Med Klin Intensivmed Notfmed 2020 · 115
(Suppl 1):S10–S14
<https://doi.org/10.1007/s00063-020-00683-2>
Received: 1 January 2020
Accepted: 14 January 2020
Published online: 14 April 2020
© Springer Medizin Verlag GmbH, ein Teil von
Springer Nature 2020

Redaktion

M. Bauer, Jena
M. Singer, London

Y. G. Ghnewa^{1,2} · M. Fish^{1,2} · A. Jennings^{1,2} · M. J. Carter^{1,2} · M. Shankar-Hari^{1,2}

¹ Guy's and St Thomas' NHS Foundation Trust, ICU Support Offices, St Thomas' Hospital, Floor 5, London, UK

² School of Immunology and Microbial Sciences, Kings College London, London, UK

Goodbye SIRS? Innate, trained and adaptive immunity and pathogenesis of organ dysfunction

The Sepsis-3 definitions introduced in 2016, proposed several conceptual changes that questioned the status quo proposed by the earlier (1992 and 2001) sepsis definitions. There were several novel concepts introduced by the Sepsis-3 definitions. First, the excessive focus on inflammation was replaced with a dysregulated host response that includes immune as well as nonimmune responses. Second, the term 'severe' in severe sepsis was considered redundant. Third, the systemic inflammatory response syndrome (SIRS) criteria were compared to other severity scores and a parsimonious quick Sepsis-related Organ Failure Assessment (qSOFA) score was proposed [18]. Fourth, the former sepsis illness model where infection follows a continuum through to sepsis to severe sepsis and finally to septic shock was felt inadequate to explain the pathobiology. Fifth, septic shock was explicitly placed as a subset of sepsis. Finally, for the first time, data-driven clinical criteria that had predictive validity were proposed. Thus, sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [23] and septic shock is defined as a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities resulting in a greater risk of death compared to sepsis alone [21].

In this brief narrative review, after discussing the reasons for saying goodbye to SIRS, we provide a brief overview of the immune system and the acute immune

changes in sepsis, using data primarily from human studies.

Goodbye SIRS

There are several conceptual issues, aside from the well-recognised lack of sensitivity and specificity with SIRS criteria [7, 24]. First, the components of the SIRS criteria and their cut-offs were arbitrary. Second, the SIRS criteria were not derived to function as clinical decision rules but were used as such. Third, two elements of the SIRS criteria that require laboratory tests namely leukocyte count, including the proportion of band forms and partial pressure of carbon dioxide (PaCO₂), inevitably adds delay to sepsis diagnosis. Fourth, the prevalence of SIRS criteria in hospitalised patients is high, making it impractical as a screening tool either for infection or for sepsis or for starting antibiotic therapy. Fifth, improvements in SIRS or absence of SIRS criteria does not necessarily equate to the improvement of sepsis illness, as critically ill patients with sepsis could be SIRS criteria negative [11, 20]. Sixth, the prognostic value of SIRS criteria is often due to collinearity with confounders in the causal path between sepsis and outcome.

Innate and adaptive immune systems—the basics

The human immune system is a complex interlinked system of cells, receptors, secreted proteins, enzymes, structural and chemical defence elements that pro-

tect the human body from infections. This protection against infections involves four interlinked tasks: danger signal surveillance and recognition from non-self, effector response to removing danger signals, restoration of immune homeostasis after clearing danger signals, and generation of immunological memory in certain situations [5]. In autoimmune diseases, a person's own antigens (self) become danger signals.

Functionally distinct innate and adaptive immune systems work in synergy to perform these tasks. The innate immune system, the first line of defence against infections (surveillance and recognition of non-self), consists of cells of both myeloid and lymphoid lineages (such as granulocytes, monocytes/macrophages, dendritic cells, natural killer cells, and other innate lymphoid cells). The intracellular and cell surface receptors that recognise danger signals are referred to as *pattern recognition* receptors (PRRs). The epithelial and mucosal-associated barriers form the structural and chemical defence mechanisms. On breaching the epithelial surface barriers, the pathogen encounters the complement system proteins, which can be activated by antibody-coated pathogens (classical pathway) or by pathogen alone (alternative pathway), or by carbohydrate-binding protein (mannose-binding lectin or ficolins) coated pathogens (lectin pathway). The extracellular bacteria are either phagocytosed by cells or undergo complement-mediated lysis and the intracellular bacteria undergo au-

tophagy and killing via lysosomal fusion. Innate immune responses to infection could be broadly categorised into the *immediate response* (0 to 4 h), where the infection is recognised by preformed non-specific and broadly specific effectors such as the complement system. The *early-induced immune response* (beyond 4 h) follows, where there is recruitment and activation of effector cells that rely on evolutionarily conserved PRRs of danger signals for infection clearance.

The adaptive immune system consists of two major cell types B and T lymphocytes. Adaptive immunity generates specific immune responses against the inciting pathogen. The innate immune cells provide the support needed for an effective adaptive immune system response. The innate cell's ability to process and present antigens (*antigen-presenting cells* [APCs] such as dendritic cells) and the innate cells' ability to produce chemical mediators (such as cytokines, chemokines) allow them to communicate danger to adaptive cells both near and far. The adaptive immune responses that occur in the secondary lymphoid organs (which include the spleen, lymph nodes, and mucosal-associated lymphoid tissues [MALT]) generate pathogen-specific immunity by intricate recombinations of cell surface receptors (B cell receptors [BCR] and T cell receptors [TCR]). These cells also form immunological memory which provides the ability to rapidly respond to antigens on second and subsequent challenges [10].

Alterations to the innate immune system in sepsis

When pathogen-associated molecular patterns (PAMPs) are sensed via the germline-encoded PRRs, the host innate immune responses seen in sepsis are initiated. Heterogeneous protein complexes are assembled in the cytosol after sensing danger signals are referred to as the signalosome and the inflammasome complexes.

The innate immune cellular level changes in sepsis are profound [9]. Neutrophils are activated, with a longer half-life, reduced oxidative burst ca-

capacity, with more immature forms in circulation alongside a release of neutrophil extracellular traps consisting of nuclear material that causes endothelial dysfunction and altered coagulation. Monocytes are activated, with reduced HLA-DR expression, reduced antigen-presenting capacity and shift towards an inhibitory phenotype. There is also an increase in the heterogeneous population of myeloid-derived suppressor cells (MDSC), which may contribute to accelerated T cell loss in sepsis. There is a reduction in the frequency of follicular dendritic cells resulting in decreased B cell antigen presentation frequency in secondary lymphoid organs. Furthermore, there is a reduction in dendritic cells and natural killer (NK) cells, alongside a reduction in their functional ability such as to present antigens to T cells by dendritic cells and to NK-cell-mediated cytotoxicity.

The transcriptional programs within innate immune cells that are also acutely altered. Key examples include interferon signalling, nuclear factor-kappa b signalling, Toll-like receptor signalling, protein catabolism and translation signalling such as protein ubiquitination pathways [17]. Production of cytokines and chemokines by phagocytes helps induce and maintain inflammation, dendritic cells migration towards secondary lymphoid organs, T lymphocyte polarisation, stimulates the production of acute-phase proteins from the liver, activates lymphocytes and increases tissue access of effector cells by vasodilation and adhesion molecule expression [3, 4, 29]. In sepsis, the host immune responses result in elevated levels of proinflammatory cytokines (such as interleukin-6 [IL-6]), anti-inflammatory cytokines (such IL-10) and cell damage proteins (such as heat shock proteins) in the peripheral circulation. The organ-level immune responses may mirror the circulating inflammatory mediator profile, at least initially.

Alterations to the adaptive immune system in sepsis

Phagocytes secrete level-1 cytokines and chemokines (such as IL-1, IL-6, tumor

necrosis factor [TNF]) that activate lymphocytes, initiating the adaptive immune responses. Activated T cells secrete further cytokines referred to as level-2 cytokines (such as interferon-gamma, IL-21, IL-17). This generates more specific effector mechanisms such as antibodies against inciting pathogens by B cells and further activation of innate phagocytes for the targeted killing of opsonised (complement and antibody-coated) pathogens [10].

Immune responses in sepsis assessed using pan-leukocyte transcriptome (with microarray as the analytic platform) [6, 17, 27] show that despite the pan-leukocyte transcriptome being dominated by innate immune signatures, there are profound changes to the lymphocyte compartment. In sepsis, at the transcriptome level, both BCR and TCR signalling are acutely impaired, alongside the upregulation of mitochondrial and death receptor apoptosis pathways. Within T cells, there are alterations in CD28 signalling, OX40 signalling, IL-4 signalling and inducible costimulatory and its ligand (ICOS-ICOSL) signalling explaining the major functional defects observed in T helper cells. There are more differentially expressed genes in CD4+ T cells than CD8+ T cells in sepsis [31].

The adaptive immune cellular level changes are also profound [9]. Nearly two-thirds of sepsis patients have absolute lymphopenia on the day of admission, at least partially due to accelerated apoptosis. Importantly, non-apoptotic lymphocytes are functionally impaired. TCR repertoire diversity is decreased. There is a decrease in CD28 expression, increase in inhibitory checkpoint molecule expression on T cells, decreased proliferation capacity and a decrease in cytokine production in response to ex vivo stimulation. There is T-helper 2 polarisation explained by the acute alterations in micro RNA-31 in helper T cells [30]. Although T cell exhaustion is consistently reported in sepsis, the molecular mechanisms are incompletely understood. The regulatory T cells (Treg), an important T CD4+ T cell subset with immunosuppressive properties, are relatively preserved in sepsis. Total

B cell counts are decreased with exaggerated loss of memory B cell subsets despite normal B cell-specific survival factor levels [19], with evidence of B cell exhaustion and increased proportions of regulatory B cells [8]. Preliminary results from an animal model highlight that the antibody-independent effect of B cells on the immune system such as granulocyte-monocyte colony-stimulating factor secretion [16] and cytokine secretion [12] may be relevant in sepsis biology, which require further investigation.

Trained immunity—the basics

The activation of the innate immune cells (such as monocytes, macrophages, natural killer [NK] cells) by infections or vaccinations leads to functional reprogramming of these cells, referred to as trained immunity. The underpinning mechanisms are the epigenetic changes, specifically histone modifications, which alter the transcriptional programs and induce a metabolic shift towards aerobic glycolysis in the innate immune cells [15]. The beneficial features of trained immunity include enhanced responsiveness and the ability to respond to secondary infections. The adverse consequences include excessive inflammation and immunosuppression persisting beyond the acute illness, which may contribute towards the adverse outcomes seen acutely in sepsis and over a longer-term in sepsis survivors. There is limited human data on trained immunity in sepsis.

Relationship between immune system alterations and organ dysfunction in sepsis

An important consequence of these immune responses, in particular, the exaggerated concentrations of cytokines include tissue damage and necrotic cell death [2]. Although the mechanisms of organ dysfunction in sepsis are poorly understood, it is thought that the severity of early sepsis illness and organ dysfunction is related to these immune responses. Several observations suggest that reversible functional impairment is the most likely mechanism of organ dys-

Med Klin Intensivmed Notfmed 2020 · 115 (Suppl 1):S10–S14
<https://doi.org/10.1007/s00063-020-00683-2>
 © Springer Medizin Verlag GmbH, ein Teil von Springer Nature 2020

Y. G. Ghnewa · M. Fish · A. Jennings · M. J. Carter · M. Shankar-Hari

Goodbye SIRS? Innate, trained and adaptive immunity and pathogenesis of organ dysfunction

Abstract

The novel concepts within Sepsis-3 criteria include a focus on dysregulated host responses, removal of the systemic inflammation response syndrome (SIRS) criteria from sepsis diagnosis, the use of Sepsis-related (Sequential) Organ Failure Assessment (SOFA) scores to define organ dysfunction, and the explicit recognition of the septic shock as a subset of sepsis. Protection against infection requires a surveillance system, an effector response against “perceived” pathogens, a method for regaining immune homeostasis following an immune response, and generation of immunological memory. In comparison to normally regulated responses to infection, the innate immune system shows profoundly abnormal neutrophil and macrophage function. Similarly, the adaptive immune system is typically depleted numerically of lymphocytes and functionally

with T and B cell exhaustion. Although there are numerous proposed mechanisms by which these dysregulated immune responses may be associated with organ failure, it is unclear what the unifying organ failure mechanisms in sepsis are. Furthermore, in sepsis survivors, the epigenetic changes on immune cells and widespread changes to lymphocyte populations may increase the risk of adverse events such as rehospitalisation and mortality. Finally, our current gaps in understanding of the immune response trajectory and the associated modifiable mechanisms in sepsis leave us a long way from successful immunomodulation for these patients. This article is freely available.

Keywords

Sepsis · Exhaustion · Apoptosis · Inflammation · Suppression

Auf Wiedersehen SIRS? Angeborene, trainierte und adaptive Immunität und Pathogenese von Organfunktionsstörungen

Zusammenfassung

Zu den innovativen Konzepten innerhalb der Sepsis-3-Kriterien gehören eine Fokussierung auf dysregulierte Wirtsreaktionen, die Streichung des SIRS (Systemic Inflammation Response Syndrome)-Kriteriums aus der Sepsisdiagnose, die Verwendung von SOFA (Sequential Organ Failure Assessment)-Scores zur Definition von Organdysfunktionen und die explizite Anerkennung des septischen Schocks als ein Subset der Sepsis. Schutz vor Infektionen erfordert ein Überwachungssystem, eine Effektorreaktion gegen „wahrgenommene“ Pathogene, eine Methode zur Wiedererlangung der Immunhomöostase nach einer Immunantwort und die Entstehung eines immunologischen Gedächtnisses. Im Vergleich zu den normal regulierten Reaktionen auf eine Infektion zeigt das angeborene Immunsystem hochgradig von der Norm abweichende Neutrophilen- und Makrophagenfunktionen. In ähnlicher Weise wird in der Regel das adaptive Immunsystem erschöpft: numerisch an Lymphozyten und funktionell durch T-/B-Zell-Überlastung. Zwar wurden Hypothesen generiert zu

zahlreichen Mechanismen, durch welche diese dysregulierten Immunantworten mit einem Organversagen in Verbindung gebracht werden können. Nicht klar ist jedoch, worin die vereinheitlichenden Mechanismen des Organversagens bei einer Sepsis bestehen. Bei Sepsis-Überlebenden können darüber hinaus epigenetische Veränderungen an Immunzellen und weitgehend veränderte Lymphozytenpopulationen das Risiko unerwünschter Ereignisse, wie Rehospitalisierung und Mortalität, erhöhen. Und schließlich sind wir aufgrund unserer noch bestehenden Defizite im Verständnis des Verlaufs der Immunantwort und der damit verbundenen modifizierbaren Mechanismen bei der Sepsis noch weit von einer erfolgreichen Immunmodulation für diese Patienten entfernt. Dieser Artikel ist frei verfügbar.

Schlüsselwörter

Sepsis · Erschöpfung · Apoptose · Entzündung · Unterdrückung

function in sepsis. First, post-mortem studies on patients dying of protracted sepsis, the myocardium show minimal macroscopic damage. The major myocardial abnormalities in sepsis are focal necrosis, redistribution of connexin-43 to the lateral membrane and hydropic mitochondria, with the myocardial transcriptome showing decreased expression of genes involved in bioenergetics and contractility [14, 28]. Similarly, kidneys show focal tubular injury [28], liver dysfunction is characterised by non-specific hepatitis alongside cholestasis [26], and brain injury is characterised by blood–brain barrier dysfunction and altered neurotransmission [25]. The association between the immune system alterations (such as cytokine storm, apoptosis, focal necrosis) and organ dysfunction in sepsis could also be mediated through cellular stress [1, 22]. For example, endoplasmic reticulum stress and the unfolded protein responses to restore homeostasis are acutely altered in sepsis, which may be another explanation as to how cellular stress leads to organ dysfunction in sepsis [13].

Conclusion

The immune responses in sepsis involve simultaneous activation and suppression of both innate and adaptive immune systems. The immune responses directly and indirectly, via cellular stress and altered bioenergetics, influence the severity of organ dysfunction seen in sepsis. Thus, immune responses are still intricately linked to clinical outcomes in patients. Either our understanding of immune responses is fundamentally flawed in some way or we are still a long way away from knowing when to treat and which immunomodulatory agent to use in critically ill patients with sepsis.

Corresponding address

M. Shankar-Hari, MSc PhD FRCA FFICM
Guy's and St Thomas' NHS Foundation Trust,
ICU Support Offices, St Thomas' Hospital,
Floor 5
Southwark Wing, SE1 9RT, London, UK
manu.shankar-hari@kcl.ac.uk

Author Contribution. All authors developed the outline. Y.G. Ghnewa and M. Shankar-Hari wrote the first draft. All authors contributed to the critical revision of the manuscript for important intellectual content.

Compliance with ethical guidelines

Conflict of interest. Y.G. Ghnewa and A. Jennings declare that they have no competing interests. M. Shankar-Hari is supported by the National Institute for Health Research Clinician Scientist Award (CS-2016-16-011). M. Shankar-Hari is on the Editorial Board for *Intensive Care Medicine* and declares no competing interests. M.J. Carter is supported by the National Institute for Health Research Academic Clinical Lectureship. M. Fish is supported by the National Institute of Academic Anaesthesia BJA-RCOA PhD Fellowship. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

The supplement containing this article is not sponsored by industry.

References

1. Abraham E, Singer M (2007) Mechanisms of sepsis-induced organ dysfunction. *Crit Care Med* 35(10):2408–2416
2. Angus DC, van der Poll T (2013) Severe sepsis and septic shock. *N Engl J Med* 369(9):840–851
3. Arango Duque G, Descoteaux A (2014) Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol* 5:491
4. Chijioke O, Munz C (2013) Dendritic cell derived cytokines in human natural killer cell differentiation and activation. *Front Immunol* 4:365
5. Conway-Morris A, Wilson J, Shankar-Hari M (2018) Immune Activation in Sepsis. *Crit Care Clin* 34(1):29–42
6. Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC et al (2016) Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* 4(4):259–271
7. Fernando SM, Tran A, Taljaard M, Cheng W, Rochwerg B, Seely AJE et al (2018) Prognostic Accuracy of the Quick Sequential Organ Failure Assessment for Mortality in Patients With Suspected Infection: A Systematic Review and Meta-analysis. *Ann Intern Med* 168(4):266–275
8. Gustave CA, Gossez M, Demaret J, Rimmele T, Lepape A, Malcus C et al (2018) Septic Shock Shapes B Cell Response toward an Exhausted-like/Immunoregulatory Profile in Patients. *J Immunol* 200(7):2418–2425
9. Hotchkiss RS, Monneret G, Payen D (2013) Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol* 13(12):862–874
10. Iwasaki A, Medzhitov R (2015) Control of adaptive immunity by the innate immune system. *Nat Immunol* 16(4):343–353
11. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R (2015) Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 372(17):1629–1638
12. Kelly-Scumpia KM, Scumpia PO, Weinstein JS, Delano MJ, Cuenca AG, Nacionales DC et al (2011) B cells enhance early innate immune responses during bacterial sepsis. *J Exp Med* 208(8):1673–1682
13. Khan MM, Yang WL, Wang P (2015) Endoplasmic Reticulum Stress in Sepsis. *Shock* 44(4):294–304
14. Matkovich SJ, Al Khiami B, Efimov IR, Evans S, Vader J, Jain A et al (2017) Widespread Down-Regulation of Cardiac Mitochondrial and Sarcomeric Genes in Patients With Sepsis. *Crit Care Med* 45(3):407–414
15. Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG et al (2016) Trained immunity: a program of innate immune memory in health and disease. *Science* 352(6284):aaf1098
16. Rauch PJ, Chudnovskiy A, Robbins CS, Weber GF, Etzrodt M, Hilgendorf I et al (2012) Innate response activator B cells protect against microbial sepsis. *Science* 335(6068):597–601 (Feb)
17. Scicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL et al (2017) Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respir Med* 5(10):816–826
18. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A et al (2016) Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315(8):762–774
19. Shankar-Hari M, Fear D, Lavender P, Mare T, Beale R, Swanson C et al (2017) Activation-Associated Accelerated Apoptosis of Memory B Cells in Critically Ill Patients With Sepsis. *Crit Care Med* 45(5):875–882
20. Shankar-Hari M, Harrison DA, Rowan KM (2016) Differences in Impact of Definitional Elements on Mortality Precludes International Comparisons of Sepsis Epidemiology—A Cohort Study Illustrating the Need for Standardized Reporting. *Crit Care Med* 44(12):2223–2230
21. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS et al (2016) Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 315(8):775–787
22. Singer M, De Santis V, Vitale D, Jeffcoate W (2004) Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 364(9433):545–548
23. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M et al (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315(8):801–810
24. Singer M, Shankar-Hari M (2018) qSOFA, Cue Confusion. *Ann Intern Med* 168(4):293–295
25. Sonnevile R, Verdonk F, Rauturier C, Klein IF, Wolff M, Annane D et al (2013) Understanding brain dysfunction in sepsis. *Ann Intensive Care* 3(1):15
26. Strnad P, Tacke F, Koch A, Trautwein C (2017) Liver—guardian, modifier and target of sepsis. *Nat Rev Gastroenterol Hepatol* 14(1):55–66
27. Sweeney TE, Shidham A, Wong HR, Khatri P (2015) A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation

- reveals a robust diagnostic gene set. *Sci Transl Med* 7(287):287ra71. <https://doi.org/10.1126/scitranslmed.aaa5993>
28. Takasu O, Gaut JP, Watanabe E, To K, Fagley RE, Sato B et al (2013) Mechanisms of cardiac and renal dysfunction in patients dying of sepsis. *Am J Respir Crit Care Med* 187(5):509–517
 29. Tecchio C, Micheletti A, Cassatella MA (2014) Neutrophil-derived cytokines: facts beyond expression. *Front Immunol* 5:508
 30. van der Heide V, Mohnle P, Rink J, Briegel J, Kreth S (2016) Down-regulation of MicroRNA-31 in CD4+ T Cells Contributes to Immunosuppression in Human Sepsis by Promoting TH2 Skewing. *Anesthesiology* 124(4):908–922
 31. Washburn ML, Wang Z, Walton AH, Goedegebuure SP, Figueroa DJ, Van Horn S et al (2019) T Cell- and Monocyte-Specific RNA-Sequencing Analysis in Septic and Nonseptic Critically Ill Patients and in Patients with Cancer. *J Immunol* 203(7):1897–1908