.C.; Mohr, A.M.; Leeuwenburgh, C.; Moldawer, L.L.; Efron, P.A.; Brakenridge, S.C.; et al. Older sepsis survivors suffer persistent disability burden and poor long-term survival. J. Am. Geriatr. Soc. 2020, 68, 1962–1969. [CrossRef]
12. Iwashyna, T.J.; Cooke, C.R.; Wunsch, H.; Kahn, J.M. Population burden of long-term survivorship after severe sepsis in older Americans. J. Am. Geriatr. Soc. 2012, 60, 1070–1077. [CrossRef]

13. Stortz, J.A.; Mira, J.C.; Raymond, S.L.; Loftus, T.J.; Ozragat-Baslanti, T.; Wang, Z.; Ghita, G.L.; Leeuwenburgh, C.; Segal, M.S.; Bihorac, A.; et al. Benchmarking clinical outcomes and the immunocatabolic phenotype of chronic critical illness after sepsis in surgical intensive care unit patients. J. Trauma Acute Care Surg. 2018, 84, 342–349. [CrossRef]

14. Guirgis, F.W.; Brakenridge, S.; Sutchu, S.; Khadpe, J.D.; Robinson, T.; Westenbarger, R.; Topp, S.T.; Kalynych, C.J.; Reynolds, J.; Dodani, S. The long-term burden of severe sepsis and septic shock: Sepsis recidivism and organ dysfunction. J. Trauma Acute Care Surg. 2016, 81, 525–532. [CrossRef]

15. Puthucheary, Z.A.; Rawal, J.; McPhail, M.; Connolly, B.; Ratnayake, G.; Chan, P.; Hopkinson, N.S.; Padhke, R.; Dew, T.; Sidhu, P.S.; et al. Acute skeletal muscle wasting in critical illness. J. Am. Med Assoc. 2013, 310, 1591–1600. [CrossRef]

16. Gentile, L.F.; Cuenca, A.G.; Efron, P.A.; Ang, D.; McKinley, B.A.; Moldawer, L.L.; Moore, F.A. Persistent inflammation and immunosuppression: A common syndrome and new horizon for surgical in-tensive care. J. Trauma Acute Care Surg. 2012, 72, 1491–1501. [CrossRef] [PubMed]

17. Hotchkiss, R.S.; Moldawer, L.L. Parallels between cancer and infectious disease. N. Engl. J. Med. 2014, 371, 380–383. [CrossRef] [PubMed]

18. Hesselink, L.; Hoepelman, R.J.; Spijkerman, R.; De Groot, M.C.H.; Van Wessem, K.J.P.; Koenderman, L.; Leenen, L.P.H.; Hietbrink, F. Persistent inflammation, immunosuppression and catabolism syndrome (PICS) after polytrauma: A rare syndrome with major consequences. J. Clin. Med. 2020, 9, 191. [CrossRef]

19. Horiguchi, H.; Loftus, T.J.; Hawkins, R.B.; Raymond, S.L.; Stortz, J.A.; Hollen, M.K.; Weiss, B.P.; Miller, E.S.; Bihorac, A.; Larson, S.D.; et al. Innate immunity in the persistent inflammation, immunosuppression, and catabolism syndrome and its implications for therapy. Front. Immunol. 2018, 9, 595. [CrossRef]

20. Rosenthal, M.D.; Kamel, A.Y.; Rosenthal, C.M.; Brakenridge, S.; Croft, C.A.; Moore, F.A. chronic critical illness: Application of what we know. Nutr. Clin. Pract. 2018, 33, 39–45. [CrossRef] [PubMed]

21. Rosenthal, M.D.; Moore, F.A. Persistent inflammatory, immunosuppressed, catabolic syndrome (PICS): A new phenotype of multiple organ failure. J. Adv. Nutr. Hum. Metab. 2015, 1, 10. [CrossRef]

22. Fenner, B.P.; Darden, D.B.; Kelly, L.S.; Rincon, J.; Brakenridge, S.C.; Larson, S.D.; Moore, F.A.; Efron, P.A.; Moldawer, L.L. Immunological endotyping of chronic critical illness after severe sepsis. Front. Med. 2021, 7, 616694. [CrossRef]

23. Hotchkiss, R.S.; Moldawer, L.L.; Opal, S.M.; Reinhart, K.; Turnbull, I.R.; Vincent, J.L. Sepsis and septic shock. Nat. Rev. Dis. Primers. 2016, 2, 16045. [CrossRef] [PubMed]

24. Delano, M.J.; Ward, P.A. Sepsis-induced immune dysfunction: Can immune therapies reduce mortality? J. Clin. Investig. 2016, 126, 23–31. [CrossRef] [PubMed]

25. Rivera, A.; Siracusa, M.C.; Yap, G.S.; Gause, W.C. Innate cell communication kick-starts pathogen-specific immunity. Nat. Immunol. 2016, 17, 356–363. [CrossRef] [PubMed]

26. Hawkins, R.B.; Stortz, J.A.; Holden, D.C.; Wang, Z.; Raymond, S.L.; Cox, M.C.; Efron, P.A.; Brakenridge, S.C.; Moore, F.A.; Moldawer, L.L. Persistently increased cell-free DNA concentrations only modestly contribute to outcome and host response in sepsis survivors with chronic critical illness. Surgery 2020, 167, 646–652. [CrossRef] [PubMed]

27. Kawai, T.; Akira, S. The role of pattern-recognition receptors in innate immunity: Update on Toll-like receptor 3. Nature 2001, 410, 398–402. [CrossRef]

28. Bruns, A.M.; Pollpeter, D.; Hadizadeh, N.; Myong, S.; Marko, J.F.; Horvath, C.M. ATP hydrolysis enhances RNA recognition and antiviral signal transduction by the innate immune sensor, laboratory of genetics and physiology 2 (LGP2). J. Biol. Chem. 2013, 288, 938–946. [CrossRef] [PubMed]

29. Sabbah, A.; Chang, T.H.; Harnack, R.; Frohlich, V.; Tominaga, K.; Dube, P.H.; Xiang, Y.; Bose, S. Activation of innate immune antiviral responses by Nod2. Nat. Immunol. 2009, 10, 1073–1080. [CrossRef] [PubMed]

30. Alexopoulou, L.; Holt, A.C.; Medzhitov, R.; Flavell, R.A. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature 2001, 413, 732–738. [CrossRef] [PubMed]

31. Kingeter, L.M.; Lin, X. C-type lectin receptor-induced NF-kappaB activation in innate immune and inflam-matory responses. Cell Mol. Immunol. 2012, 9, 105–112. [CrossRef]

32. Hayashi, F.; Smith, K.D.; Ozinsky, A.; Hawn, T.R.; Yi, E.C.; Goodlett, D.R.; Eng, J.K.; Akira, S.; Underhill, D.M.; Aderem, A. The innate immune response to bacterial flagellin is mediated by Toll-like receptor 5. Nat. Cell Biol. 2001, 410, 1099–1103. [CrossRef] [PubMed]

33. Byun, K.; Yoo, Y.; Son, M.; Lee, J.; Jeong, G.-B.; Park, Y.M.; Salekdeh, G.H.; Lee, B. Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases. Pharmacol. Ther. 2017, 177, 44–55. [CrossRef] [PubMed]

34. Skeldon, A.; Saleh, M. The inflammasomes: Molecular effectors of host resistance against bacterial, viral, parasitic, and fungal infections. Front. Microbiol. 2011, 2, 15. [CrossRef]

35. Janeway, C.A.; Medzhitov, R. Innate immune recognition. Annu. Rev. Immunol. 2002, 20, 197–216. [CrossRef] [PubMed]
37. Hemmi, H.; Takeuchi, O.; Kawai, T.; Kaisho, T.; Sato, S.; Sanjo, H.; Matsumoto, M.; Hoshino, K.; Wagner, H.; Takeda, K.; et al. A Toll-like receptor recognizes bacterial DNA. *Nat. Cell Biol.* 2000, 408, 740–745. [CrossRef]

38. Banchereau, J.; Steinman, R.M. Dendritic cells and the control of immunity. *Nature* 1998, 392, 245–252. [CrossRef]

39. Walton, A.H.; Muenzer, J.T.; Rasche, D.; Boomer, J.S.; Sato, B.; Brownstein, B.H.; Pachot, A.; Brooks, T.L.; Deych, E.; Shannon, W.D.; et al. Reactivation of multiple viruses in patients with sepsis. *PloS ONE* 2014, 9, e89819. [CrossRef]

40. Fleschner, M.; Crane, C.R. Exosomes, DAMPs and miRNA: Features of stress physiology and immune homeostasis. *Trends Immunol.* 2017, 38, 768–776. [CrossRef] [PubMed]

41. Kang, J.-W.; Kim, S.-J.; Cho, H.-I.; Lee, S.-M. DAMPs activating innate immune responses in sepsis. *Ageing Res. Rev.* 2015, 24, 54–65. [CrossRef] [PubMed]

42. Maslanik, T.; Mahaffey, L.; Kann, K.; Beninson, L.; Greenwood, B.N.; Fleschner, M. The inflammasome and danger associated molecular patterns (DAMPs) are implicated in cytokine and chemokine responses following stressor exposure. *Brain Behav. Immun.* 2013, 28, 54–62. [CrossRef] [PubMed]

43. Fleschner, M. Stress-evoked sterile inflammation, danger associated molecular patterns (DAMPs), microbial associated molecular patterns (MAMPs) and the inflammasome. *Brain Behav. Immun.* 2013, 27, 1–7. [CrossRef] [PubMed]

44. Hu, Q.; Ren, J.; Wu, J.; Li, G.; Wu, X.; Liu, S.; Li, J.; Gu, G.; Wang, G. Elevated levels of plasma mitochondrial DNA are associated with clinical outcome in in-tra-abdominal infections caused by severe trauma. *Surg. Infect. 2017, 18*, 610–618. [CrossRef]

45. Timmermans, K.; Kox, M.; Scheffer, G.J.; Pickkers, P. Plasma nuclear and mitochondrial DNA levels, and markers of inflammation, shock, and organ damage in patients with septic shock. *Shock 2016, 45*, 607–612. [CrossRef]

46. Ingels, C.; Derese, I.; Wouters, P.; et al. Van den Berge, G.; Vanhorebeek, I. Soluble RAGE and the RAGE ligands HMGB1 and S100A12 in critical illness: Impact of glycemic control with insulin and relation with clinical outcome. *Shock 2015, 43*, 109–116. [CrossRef] [PubMed]

47. Achouiti, A.; Föll, D.; Vogl, T.; van Till, J.W.; Dugernier, T.; Wittebole, X.; Boermeester, M.A.; Roth, J.; van der Poll, T.; et al. S100A12 and soluble receptor for advanced glycation end products levels during human severe sepsis. *Shock 2013, 40*, 188–194. [CrossRef] [PubMed]

48. Ohi, K.; Tenbrock, K. Reactive oxygen species as regulators of MDSC-mediated immune suppression. *Front. Immunol.* 2018, 9, 2499. [CrossRef]

49. Hue, O.; Dupic, L.; Harrois, A.; Duranteau, J. Oxidative stress and endothelial dysfunction during sepsis. *Front. Biosci.* 2011, 16, 1986–1995. [CrossRef] [PubMed]

50. Chan, E.L.; Murphy, J.T. Reactive oxygen species mediate endotoxin-induced human dermal endothelial NF-kappaB activation. *J. Surg. Res.* 2003, 111, 120–126. [CrossRef]

51. Singer, M. Metabolic failure. *Crit. Care Med.* 2005, 33, S539–S542. [CrossRef] [PubMed]

52. Veglia, F.; Perego, M.; Gabrilovich, D. Myeloid-derived suppressor cells coming of age. *Nat. Immunol.* 2018, 19, 108–119. [CrossRef]

53. Barter, J.; Kumar, A.; Stortz, J.A.; Hollen, M.; Nacionales, D.; Efron, P.A.; Moldawer, L.L.; Foster, T.C. Age and sex influence the molecular signature of CD8+ T cell exhaustion during chronic viral infection. *J. Immunol.* 2018, 200, 1543–1553. [CrossRef]

54. Drewry, A.M.; Ablordeppey, E.A.; Murray, E.T.; Beiter, E.R.; Walton, A.H.; Hall, M.W.; Hotchkiss, R.S. Comparison of monocyte molecular patterns (MAMPs) and the inflammasome. *Brain Behav. Immun.* 2013, 27, 1–7. [CrossRef] [PubMed]

55. Banchereau, J.; Steinman, R.M. Dendritic cells and the control of immunity. *Nature* 1998, 392, 245–252. [CrossRef]

56. Barter, J.; Kumar, A.; Stortz, J.A.; Hollen, M.; Nacionales, D.; Efron, P.A.; Moldawer, L.L.; Foster, T.C. Age and sex influence the molecular signature of CD8+ T cell exhaustion during chronic viral infection. *J. Immunol.* 2018, 200, 1543–1553. [CrossRef]

57. Drewry, A.M.; Ablordeppey, E.A.; Murray, E.T.; Beiter, E.R.; Walton, A.H.; Hall, M.W.; Hotchkiss, R.S. Comparison of monocyte molecular patterns (MAMPs) and the inflammasome. *Brain Behav. Immun.* 2013, 27, 1–7. [CrossRef] [PubMed]

58. Banchereau, J.; Steinman, R.M. Dendritic cells and the control of immunity. *Nature* 1998, 392, 245–252. [CrossRef]

59. Barter, J.; Kumar, A.; Stortz, J.A.; Hollen, M.; Nacionales, D.; Efron, P.A.; Moldawer, L.L.; Foster, T.C. Age and sex influence the molecular signature of CD8+ T cell exhaustion during chronic viral infection. *J. Immunol.* 2018, 200, 1543–1553. [CrossRef]

60. Ayala, A.; Chaudry, I.H. Immune dysfunction in murine polymicrobial sepsis: Mediators, macrophages, lymphocytes and apoptosis. *Shock 1996, 6*, 27–38. [CrossRef]

61. Jensen, I.J.; Sjaastad, F.V.; Griffith, T.S.; Badovinac, V.P. Sepsis-induced T cell immunoparalysis: The ins and outs of impaired T cell immunity. *J. Immunol.* 2018, 200, 1543–1553. [CrossRef]

62. Hotchkiss, R.S.; Monneret, G.; Payen, D. Sepsis-induced immunosuppression: From cellular dysfunctions to immunotherapy. *Nat. Rev. Immunol.* 2013, 13, 862–874. [CrossRef]

63. Wherry, E.J.; Ha, S.-J.; Kaech, S.M.; Haining, W.N.; Sarkar, S.; Kalia, V.; Subramaniam, S.; Blattman, J.N.; Barber, D.L.; Ahmed, R. Molecular signature of CD8+ T cell exhaustion during chronic viral infection. *Immunology 2007, 27*, 670–684. [CrossRef]

64. Loss, S.H.; Nunes, D.S.L.; Franzosi, O.S.; Salazar, G.S.; Teixeira, C.; Vieira, S.R.R. Chronic critical illness: Are we saving patients or creating victims? *Rev. Bras. Ter. Intensiva* 2017, 29, 87–95. [CrossRef]
88. Darcy, C.J.; Minigo, G.; A Piera, K.; Davis, J.S.; McNeil, Y.R.; Chen, Y.; Volkheimer, A.D.; Weinberg, J.B.; Anstey, N.M.; Woodberry, T. Neutrophils with myeloid derived suppressor function deplete arginine and constrain T cell function in septic shock patients. *Crit. Care* 2014, 18, R163. [CrossRef]

89. Meisel, C.; Scheid, J.C.; Pschowski, R.; Baumann, T.; Hatz, T.; Weber-Carstens, S.; Keh, D.; Zuckermann, H.; et al. Granulocyte-macrophage colony-stimulating factor to reverse sepsis-associated immuno-suppression: A double-blind, randomized, placebo-controlled multicenter trial. *Am. J. Respir. Crit. Care Med.* 2009, 180, 640–648. [CrossRef]

90. Root, R.K.; Lodato, R.F.; Patrick, W.; Cade, J.F.; Fotheringham, N.; Kilbee, S.; Vincent, J.L.; Torres, A.; Rello, J.; Nelson, S.; et al. Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hos-pitalized with pneumonia and severe sepsis. *Crit. Care Med.* 2003, 31, 367–377. [CrossRef]

91. Nelson, S.; Belknap, S.M.; Carlson, R.W.; Dale, D.; DeBoisblanc, B.; Farkas, S.; Fotheringham, N.; Ho, H.; Marrie, T.; Movahhed, H.; et al. A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hos-pitalized patients with community-acquired pneumonia. CAP Study Group. *J. Infect. Dis.* 1998, 178, 1075–1080. [CrossRef] [PubMed]

92. Bo, L.; Wang, F.; Zhu, J.; Li, J.; Deng, X. Granulocyte-colony stimulating factor (G-CSF) and granulo-cyte-macrophage colony stimulating factor (GM-CSF) for sepsis: A meta-analysis. *Crit. Care* 2011, 15, R58. [CrossRef]

93. Shankar-Hari, M.; Ambler, M.; Mahalingasivam, V.; Jones, A.; Rowan, K.; Rubenfeld, G.D. Evidence for a causal link between sepsis and long-term mortality: A systematic re-review of epidemiologic studies. *Crit. Care* 2016, 20, 101. [CrossRef] [PubMed]

94. Winters, B.D.; Eberlein, M.; Leung, J.; Needham, D.M.; Pronovost, P.J.; Sevransky, J.E. Long-term mortality and quality of life in sepsis: A systematic review. *Crit. Care Med.* 2010, 38, 1276–1283. [CrossRef] [PubMed]

95. Conlon, K.C.; Lugli, E.; Welles, H.C.; Rosenberg, S.A.; Fojo, A.T.; Fleisher, T.A.; McDunn, J.E.; et al. IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sepsis. *Crit. Care Med.* 2010, 184, 3768–3779. [CrossRef] [PubMed]

96. Sportes, C.; Hakim, T.; Memon, S.A.; Zhang, H.; Chua, K.S.; Brown, M.R.; Fleisher, T.A.; Kraumlauf, M.C.; Babb, R.R.; Chow, C.K.; et al. Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferen-tial expansion of naive T cell subsets. *J. Exp. Med.* 2008, 205, 1701–1714. [CrossRef] [PubMed]

97. Venet, F.; Foray, A.-P.; Villars-Méchin, A.; Malcus, C.; Poitevin-Later, F.; Lepape, A.; Monneret, G.; Sawant, D.V.; Sehra, S.; Nguyen, E.T.; et al. IL-7 restores lymphocyte functions in septic patients. *J. Immunol.* 2012, 189, 5073–5081. [CrossRef]

98. Mackall, C.L.; Fry, T.J.; Gress, R.E. Harnessing the biology of IL-7 for therapeutic application. *Nat. Rev. Immunol.* 2011, 11, 330–342. [CrossRef]

99. Unsinger, J.; McGlynn, M.; Kasten, K.R.; Hoekzema, A.S.; Watanabe, E.; Muenzer, J.T.; McDonough, J.S.; Tschoep, J.; Ferguson, T.A.; McDunn, J.E.; et al. IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sep-sis. *J. Immunol.* 2010, 184, 791–796. [CrossRef]

100. Unsinger, J.; Burnham, C.-A.D.; McDonough, J.; Morre, M.; Prakash, P.S.; Caldwell, C.C.; Dunne, W.M.; Hotchkiss, R.S. Interleukin-7 ameliorates immune dysfunction and improves survival in a 2-hit model of fungal sepsis. *J. Infect. Dis.* 2012, 206, 606–616. [CrossRef]

101. Venet, F.; Filipé-Santos, O.; Lepape, A.; Malcus, C.; Poitevin-Later, F.; Grives, A.; Plantier, N.; Pasqual, N.; Monneret, G. Decreased T-cell repertoire diversity in sepsis: A preliminary study. *Crit. Care Med.* 2013, 41, 111–119. [CrossRef]

102. Francois, B.; Jeannet, R.; Daix, T.; Walton, A.H.; Shotwell, M.S.; Unsinger, J.; Monneret, G.; Rimmelé, T.; Blood, T.; Morre, M.; et al. Interleukin-7 restores lymphocytes in septic shock: The IRIS-7 randomized clinical trial. *JCI Insight* 2018, 3. [CrossRef]

103. Demaret, J.; Dupont, G.; Venet, F.; Friggeri, A.; Lepape, A.; Rimmele, T.; Morel, J.; Monneret, G. STAT5 phosphorylation in T cell subsets from septic patients in response to recombinant human interleukin-7: A pilot study. *J. Leukoc. Biol.* 2015, 97, 791–796. [CrossRef]

104. Levy, Y.; Sereti, I.; Tambussi, G.; Routy, J.P.; Lelièvre, J.D.; Delfraissy, J.F.; Molina, J.M.; A Fischl, M.; Goujard, C.; Rodriguez, B.G.; et al. Effects of recombinant human interleukin 7 on t-cell recovery and thymic output in hiv-infected patients receiving antiretroviral therapy: Results of a phase i/ia randomized, placebo-controlled, multicenter study. *Clin. Infect. Dis.* 2012, 55, 291–300. [CrossRef]

105. Rosenberg, S.A.; Sportes, C.; Ahmadzadeh, M.; Fry, T.J.; Ngo, L.T.; Schwarz, S.L.; Stetler-Stevenson, M.; Morton, K.E.; Mavroukakis, S.A.; Morre, M.; et al. IL-7 administration to humans leads to expansion of CD8+ and CD4+ cells but a rela-tive decrease of CD4+ T-regulatory cells. *J. Immunother.* 2006, 29, 313–319. [CrossRef]

106. Scumpia, P.O.; Delano, M.J.; Kelly, K.M.; O’Malley, K.A.; Efron, P.A.; McAuliffe, P.F.; Brusko, T.; Ungaro, R.; Barker, T.; Wynn, J.L.; et al. Increased natural CD4+CD25+ regulatory T cells and their suppressor activity do not contribute to mortality in murine polymicrobial sepsis. *J. Immunol.* 2006, 177, 7943–7949. [CrossRef] [PubMed]

107. Borden, E.C.; Sen, G.C.; Uze, G.; Silverman, R.H.; Ransohoff, R.M.; Foster, G.R.; Stark, G.R. Interferons at age 50: Past, current and future impact on biomedicine. *Nat. Rev. Drug Discov.* 2007, 6, 975–990. [CrossRef] [PubMed]

108. Boomer, J.; Shuherk-Shaffer, J.; Hotchkiss, R.S.; Green, J.M. A prospective analysis of lymphocyte pheno-type and function over the course of acute sepsis. *Crit. Care* 2012, 16, R112. [CrossRef] [PubMed]

109. Boomer, J.; To, K.; Chang, K.C.; Takasu, O.; Osborne, D.F.; Walton, A.H.; Bricker, T.L.; Jarman, S.D.; Kreisel, D.; Krupnick, A.S.; et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *J. Am. Med. Assoc.* 2011, 306, 2594–2605. [CrossRef] [PubMed]
110. Chang, K.C.; Burnham, C.-A.; Compton, S.M.; Rasche, D.P.; Mazuski, R.; SMcDonough, J.; Unsinger, J.; Korman, A.J.; Green, J.M.; Hotchkiss, R.S. Blockade of the effector co-stimulatory molecules PD-1 and CTLA-4 improves survival in primary and secondary fungal sepsis. Crit. Care Med. 2013, 17, R85. [CrossRef] [PubMed]

111. Patil, N.K.; Bohannon, J.K.; Sherwood, E.R. Immunotherapy: A promising approach to reverse sepsis-induced immunosuppression. J. Clin. Med. 2021, 10, 1742. [CrossRef] [PubMed]

112. Döcke, W.D.; Randow, F.; Syrbe, U.; Krausch, D.; Asadullah, K.; Reinke, P.; Volk, H.D.; Kox, W. Monocyte deactivation in septic patients: Restoration by IFN-gamma treatment. Nat. Med. 1997, 3, 678–681. [CrossRef] [PubMed]

113. Döcke, W.D.; Randow, F.; Syrbe, U.; Krausch, D.; Asadullah, K.; Reinke, P.; Volk, H.D.; Kox, W. Monocyte deactivation in septic patients: Restoration by IFN-gamma treatment. Nat. Med. 1997, 3, 678–681. [CrossRef] [PubMed]

114. Dries, D.J.; Jurkovich, G.J.; Maier, R.V.; Clemmer, T.P.; Struve, S.N.; Lee, J.; Wang, J.; Champion, H.R.; et al. Interferon gamma-1b in the treatment of compensatory anti-inflammatory response syndrome. A new approach: Proof of principle. Arch. Intern. Med. 1997, 157, 389–393. [CrossRef] [PubMed]

115. Dries, D.J.; Jurkovich, G.J.; Maier, R.V.; Clemmer, T.P.; Struve, S.N.; Weigel, J.A.; Stanford, G.G.; Herr, D.L.; Champion, H.R.; Lewis, F.R.; et al. Effect of interferon gamma on infection-related death in patients with severe injuries. Arch. Surg. 1994, 129, 1031–1041. [CrossRef] [PubMed]

116. Guignant, C.; Lepape, A.; Huang, X.; Kherouf, H.; Denis, L.; Poitevin, F.; Malcus, C.; Cheron, A.; Allaouchiche, B.; Gueyffier, F.; et al. Programmed death-1 levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients. Crit. Care Med. 2013, 41, 1175–1185. [CrossRef] [PubMed]

117. Day, C.L.; Kaufmann, D.E.; Kiepiela, P.; Brown, J.A.; Moodley, E.S.; Reddy, S.; Mackey, E.W.; Miller, J.D.; Leslie, A.J.; dePierres, A.; et al. Interferon gamma-1b in the treatment of compensatory anti-inflammatory response syndrome. A new approach: Proof of principle. Arch. Intern. Med. 1997, 157, 389–393. [CrossRef] [PubMed]

118. Chen, L.; Han, X. Anti–PD-1/PD-L1 therapy of human cancer: Past, present, and future. J. Exp. Med. 2016, 111, 688–702. [CrossRef] [PubMed]

119. Lewis, F.R.; et al. Effect of interferon gamma on infection-related death in patients with severe injuries. Arch. Surg. 1994, 129, 1031–1041. [CrossRef] [PubMed]

120. Zhang, Y.; Zhou, Y.; Lou, J.; Zhou, Y.; Zhu, K.; Wang, X.; Cai, Z.; Deng, X.; Cai, Z.; Deng, X.; et al. Upregulation of programmed death-1 on T cells and programmed death ligand-1 on mono-cytes in septic shock patients. Crit. Care Med. 2011, 15, R99. [CrossRef] [PubMed]

121. Iwai, Y.; Terawaki, S.; Ikegawa, M.; Okazaki, T.; Honjo, T. PD-1 inhibits antiviral immunity at the effector phase in the liver. J. Exp. Med. 2003, 198, 39–50. [CrossRef] [PubMed]

122. Barber, D.L.; Wherry, E.J.; Masopust, D.; Zhu, B.; Allison, J.P.; Sharpe, A.H.; Freeman, G.J.; Ahmed, R. Restoring function in exhausted CD8 T cells reverses immune dysfunction and improves survival during sepsis. J. Leukoc. Biol. 2010, 88, 233–240. [CrossRef] [PubMed]

123. Poe, S.L.; Arora, M.; Oriss, T.B.; Varlagadda, M.; Isse, K.; Khare, A.; Levy, D.E.; Lee, J.S.; Mallampalli, R.K.; Chan, Y.R.; et al. STAT1-regulated lung MDSC-like cells produce IL-10 and effecoryocytes apoptotic neutrophils with relevance in resolution of bacterial pneumonia. Mucosal Immunol. 2013, 6, 189–199. [CrossRef] [PubMed]

124. Schrijver, I.T.; Théroude, C.; Roger, T. Myeloid-derived suppressor cells in sepsis. Front. Immunol. 2019, 10, 327. [CrossRef] [PubMed]

125. Law, A.M.; Valdes-Mora, F.; Gallego-Ortega, D. Derived suppressor cells as a therapeutic tar-get for cancer. Cells 2020, 9, 561. [CrossRef] [PubMed]

126. Noel, G.; Wang, Q.; Osterburg, A.; Schwemberger, S.; James, L.; Haar, L.; Giacalone, N.; Thomas, I.; Ogle, C. A Ribonucleotide reductase inhibitor reverses inflammatory defects. Shock 2010, 34, 535–544. [CrossRef] [PubMed]

127. Sander, L.E.; Sackett, S.D.; Dierssen, U.; Beraza, N.; Linke, R.P.; Müller, M.; Blander, J.M.; Tacke, F.; Trautwein, C. Hepatic acute-phase proteins control innate immune responses during infection by pro-moting myeloid-derived suppressor cell function. J. Exp. Med. 2012, 207, 1453–1464. [CrossRef] [PubMed]