HHS Public Access

Author manuscript

Lancet Respir Med. Author manuscript; available in PMC 2024 April 18.

Published in final edited form as:

Lancet Respir Med. 2024 April ; 12(4): 323–336. doi:10.1016/S2213-2600(23)00468-X.

Reframing sepsis immunobiology for translation: towards informative subtyping and targeted immunomodulatory therapies

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MS-H and TvdP wrote the first draft of the manuscript. Individual co-authors contributed preliminary ideas for specific topics in the first draft as follows: TC, trained immunity; MPS, disease tolerance; MB, immune resilience; JM, resolution; WJW, microbiome; HCP, sepsis survivors; JCK, phenotypes; and IBM, immune-mediated inflammatory diseases.
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Declaration of interests

JM reports grants from the Canadian Institutes of Health Research and has served as chair of data and safety monitoring boards for AM Pharma and Adrenomed. CWS reports grants from the US National Institutes of Health National Institute of General Medical Sciences, during the conduct of the study, and personal fees from Inotrem and Beckman Coulter, outside of the submitted work. IBM has received funding or consultancy fees from Abbvie, Amgen, Bristol Myers Squibb, Cabaletta, Causeway, Eli Lilly, Evelo, GSK, Janssen, Moonlake, Novartis, Pfizer, and UCB. TvdP has received grants from the EU's Horizon 2020 research and innovation funding programme (grant agreements: Flagellin Aerosol Therapy in Treatment of Drug-resistant Bacterial Pneumonia, 847786; ImmunoSEP, 847422). All other authors declare no competing interests.

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Abstract

Sepsis is a common and deadly condition. Within the current model of sepsis immunobiology, the framing of dysregulated host immune responses into proinflammatory and immunosuppressive responses for the testing of novel treatments has not resulted in successful immunomodulatory therapies. Thus, the recent focus has been to parse observable heterogeneity into subtypes of

sepsis to enable personalised immunomodulation. In this Personal View, we highlight that many fundamental immunological concepts such as resistance, disease tolerance, resilience, resolution, and repair are not incorporated into the current sepsis immunobiology model. The focus for addressing heterogeneity in sepsis should be broadened beyond subtyping to encompass the identification of deterministic molecular networks or dominant mechanisms. We explicitly reframe the dysregulated host immune responses in sepsis as altered homoeostasis with pathological disruption of immune-driven resistance, disease tolerance, resilience, and resolution mechanisms. Our proposal highlights opportunities to identify novel treatment targets and could enable successful immunomodulation in the future.

Introduction

Sepsis is a common and deadly condition, with global estimates of about 49 million incident cases per annum and about 11 million deaths per annum.[1] Sepsis is a medical diagnosis, informed by clinical history and physiological and laboratory data. In the current consensus definitions (referred to as Sepsis-3), sepsis is defined as a dysregulated host response to infection resulting in life-threatening organ dysfunction, and septic shock is defined as a subtype of sepsis with profound circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of death than is sepsis alone.[2–4]

To enable bedside diagnosis and management, the Sepsis-3 definitions and criteria have necessary compromises, which might contribute to the observed heterogeneity of dysregulated host responses in patients diagnosed with sepsis. Indeed, according to the Sepsis-3 definitions,[2–4] infection can be suspected or microbiologically confirmed; however, many critically ill patients with suspected infection are, in retrospect, classified as having a non-infectious condition.[5] Although sepsis commonly arises from either bacterial or viral infections (a recent example being SARS-CoV-2), fungal, protozoal, or parasitic infections, or combinations of pathogens (eg, bacterial coinfections with influenza[6] or malaria[7]) can result in sepsis. The site of infection differs between patients and affects immune responses. Organ dysfunction is quantified by physiological derangements (eg, hypotension) as well as treatment variables (eg, mechanical ventilation). Illness severity is linked to host responses and varies between sepsis cohorts. We have neither a definition nor widely accepted diagnostic test(s) for these dysregulated immune responses, despite the availability of a plethora of biomarkers. As such, the clinical definition has minimal relationship to the current framework for sepsis immunobiology.[8]

These limitations emphasise the need to define explicitly the dysregulated immune response in patients with sepsis. Defining dysregulated immune responses might enable identification of previously unrecognised features of sepsis, allow more sophisticated immunological assessments, and highlight novel treatment opportunities. In this Personal View, we attempt to define dysregulated immune responses by discussing how fundamental immunological concepts (such as immune resistance, disease tolerance, resilience, and resolution) relate to sepsis immunobiology. After outlining the current sepsis immunobiology–immunomodulation paradigm and its role in unsuccessful trials of immunomodulatory therapies, which have provided further rationale for reframing sepsis immunobiology, we

summarise key lessons for success with immunomodulation that can be learnt from immune-mediated inflammatory diseases (IMIDs). Furthermore, we suggest a working definition for dysregulated immune responses in sepsis. Finally, we propose a research roadmap for reframing sepsis immunobiology. We acknowledge that progress in realising the potential of immunomodulation based on the arguments presented in this conceptual paper will require global engagement among clinicians, researchers, patients, and other stakeholders, as well as further research to enable change.

Conventional sepsis immunobiology–immunomodulation paradigm

Sepsis immunobiology has been reviewed in *The Lancet Respiratory Medicine*, by Cajander and colleagues,[9] and elsewhere.[8,10–12] Dysregulated immune responses in sepsis are characterised by concurrent hyperinflammation and immunosuppression, two normally opposing responses that involve distinct cell types and organ systems. Hyperinflammation is caused by the uncontrolled activity of proinflammatory effector mechanisms, involving activated leukocytes and endothelial cells with concomitant dysregulated production of oxygen or nitrogen radicals and cytokines, and activation of the complement and coagulation systems. Although activation of these mechanisms is part of the innate immune response to infection (ie, through a trade-off between inflammatory and protective responses[13]), their uncontrolled activity can cause collateral damage and contribute to the pathogenesis of sepsis.[8] These unbalanced responses also contribute to the development of immune suppression, which involves different cell types[10,11,14] and is associated with a higher risk of new infections, including reactivation of latent viruses. Sepsis-induced immunosuppression results from widespread programmed cell death of lymphocytes,[15] an impaired functional state in T cells (exhaustion), relative increases in the number of regulatory T cells, increases in myeloid-derived suppressor cells, and reduced surface expression of the HLA-DR isotype on monocytes, indicative of reduced antigen-presentation capacity.[8] These maladaptive responses are typically present to variable degrees in patients with sepsis and change over the natural history of sepsis between patients, which contributes to the observed immunological heterogeneity.[8,9]

More than 200 randomised controlled trials have tested the hypothesis that modulating these dysregulated immune responses could improve outcomes from all-cause sepsis. There are numerous reasons why none of the trials has resulted in new immunomodulatory treatments for all-cause sepsis.[16–19] It is possible that eligibility criteria in clinical trials have prevented enrolment of patients with the sepsis subtype(s) that might respond best to the immunomodulator under investigation or that the immunomodulator was not administered in the right dose or at the right time to achieve an optimal immunomodulatory effect. Although we can identify, and possibly correct, single biological derangements, whether blocking one or more elements of the maladaptive responses (eg, by inhibiting the production or action of elevated cytokines such as interleukin-6 [IL-6]) or stimulating impaired host responses (eg, by increasing lymphocyte counts and improving lymphocyte function) could improve outcomes from sepsis remains unknown. Moreover, understanding of how the host immune response in sepsis changes over time is limited owing to a lack of high-quality cohort studies with longitudinal multidomain immunological data. Although not a focus of our Personal View, understanding of how the non-immune component of the dysregulated host response

in sepsis interacts with the immune response is incomplete. These uncertainties provide additional reasons to reframe the sepsis immunobiology model into its component parts of the immune response to pathogens.

Lessons from IMIDs for sepsis immunobiology

IMIDs are clinically diverse conditions that are characterised by chronic inflammation, underlying immunological dysregulation, and end-organ damage. IMIDs include inflammatory arthropathies, (eg, rheumatoid arthritis and spondyloarthropathies), connective tissue disorders (eg, systemic lupus erythematosus), cutaneous inflammatory conditions, inflammatory bowel disease, and autoimmune neurological diseases. Historically, the cornerstone of treatment was broad immunosuppression, regardless of pathogenesis, including glucocorticoids with or without other agents such as methotrexate, azathioprine, cyclophosphamide, or gold salts. Such therapeutics were only partially effective and were dose-limited by serious toxicities.

Recently, increased understanding of the pathogenesis of IMIDs established the pivotal role of inflammatory cytokines, particularly tumour necrosis factor (TNF), in disease aetiology.[20,21] TNF inhibition in rheumatoid arthritis was the first therapeutic success, which was extended to include other IMIDs shortly thereafter.[20] A broad range of cytokine inhibitors targeting, for example, the IL-6 receptor, IL-1, IL-4, IL-13, IL-17A/F, IL-12/23, and IL-23 are now used in clinical practice.[21] Cell-targeting agents such as abatacept (targeting the CD28/CTLA4 pathway) and B-cell-depleting biologics (anti-CD20) are efficacious in several IMIDs.[21] These advances in biologics have led to higher rates of response and remission, with substantially reduced toxicity.[20] Moreover, positive effects have been observed on comorbidities involving cardiovascular, bone, and psychological function,[20] reflecting the broader benefits of modulating systemic inflammation. More recently, oral Janus kinase inhibitors (eg, baricitinib) have been approved that recapitulate the high levels of efficacy achieved with biologics.[20]

This revolution in treatment is driving a transition from organ-affected classification to molecular-based classifications.[20,21] The therapeutic efficacy of individual cytokine inhibitors suggests the existence of dominant signature cytokines in distinct diseases. For example, IL-23p19 inhibitors are beneficial in psoriasis, psoriatic arthritis, and inflammatory bowel disease, but not in rheumatoid arthritis or axial spondyloarthritis, suggesting that these diseases have discrete aetiopathogenetic features that can be parsed by cytokine therapeutics.[20,21] By contrast, IL-17A inhibitors are effective in axial spondyloarthritis, psoriasis, and psoriatic arthritis, but not in rheumatoid arthritis or inflammatory bowel disease.[20,21] The complex interrelationships of cytokine pathways and associated cytokine profiles in IMIDs could enable a precision medicine-based approach, which might be applicable to sepsis given the similarities in cytokine profiles to those of IMIDs and the success of similar interventions in COVID-19.[22]

A further key development in IMID therapeutics was the recognition that strict control of inflammation enabled either more frequent remission or maintenance of a low disease-activity state and prevented progressive target organ damage.[20] Moreover, earlier

intervention leads to substantially improved outcomes, suggesting that the timing of interventions is crucial to restore homoeostasis.[20]

These concepts are useful when reframing sepsis immunobiology. On the basis of the IMID experience, detailed consideration should be given not simply to concentrations of individual cytokines, but rather to the identification of networks of cytokines, defined as profiles, that are correlated with disease kinetics, current immune state, relevant comorbidities, and response to therapeutics, and thereby with probable trajectories of immunologically mediated tissue damage. The process of reframing sepsis immunobiology will be complex. Even in IMIDs in which dominant cytokine hierarchies have been identified, there are no biomarkers that positively or negatively predict treatment response at present. The availability of multiplex technologies, supportive software, and artificial intelligence bioinformatics methods should bring new opportunities. For example, network analysis enabled the identification of a network formed by plasminogen activator inhibitor type 1, IL-6, IL-8, monocyte-chemoattractant protein-1, and IL-10 that persisted over the first 4 days of acute sepsis;[23] IL-6 had the maximum value as the treatment target cytokine, further supported by evidence from severe COVID-19[24] and mendelian randomisation studies.[25]

Key concepts for reframing sepsis immunobiology

An overview of sepsis immunobiology is presented in figure 1. We argue that six additional key concepts should be considered in reframing the immunobiology of sepsis for translation: (1) immune resistance, disease tolerance, and resilience; (2) different scales of microbial threat; (3) compartmentalisation of immune dysregulations; (4) resolution of inflammation; (5) trained immunity; and (6) subtypes of sepsis.

Immune resistance, disease tolerance, and resilience

Humans can protect themselves from or recover from (survive) microbial threats using three distinct strategies: avoidance, resistance, and disease tolerance. In sepsis, the avoidance strategy has been bypassed and the human host has an established infection. Thus, recovery in humans depends on—and a reframing of sepsis immunobiology needs to consider—resistance, disease tolerance, and the related immunological concepts of resilience and resolution.

Therefore, immune responses in sepsis include two distinct (often opposing) immunological and metabolic programmes of immune effector mechanisms aimed at pathogen elimination (ie, resistance) versus those aimed at limiting tissue damage or promoting repair or resolution (ie, disease tolerance), leading ultimately to the restoration of immune system homoeostasis. Restoration of homoeostasis also depends on resilience, which is a trade-off between resistance and disease tolerance mechanisms.[26–29] Recent data suggest that identification and targeting of mechanisms of immune resilience might be useful in infectious diseases.[30] In the context of sepsis (and infectious threat, such as pneumonia leading to acute respiratory distress syndrome [ARDS] or other critical illness syndromes), the term immune resilience refers to the capacity of the immune system to rapidly restore the regulated state that it was in before the infectious threat, while limiting the inflammatory

cost to the host. The clinical equivalents of the inflammatory cost to the host are the adverse outcomes in patients with sepsis.

Resistance strategies protect the human host when a microbial threat has been sensed by reducing (or eliminating) invading microbes through neutralisation or killing. Resistance strategies are functions of the innate and adaptive immune systems. Resistance strategies are anabolic and carry a substantial inflammatory cost to the host, because elimination of pathogens is accompanied by collateral tissue damage and harm to normal tissue function. Inflammation has been conceptualised as "a response to deviations from homeostasis that cannot be reversed by homeostatic mechanisms alone".[31] In the context of inflammation, homoeostasis refers to the active maintenance of certain quantitative characteristics of the system, known as regulated variables, within a desired range (set point), which are altered during inflammation. Thus, resistance mechanisms in sepsis can be reframed as altered homoeostasis of the immune system caused by infection, resulting in inflammation of observable magnitude that requires active intervention to restore baseline immune homoeostasis.

Disease tolerance refers to an evolutionarily conserved defence strategy that limits the severity of infectious diseases, without directly affecting pathogen burden. Disease tolerance reduces host susceptibility to metabolic dysfunction and tissue damage caused directly by pathogens or indirectly by immune responses to pathogens.[32,33] The establishment of disease tolerance to infection might also involve mechanisms that pertain to host–microbiota interactions,[34] such as those involving microbiota-derived metabolites (eg, butyrate). The microbiome of critically ill patients with sepsis is disrupted, resulting in the selection of microorganisms that can cause harm under certain circumstances.[34] This harm occurs through further dysregulation of host defence mechanisms and reduced production of beneficial metabolites such as some short-chain fatty acids.[34] However, this link between disease tolerance and the microbiome is poorly understood.

The successful therapeutic targeting of tissue damage control mechanisms in murine models also helps to establish disease tolerance as a mechanism of interest in sepsis. The best evidence comes from studies of haemopexin, a plasma protein that neutralises the pathogenic effects of labile haem[35] or soluble ferritin.[36] Labile haem is a prototypical iron-based damage-associated molecular pattern,[37] generated as a by-product of haemolysis, that dysregulates host energy metabolism[36] and regulated cell death,[38] compromising disease tolerance to sepsis.[35] These pathogenic effects of labile haem might explain why targeting different regulatory components of haem metabolism exerts protective effects against sepsis and other infectious diseases associated with haemolysis.[35,37] In murine models of sepsis, therapeutic effects via disease tolerance mechanisms have been reported with anthracyclines (eg, daunorubicin, doxorubicin) through the activation of DNA damage responses and autophagy pathways,[39] and with tetracyclines (eg, doxycycline)[40] via the mitochondrial ribosome inhibition of protein synthesis, perturbation of the electron transport chain, increased fatty acid oxidation, and glucocorticoid sensitivity.[40]

Conceptually, most immunomodulation trials in sepsis to date have directly targeted selected components of immune resistance mechanisms. However, there are multiple causal

pathways that lead from infection to immune resistance mechanisms to outcomes.[41] Thus, it could be argued that effector pathways that have been targeted in immunomodulation trials thus far are not necessarily true proximate determinants of outcomes, or that altering them does not completely remove the excess risk from sepsis. Moreover, some patients might have suffered harm that offset any benefit in the trial population. A simple example of the challenges of selective targeting is that most microorganisms can be recognised by a handful of pattern-recognition receptors, which in turn can induce multiple effector responses.[8] Thus, blocking single pathways might not improve sepsis outcomes, as was observed in a trial of Toll-like receptor 4 antagonist therapy.[42] This inference is also supported by observations that molecular subtypes respond differently to treatments (eg, hydrocortisone has been associated with increased mortality in a subset of patients with septic shock).[43]

Different scales of microbial threat

The immune responses of the human host to microbial threats and microorganisms themselves have co-evolved. Thus, the acquired subversion mechanisms of microorganisms could target human innate immune system detection mechanisms or avoid inflammatory responses. To survive infections, the immune system must invoke responses appropriate to the scale of the microbial threat, which could be scaled from low to high.[44,45] Soluble pathogen-associated molecular patterns (PAMPs) pose the lowest threat. The scale of microbial threat is higher when dead microorganisms are sensed and increases further when viable microorganisms are detected. The microbial load might be an additional factor. The scale of threat is highest when viable microorganisms that express genes encoding virulence factors, which actively disrupt or alter host tissue homoeostasis (so called vita-PAMPs), are sensed.[44,45] However, current microbiological assessments in sepsis are limited to determining whether a pathogen has been identified and the class of pathogen. Although we acknowledge that immune responses differ by pathogen class (such as bacterial *vs* viral[46]), studying the differences in immune responses to different scales of microbial threat could explain some of the observable heterogeneity in sepsis[45] and perhaps enable identification of novel therapeutic targets.

Compartmentalisation of immune dysregulations

Every organ has a distinctive set of immune sensors and effectors, as organs consist of organ-specific cells, resident immune cells, and immune cells that are recruited during inflammation. In humans, each organ has a unique resident immune cell composition[47] and proteomic signature.[48,49] These organ-specific cells and immune cells display numerous abnormalities in sepsis.[50–52] In animal models of infection, there are organ-specific differences in immune responses,[53] which might also occur in patients with sepsis. Currently, the possibility that the immune responses within organs might differ from those observed in blood and the risk of adverse consequences from immunotherapy are not explicitly considered during therapeutic trials in sepsis.[54,55] For example, when immunostimulants are administered for a blood-level diagnosis of immunosuppression, but the lungs are not in a similar immunosuppressed state, then the lung injury could theoretically worsen.

To explicitly test this hypothesis, we need to identify biomarkers that provide information on organ-specific immune states to compare with blood immune states. This concept is supported by observations of differences between blood-specific and organ-specific immune states in ARDS[56] and COVID-19.[57] We acknowledge that it is neither feasible to sample all vital organs to assess organ-specific immune states nor possible in every patient with sepsis. However, there are accessible spaces such as respiratory, urinary, and gastrointestinal tracts, samples from which might provide an indication of an organ-specific immune state, although not necessarily the true tissue immune state (figure 1). Alternatively, we could search for blood biomarkers that are reflective of immune dysregulations in specific organs. We highlight compartmentalisation of immune dysregulations as a concept that might have treatment implications and should therefore be explored in future studies.

Resolution of inflammation

The problem in sepsis immunobiology might not be the initial resistance mechanisms, but their failure to turn off following elimination of a microbial threat.[58] The resolution of inflammation is an active process that is associated with the expression of anti-inflammatory and reparative genes (eg, IL-10 and transforming growth factor-β), the removal of inflammatory cells, and the restoration of tissue-resident macrophages and dendritic cells.[59]

Neutrophils provide a cardinal example of the complex interplay between the processes that support activation of an innate immune response and those that enable its resolution. Neutrophils are the most abundant circulating leukocytes[60] and provide the first line of defence against infection as they phagocytose bacteria and tissue debris, release antimicrobial compounds and reactive oxygen intermediates, and extrude their DNA as neutrophil extracellular traps.[61] They are crucial to the early response to danger, but harmful when that response persists,[62] and activated neutrophils have a pivotal pathological role in sepsis.[63–65] Each day, about 10^{11} neutrophils are released from the bone marrow.[66,67] Neutrophils are constitutively apoptotic cells, circulating for only hours after their release from the bone marrow before they undergo apoptosis. Neutrophil apoptosis and uptake by resident phagocytes activates counter-inflammatory and reparative responses.[68,69] The processes of activation and resolution through neutrophil apoptosis are intimately intertwined. Caspase 1, initially identified as a key effector of apoptosis, also activates IL-1β through a multiprotein complex called the inflammasome and thus initiates the host inflammatory response following pattern-recognition receptor engagement.[70] Caspase 8, the enzyme responsible for initiating apoptosis in response to extracellular signals, exerts anti-apoptotic activity following its tyrosine phosphorylation,[71] a post-translational modification apparent in neutrophils from patients who have sustained trauma or sepsis that results in neutrophil-mediated apoptosis of epithelial cells.[72]

The biological processes that underlie the resolution of inflammation in sepsis are poorly understood.[73] Understanding relevant mechanisms of resolution in sepsis could enable new treatment opportunities. Drugs such as acetylsalicylic acid (through enhanced production of lipoxins) or corticosteroids have pro-resolution activities. The cellular signalling pathways that sustain inflammation are complex and provide additional potential targets,

including IL-1β, heat-shock protein 90,[74] and the NAD-generating enzyme nicotinamide phosphoribosyltransferase,[75] to accelerate the resolution of inflammation.

Trained immunity

Trained immunity refers to the durable increased responsiveness of innate immune cells to secondary stimulation following prior exposure to microbial challenges and endogenous stimuli (such as oxidised low-density lipoproteins, uric acid, aldosterone, cate-cholamines, and S-100 proteins).[76] Trained immunity is acquired through extensive metabolic and epigenetic reprogramming of innate immune cells induced by the primary microbial threat—either pathogens or components thereof (eg, BCG vaccine, viral infections, β-glucan)[77–79]—and is expected to last for a few weeks or months after a primary challenge. Induction of trained immunity requires involvement of several metabolic pathways, including glycolysis, oxidative phosphorylation, glutaminolysis, cholesterol metabolism, fatty acid oxidation, and methionine and glutathione metabolism. Changes in these pathways provide the metabolites needed to induce and sustain the epigenetic and functional changes that characterise trained immunity. Important epigenetic histone modifications involved in trained immunity include the following: trimethylation of histone H3 at lysine 4 (H3K4me3), which marks active promoters; H3K4me1, which marks distal enhancers; and H3K27 acetylation, which marks both active enhancers and promoter regions.[77]

Understanding the role of trained immunity in the sepsis immune response is relevant, given that many sepsis events occur in the context of deteriorating health in the year preceding sepsis.[80] Markers of trained immunity are acquired in animal models of sepsis.[81] Furthermore, sepsis survivors often have infection-related rehospitalisation in the months after primary sepsis admission.[82] Certain live vaccines, in particular BCG vaccine and perhaps adjuvant vaccines, can reduce this excess risk in sepsis survivors, probably through heterologous vaccine effects.[83]

Subtypes of sepsis

The current subtyping of patients with sepsis (figure 2)[43,84–92] differs across investigations by study design, input data, type of analyses, and the terms used to describe the subtypes (eg, subphenotypes, treatable traits, endotypes). Sepsis molecular subtypes can be derived using data from cohort studies, with blood leukocyte gene-expression data as the input data and unsupervised clustering as the analysis type. For example, the following molecular subtypes of sepsis have been generated: molecular diagnosis and risk stratification of sepsis (MARS) endotypes 1–4,[84] sepsis response signature (SRS) subphenotypes 1 and 2[85] (and, recently, SRS-3[86]), and others (inflammopathic, adaptive, and coagulopathic[87]). Sepsis clinical subtypes[88–91,93,94] can be derived using data from cohort studies and completed randomised controlled trials, with input data including routine clinical data as well as biomarker data (such as physiological variables, leukocyte counts, and protein biomarkers in some analyses) and unsupervised clustering as the analysis type. In this way, the following clinical subtypes of sepsis have been reported: clusters 1–4;[88] alpha, beta, gamma, and delta clusters;[89] classes 1–6;[90] subphenotype-1^{V} and subphenotype-2^{V} from the VANISH (Vasopressin *vs* Norepinephrine as Initial Therapy in Septic Shock) trial;[43] and subphenotypes-1^{L}–3^{L} from the LeoPARDS (Levosimendan for the Prevention of Acute

Organ Dysfunction in Sepsis) trial.[91] The key conceptual argument in figure 2 is the need to identify overlapping subtypes or common subtypes across different studies with shared modifiable mechanisms that represent targets for immunomodulation.

Definition of dysregulated immune responses and roadmap for research

We explicitly reframe the dysregulated host immune responses in sepsis as altered homoeostasis with pathological disruption of immune-driven resistance, disease tolerance, resilience, and resolution mechanisms. This reframing has the potential to provide new opportunities for the discovery and refinement of sepsis treatments (figure 3), and might also have implications for other critical illnesses with infective aetiologies, such as ARDS.

Our conceptual definition of dysregulated immune responses also provides a tangible opportunity to highlight a research roadmap (figure 4, panel[95–101]), which will need to be refined as the field progresses. This roadmap can be grouped into two broad areas: (1) re-evaluation of currently available datasets to refine our proposed reframing of dysregulated immune responses; and (2) consideration of how future translational research could use systems biology approaches to determine dominant modifiable mechanisms and sepsis subtypes, incorporate the scale of microbial threat with sepsis diagnostics, and reach broad agreement on minimum standards of rigour or a framework for sepsis subtyping.

Revaluation of currently available and published datasets with a focus on exploring resistance, disease tolerance, and resolution pathways and factors that cause variation between patients with sepsis is an essential next step. This revaluation could be iterative in terms of input data, model testing, and subsequent validation. Such analytical models could be applied across data formats, such as clinical data or biological data, to perform either integrative[102] or explanatory (prediction) modelling.[103] Broadly, integrative models can be complete or partial. In complete-data integrative models, data are measured on the same individuals in the dataset, with the goal of building relationships between different variables to explain findings at an individual level. In partial-data integrative models, data are measured on different individuals, often in different datasets, with the goal of building relationships between different variables to make predictions at a cohort level. Although such analyses require collection and storage of a variety of samples from large numbers of patients at different stages of clinical disease (from pre-sepsis to late resolution), which are expensive and necessitate collaborative working among laboratories with different areas of expertise, such studies are already feasible given the wealth of publicly available datasets.[104]

Published literature highlights that sepsis (susceptibility and clinical features) is associated with changes at the genomic, transcriptional, translational, and post-translational biological levels, which are shown in figure 4. Specifically, genetic associations and variants[105] that underlie susceptibility to sepsis—reported in pneumonia,[106] COVID-19,[107] and other subgroups—have the potential to reveal molecular mechanisms that underlie sepsis through functional genomics. An example is the identification of multiple expression quantitative trait loci (eQTL) and protein quantitative trait loci (pQTL) that are significantly associated with life-threatening COVID-19[108] and pathogen-specific host responses.[109] There is limited information on eQTL and the relationship between eQTL and pQTL in all-cause

sepsis. Although numerous epigenetic modifications have been associated with sepsis,[110] large-scale studies have not been done to explore the effect of such changes on the resistance, disease tolerance, and resolution components of the dysregulated immune responses. For example, the presence of acquired epigenetic changes from environmental exposures might explain the exaggerated innate immune responses seen in some patients with sepsis and could highlight new immune therapeutic targets to stimulate or repress trained immunity. High-throughput assays of RNA expression, epigenetics, proteomics, metabolomics, and other omics technologies, including those with single-cell resolution, will provide further information on the different elements of the dysregulated immune responses in sepsis. Integration across these modalities is limited—for example, mRNA abundance might have low correlation with concentrations of the corresponding proteins. A further limitation is the difficulty in identifying causal relationships in highly multidimensional observational data. However, such causal relationships in multidimensional cross-scale data from sepsis cohorts can be revealed by integrating principles from human genetics and causal inference methods.[111] Understanding of the inter-relationships between and variations within the transcriptional, translational, and post-translational levels in sepsis is also limited and requires further research. Thus, a key element of the future roadmap will be to perform large-scale cohort studies, alongside approaches to enable causal inferences when evaluating multiple biological levels of data that incorporate systems biology principles.

Longitudinal biological data from deep immuno-phenotyping studies of patients with sepsis are scarce, with almost all information coming from the time of hospital admission. Biological sampling at admission provides a snapshot of immune effector responses, but will show immunological heterogeneity because the time of transition from infection to sepsis is unknown. In future studies, this issue could be addressed by having controls with a timed insult (eg, major elective surgery) and by using methods that model longitudinal information when the actual measurement time is treated as uncertain (eg, pseudotime analyses). Insights into the kinetics and inter-relationships between distinct immune dysregulations are probably crucial not only for risk assessment and timely recognition of sepsis, but also for the identification of central targets for therapeutics that could prevent or reverse sepsis by restoring immune homoeostasis.

The clinical value of omics profiling will be enhanced by the availability of such data in advance of acute illness—for example, with either broad population-level implementation of whole-genome sequencing or targeted assessments in high-risk patients or survivors of sepsis. The availability of such data will also enable exploration of concepts such as the protective versus adverse autoimmunity-inducing roles of anti-self antibodies that are generated during infections.[112] There is also the opportunity for point-of-care testing for specific gene sets, for example using multiplex RT-PCR, which could facilitate patient stratification on the basis of the underlying immune state or biomarkers for specific treatable traits.

Our roadmap for research is ambitious. The concepts presented here could be refined when sepsis-specific targetable mechanisms within immune resistance, disease tolerance, and resolution mechanisms are identified using systems immunology principles. We currently lack the information needed to design diagnostic tests that could be used to identify

the mechanistic sepsis subtypes suggested here. The longitudinal studies that we propose will enable understanding of immunological trajectories, immune state transitions, and the validity of different treatments at different timepoints. At present, it is challenging to obtain such detailed immunological information in near real time for patient management. With global engagement among clinicians, researchers, patients, and other stakeholders, it should be feasible to translate our roadmap into clinical reality within the next decade.

Conclusions

We have considered a number of key concepts in the immunobiology of sepsis and have explicitly reframed the dysregulated host immune responses as altered homoeostasis with pathological disruption of immune-driven resistance, disease tolerance, resilience, and resolution mechanisms. Sepsis subtypes are complex traits that are determined by the summation of a patient's baseline health, inherited host features, environmental influences, and dysregulated immune responses. To enable successful immunomodulation in patients with sepsis, modifiable immunological traits or deterministic biological networks or molecular features need to be identified.

Acknowledgments

We received no funding for the writing of this Personal View, which is based partly on a colloquium that was organised and supported by the International Sepsis Forum in Amsterdam, Netherlands, from June 17 to 18, 2022. We thank Elaine Rinicker for coordinating the arrangements for the colloquium, which was attended by many of the authors of this manuscript. MS-H was supported by the NIHR Clinician Scientist Award (CS-2016-16-011; 2017-2023) during the writing of the manuscript. The views expressed in this paper are those of the authors and not necessarily those of the UK National Health Service, the UK NIHR, or the UK Department of Health and Social Care.

MS-H is supported by the UK National Institute for Health and Care Research (NIHR) Clinician Scientist Award (CS-2016-16-011; 2017–2023). MPS's laboratory is supported by the Calouste Gulbenkian Foundation, La Caixa Foundation (HR18-00502), Fundação para a Ciência e a Tecnologia (GlucoInfect, 5723/2014; FEDER029411, FEDER/29411/2017; Infectenergy, PTDC/MED-FSL/4681/2020; MalBil, 2022.02426.PTDC), the Oeiras–European Research Council Frontier Research Incentive Awards, SymbNET Research Grants (H2020-WIDESPREAD-2020-5-952537), and Congento (LISBOA-01-0145-FEDER-022170). MPS is an associate member of the Deutsche Forschungsgemeinschaft (DFG) Balance of the Microverse initiative (EXC 2051; 390713860). MB is principal investigator of the DFG Balance of the Microverse initiative (EXC 2051; 390713860). JCK is supported by the Medical Research Council (MR/V002503/1), a Wellcome Trust Investigator Award (204969/Z/16/Z), and Wellcome Trust grants (090532/Z/09/Z and 203141/Z/16/Z) to the Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, and the NIHR Oxford Biomedical Research Centre.

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Key messages

- The conventional sepsis immunobiology–immunomodulation paradigm of hyperinflammation and immunosuppression has not enabled identification of any immunomodulatory treatments that improve outcomes for patients with sepsis in randomised controlled trials
- We explicitly reframe the dysregulated host immune responses in sepsis as altered homoeostasis with pathological disruption of immune-driven resistance, disease tolerance, resilience, and resolution mechanisms
- Resistance refers to effector mechanisms that reduce the pathogen burden once the infection is established through detection, neutralisation, killing, or expulsion of microorganisms and production of inflammatory mediators (also referred to as the inflammatory cost to the host)
- Disease tolerance is an evolutionarily conserved defence strategy that limits the severity of infectious diseases, without directly affecting pathogen burden
- Resilience is the capacity of the immune system to rapidly restore the regulated state that it was in before the infectious threat, while limiting the inflammatory cost to the host, which is reflected in adverse clinical outcomes
- Resolution is conceptualised as a tightly regulated and active biological process that restores tissue homoeostasis following inflammation
- A systems biology approach to research, based on this reframing of sepsis immunobiology, could eventually lead to the classification of sepsis subtypes or sepsis immune states that are complex treatable traits, defined as measurable characteristics, that have clinical consequences, reflect multiple interacting molecular mechanisms, and are modifiable with repurposed drugs or yet-to-be-discovered treatments

Panel: Examples of knowledge gaps, measurements, and analytical approaches

Knowledge gaps

Abnormal resistance

- Diagnostic tests for scale of microbial threat
- Differences between sterile inflammation and sepsis-related inflammation
- Inter-relationship between hyperinflammation and immunosuppression
- Features and diagnostic criteria for hyperinflammation and immunosuppression
- Subtypes for different hyperinflammation and immunosuppression profiles
- What happens to immunosuppression pathways when anti-inflammatory therapies are used for hyperinflammation
- How closely measurements of immune states in blood reflect vital organ immune states
- Modifiable mechanisms for resistance, disease tolerance, resilience, resolution, and repair that are affected in sepsis
- Whether outcomes will improve if different immunomodulation strategies are tested over the course of the illness with time-series analyses of immunological data
- New drug targets

Impaired disease tolerance and resilience

- Pathways involved in disease tolerance in patients with sepsis
- Prevalence of impaired resilience in sepsis cohorts
- Mechanisms contributing to impaired resilience during sepsis
- Relationship of impairments in disease tolerance and resilience pathways to sepsis illness trajectory for optimal timing of interventions
- Prevalence of impaired immune resilience during the pre-sepsis period to enable primary prevention
- New drug targets

Impaired resolution and repair

- Pathways involved in impaired resolution in patients with sepsis
- Mechanisms contributing to impaired repair in patients with sepsis
- Relationship of impairments in resolution and repair pathways to sepsis illness trajectory for optimal timing of interventions
- New drug targets

Identification of sepsis subtypes or immune states

- The immune response measurement type and combination of measurements that provide the most informative datasets for sepsis subtyping
- Agreement on minimum standard or framework for sepsis subtyping
- Integration of multiomics (cross-scale) immunology data to generate novel sepsis subtypes
- Features of and diagnostic criteria for sepsis subtypes
- Diagnostic tests for subtypes
- Refined therapeutic approaches based on reframed sepsis subtyping data

Measurements and analytical approaches

Impaired resistance, disease tolerance, resilience, resolution, and repair

- Longitudinal blood sampling in cohort studies
- Clinical sampling before and after treatment in clinical trials
- Standardisation of clinical sampling procedures and data sharing
- Standardisation of immunophenotyping as per Human Immunology Project97 guidance
- Multilayer immunomics
- Cytokine network analyses
- Mapping of the interactome for sepsis
- Time-series analyses
- Systems immunology principles
- Integration of clinical and immunological data on the basis of current knowledge to highlight pathways involved in resistance, disease tolerance, resilience, resolution, and repair affected in sepsis
- Network medicine principles
- Drug repurposing and novel discoveries using information from pathway analyses specific to sepsis
- Enhanced target discovery
- In-silico medicinal chemistry
- Diagnostics for impaired disease tolerance, resilience, resolution, and repair in patients with sepsis

Identification of sepsis subtypes or immune states

- Construction of personalised perturbation profiles to determine cell–cell regulatory mechanisms across individuals

- Integration of personalised perturbation profiles into dominant mechanism-based sepsis subtypes
- Grouping by similarities in functionally related gene-expression changes associated with dominant mechanisms-based sepsis subtypes
- Unsupervised classification or supervised machine learning using established tools
- Systems immunology

Tangible examples for the roadmap presented in the main text, based on the reframed immunobiology illustrated in figures 3 and 4. This is not an exhaustive list of possibilities. See elsewhere[95–101] for additional information on the concepts included in the panel. We envisage that our conceptual reframing will stimulate new discovery-orientated lines of research in sepsis immunobiology, which could eventually lead to improved outcomes in patients with sepsis and in survivors of sepsis.

Search strategy and selection criteria

References for this Personal View were identified by co-authors who contributed to individual sections through searches of PubMed for articles published in any language from June 30, 1992 (to coincide with the first publication of sepsis consensus definitions), to Nov 01, 2023, using the search term “sepsis” in combination with the following search terms: “immunobiology”, “phenotype”, “endotype”, “resistance”, “disease tolerance”, “resolution”, “repair”, “immunomodulation”, “immune mediated inflammatory diseases”, “and “precision medicine”. Relevant articles were also identified through searches of the authors’ personal files and references cited in previous state-of-the-art review articles. Articles resulting from these searches and relevant references were reviewed by the individual contributors and selected on the basis of their relevance to the aims of each section in this Personal View.

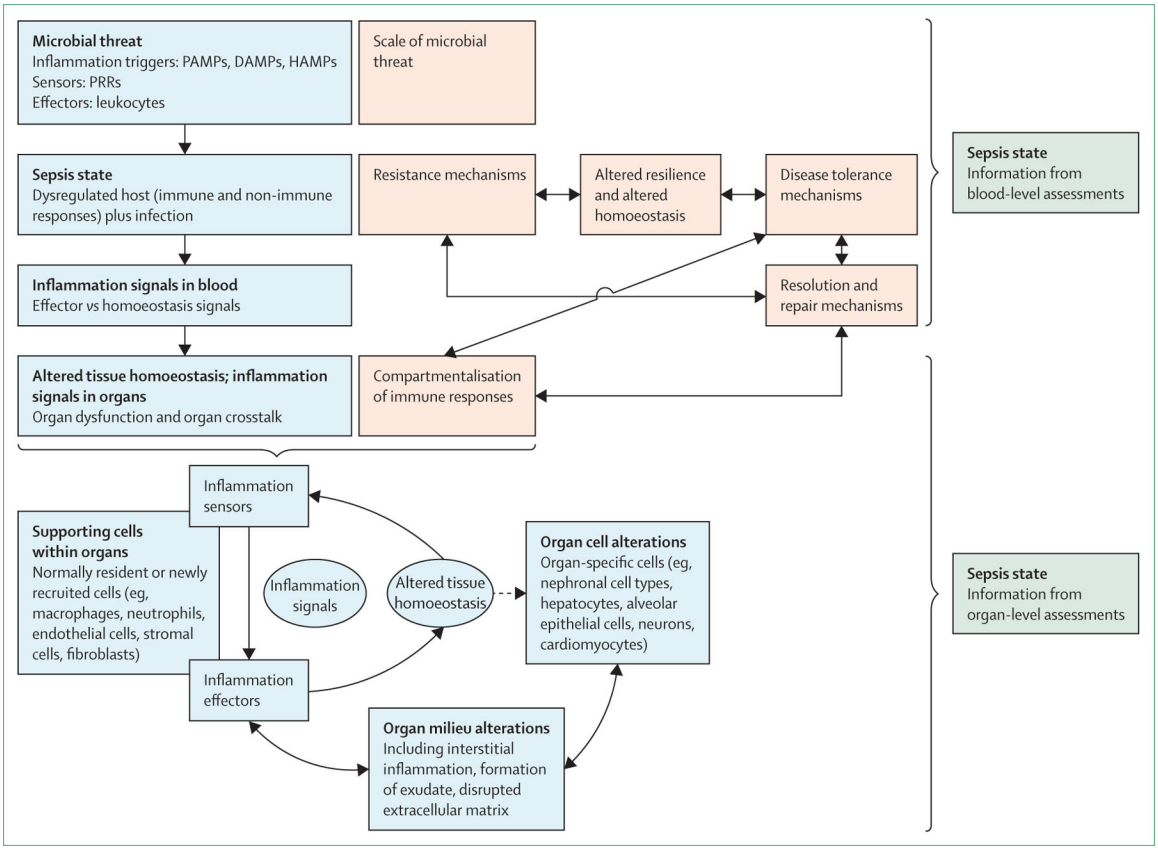

Figure 1: Overview of sepsis immunobiology and compartmentalisation of immune responses

Health is characterised by constant (re)circulation of the major cellular and humoral components of the immune system via the bloodstream and lymphatic systems, providing surveillance of danger signals. Danger signals that trigger inflammation include PAMPs from pathogens, DAMPs from stress and tissue damage, and HAMPs from disruptions to cellular homoeostasis. Sensors for these signals include PRRs as well as stress sensors expressed on leukocytes and non-leukocyte cells such as epithelial cells and endothelial cells. When danger signals are sensed, inflammation signals, effector signals, homoeostasis signals, and inflammation pathways are activated. Organ dysfunction in sepsis results from altered tissue homoeostasis with minimal tissue damage. In the context of immune responses, all organs have organ-specific cells (eg, neurons, cardiomyocytes, hepatocytes, specialised epithelial cells in the kidney, alveolar epithelial cells in the lung), tissue-resident immune cells, and newly recruited immune cells that can sense and display effector mechanisms that further alter organ milieu and function. Blue boxes provide an overview of immune responses occurring in sepsis, based on fundamental immunological principles. Orange boxes indicate concepts for which there is either a paucity of data or lack of explicit framing in current sepsis immunobiology models; see main text for discussion of these concepts to inform the proposed definition of dysregulated immune responses. Green boxes represent summary information for sepsis immune states; note that only blood-level assessments of immune responses are commonly performed at the bedside. DAMPs=damage-associated molecular patterns. HAMPs=homoeostasis-altering molecular

processes. PAMPs=pathogen-associated molecular patterns. PRRs=pattern-recognition receptors.

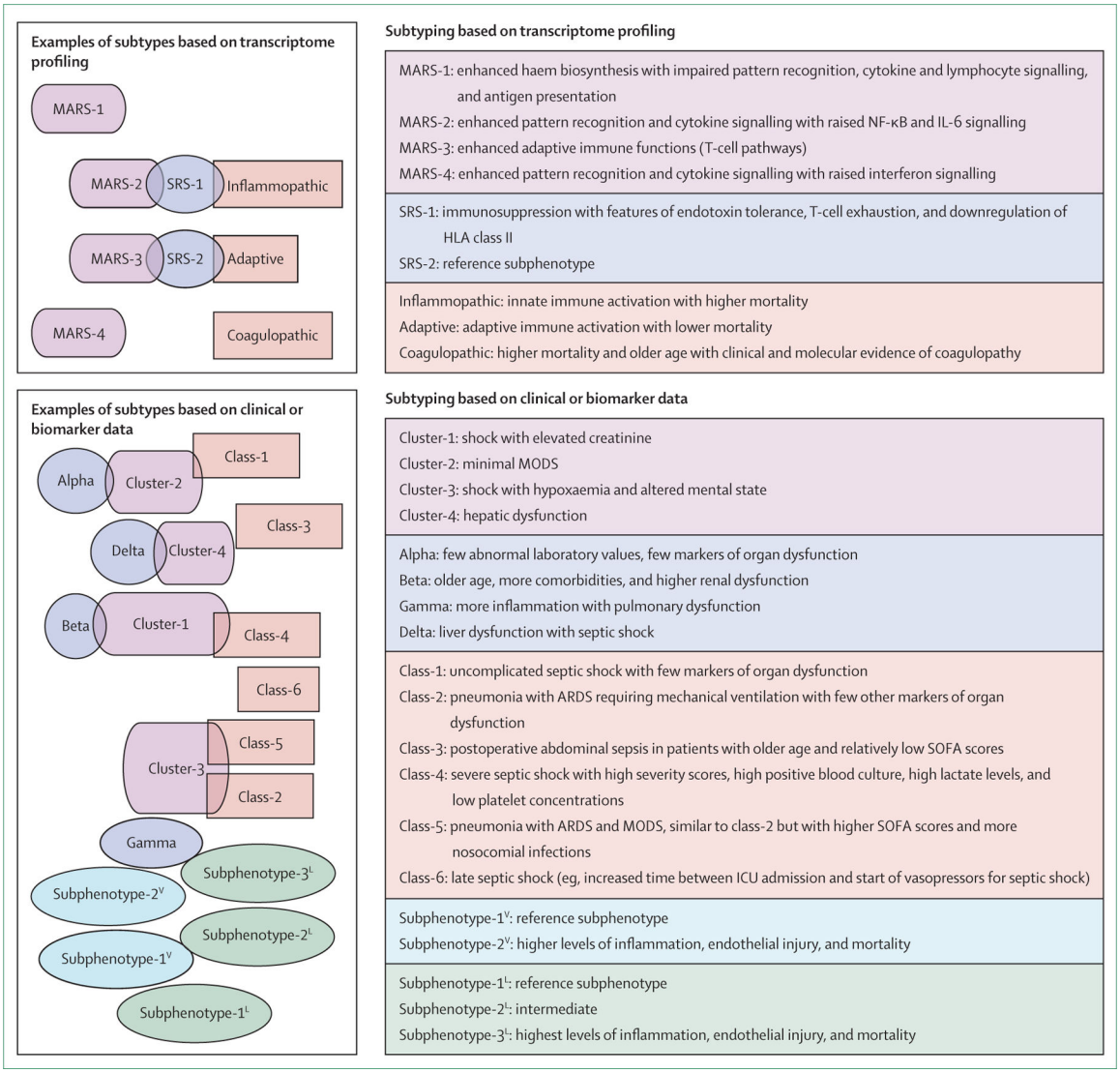

Figure 2: Overlap of subphenotypes reported in sepsis

Current sepsis subtyping is often done as a single-domain (clinical data or a single omics approach) focused analysis, which largely ignores the functional interconnections between different biological domains and is unlikely to capture the entire immunological complexity of sepsis biology. Hypothetical molecular and clinical subtypes are shown, with similar subphenotypes overlapping in the figure. Summary descriptors highlight apparent similarities between molecular subphenotypes and between clinical subphenotypes—for example, there are similarities between MARS-2, SRS-1, and inflammopathic molecular subphenotypes and between MARS-3, SRS-2, and adaptive molecular subphenotypes.[84–87] Subphenotypes are described relative to other subphenotypes within the same group. There are numerous challenges with the current approach to subphenotyping. These include (but are not limited to) differences in input data and analytical approaches for dimensionality reduction, limited use of integrated information from two or more biological data domains, and uncertainty around differential biological mechanisms linked to each subphenotype, probabilistic assignment of subphenotypes, unique targetable

mechanisms with functional relevance in a subphenotype, relevant surrogate markers or endpoints, treatment response features at a biological level for each subphenotype, and the reproducibility of subphenotypes in multiple independent datasets. There is also uncertainty about the feasibility of implementation globally, including in resource-limited settings. See original studies[43,84–91] for more details on the different groups of subtypes, and elsewhere[92] for additional information on the concepts included in the figure. ARDS=acute respiratory distress syndrome. ICU=intensive care unit. IL-6=interleukin 6. MARS=molecular diagnosis and risk stratification of sepsis. MODS=multiorgan dysfunction syndrome. NF-κB=nuclear factor κB. SOFA=Sequential Organ Failure Assessment. SRS=sepsis response signature.

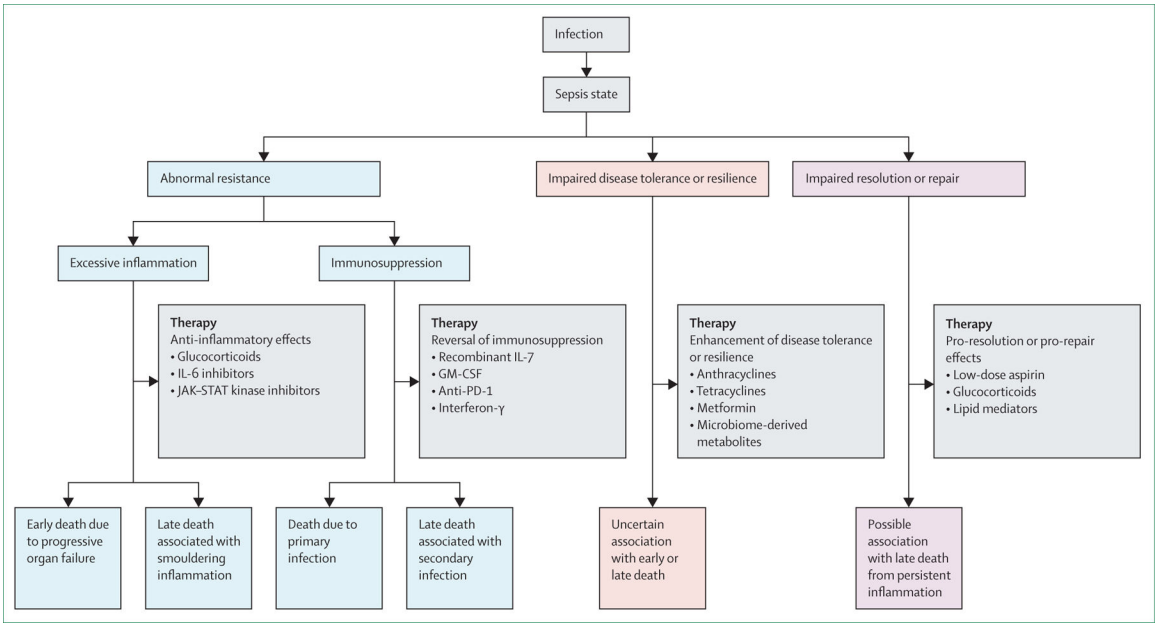

Figure 3: Reframing of dysregulated immune responses in sepsis to inform potential treatments

The degree of immunopathology in sepsis is related to the magnitude and duration of abnormalities in resistance, disease tolerance, resilience, resolution, and repair mechanisms. If future studies could identify patients with one or more dominant mechanisms that explain the sepsis state, then these mechanisms could be targeted with specific treatments in clinical trials. The proposed treatments are examples and do not represent an exhaustive list. A patient might require more than one treatment based on their dominant mechanism(s). These dominant mechanisms might vary over time when assessed with longitudinal sampling. The dominant mechanism could also differ between blood and one or more tissue compartments and is likely to vary by sepsis subtype. GM-CSF=granulocyte-macrophage colony-stimulating factor. IL=interleukin. JAK=Janus kinase. PD-1=programmed cell death 1. STAT=signal transducer and activator of transcription.

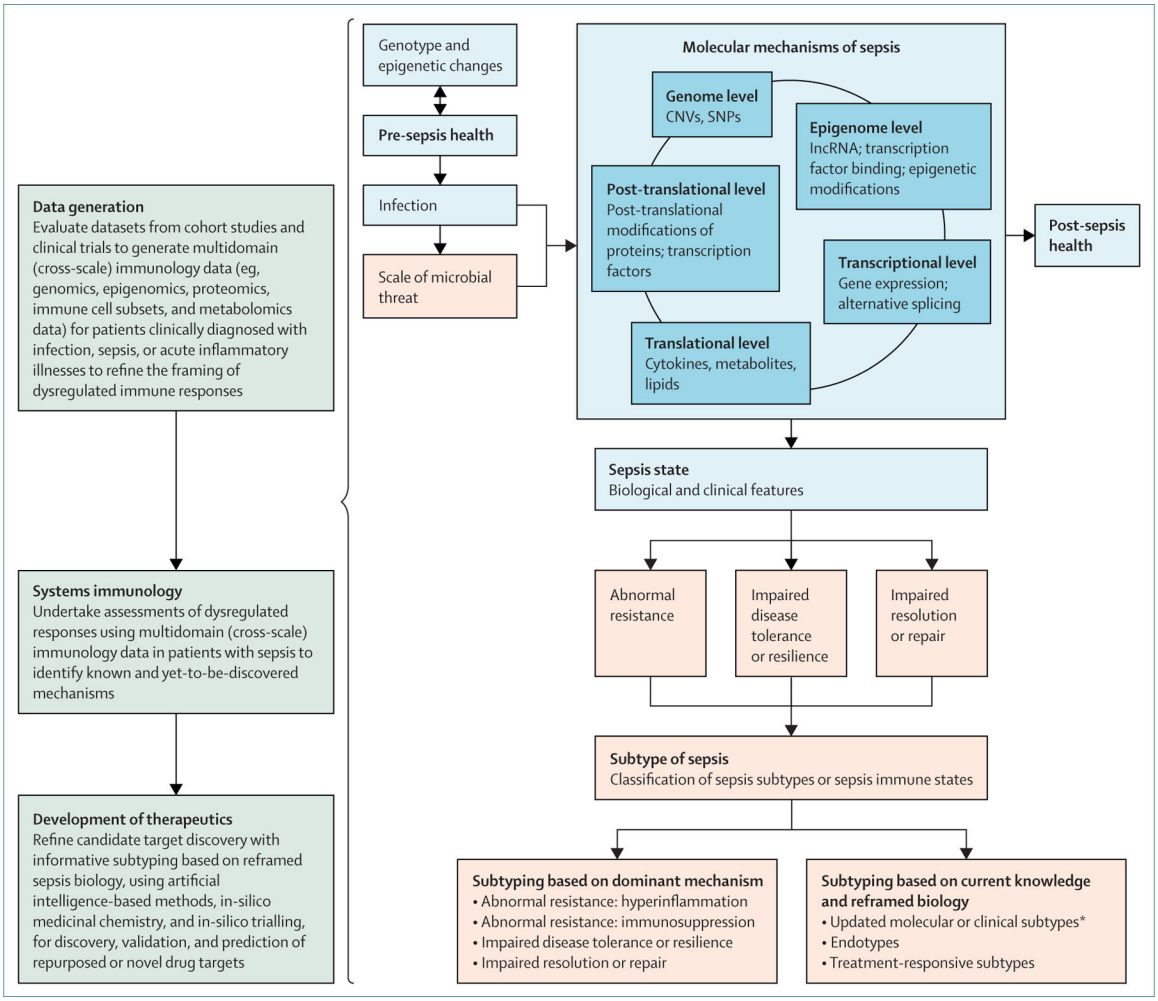

Figure 4: Identification of biological variations and classification of sepsis using systems immunology

The generation of multidomain (also termed cross-scale) immunology data from patients with infections, sepsis, and acute illnesses is needed because all omics dimensions contribute towards the observed heterogeneity in sepsis. Genotyping gives information on past population selection and genetic drift. Epigenetic changes account for lifetime exposures before sepsis and intergenerational effects. Variations within biological data occur in genomics, epigenomics, transcriptomics, and proteomics data, and at metabolome levels. The generation of protein-coding mRNAs and metabolites are complex processes. When transcription factors and RNA polymerase can access DNA and initiate transcription, protein-coding pre-mRNAs are produced. Subsequent generation of mature mRNA is essential for nuclear export, stability, and translation. Only a portion of such mRNA transcripts (including splice variants) are translated into proteins. Protein levels and biological activity are affected by SNPs in regions of genes coding for amino acids and post-translational modifications. Information flow between these biological domains and combinatorial variations across domains generate heterogenous sepsis clinical phenotypes. Systems immunology refers to the study of interactions within the immune system, their regulatory functions, and the emergent properties of immune responses. Analysis of

multidomain data to enable subtyping can be based on dominant mechanisms or on a combination of current knowledge and reframed biology for the enhancement of existing subtypes or discovery of new subtypes, with or without the data-integrative analytical approaches used in systems immunology studies. Subtyping based on reframed sepsis immunobiology could, in turn, be used to inform the development of novel therapeutics for sepsis. Blue boxes represent sources of heterogeneity in sepsis. Orange boxes indicate either proposed new concepts or future research within the roadmap (panel) that incorporates new concepts. Green boxes show the sequence of studies and methods within the proposed roadmap to enable reframing of sepsis immunobiology for translation. CNV=copy number variation. lncRNA=long non-coding RNA. SNP=single-nucleotide polymorphism. *Based on previously reported subphenotypes described in figure 2.