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REVIEW

Sepsis target validation for repurposing and combining complement and immune checkpoint inhibition therapeutics

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ABSTRACT

Introduction: Sepsis is a disease that occurs due to an adverse immune response to infection by bacteria, viruses and fungi and is the leading pathway to death by infection. The hallmarks for maladapted immune reactions in severe sepsis, which contribute to multiple organ failure and death, are bookended by the exacerbated activation of the complement system to protracted T-cell dysfunction states orchestrated by immune checkpoint control. Despite major advances in our understanding of the condition, there remains to be either a definitive test or an effective therapeutic intervention.

Areas covered: The authors consider a combinational drug therapy approach using new biologics, and mathematical modeling for predicting patient responses, in targeting innate and adaptive immune mediators underlying sepsis. Special consideration is given for emerging *complement* and *immune checkpoint* inhibitors that may be repurposed for sepsis treatment.

Expert opinion: In order to overcome the challenges inherent to finding new therapies for the complex dysregulated host response to infection that drives sepsis, it is necessary to move away from monotherapy and promote precision for personalized combinatory therapies. Notably, combinatory therapy should be guided by predictive systems models of the immune-metabolic characteristics of an individual's disease progression.

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1. Introduction

The term sepsis, derived from the ancient Greek meaning to 'make rotten' and referring to the decomposition of organic material, was first coined by Hippocrates [1,2]. Nowadays, sepsis is viewed as a complex multi-stage and multifactorial condition defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [3]. Sepsis leads to shock, multiple organ failure, and death, especially if not recognized early and treated promptly.

In sepsis, the immune response initiated by an infecting pathogen fails to revert to baseline homeostasis, consequently leading to a pathological condition characterized by sustained excessive inflammation and T-cell immune suppression. Despite the advances in diagnostic procedures and therapeutics, sepsis remains the leading cause of death in surgical and general intensive care units. In 2017 the World health Organization identified sepsis as a global health priority [4]. A precise estimate of the epidemiology burden of sepsis is difficult to ascertain; some publications estimate that every year worldwide more than 30 million people are affected, potentially leading to 6 million deaths, while other reports claim that the annual number of cases is closer to 50 million and that 19.7% of deaths worldwide are sepsis related (11 million per annum) [5,6]. Moreover, patients who survive sepsis often suffer from post-sepsis symptoms, including long-term functional disabilities and cognitive impairment with substantial health care, economic and social repercussions [4,7]. Accordingly, sepsis is a significant health issue with high mortality and morbidity, causing a major impact on human life and resource utilization [4].

The identification and treatment of sepsis is an ongoing challenge for medical professionals. Traditionally, sepsis treatment relies on the management of bacterial infections through the use of antibiotic therapy directed against the infecting organism [8]. In the majority of cases the causative agent or initial provoker is not identified, may not be bacterial or may be polymicrobial with undetectable loads. As with all infections it is the ensuing maladapted immune pathogenic pathways of the host that causes severity of disease. For this reason, a plethora of studies have been carried out focusing on the modulation of the immune system response to infection, given that, it is this response that ultimately leads to organ dysfunction [4,9,10]. The complement system is a key trigger component of innate immunity that provides an initial critical orchestration of the multifaceted defense against infection. A cardinal feature of the systemic overactive inflammatory response observed in sepsis is complement activation. There are three complement pathways – alternative (AP), classical (CP), and lectin (LP) – evolved to activate different biological functions, leading to the production of several anaphylatoxins (C3a, C5a) and other active products that impart both protective and harmful effects in sepsis [11]. Furthermore, complement receptors govern a link to adaptive immune cells where their expression on these cells provides

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Article highlights

- Sepsis is as a life-threatening complex multi-stage and multifactorial condition caused by a 'dysregulated' host response to infection.
- Diagnostic procedures and therapeutics based on a single biomarker or monotherapy have repeatedly been met with failure.
- Emerging potent biologic drugs targeting the complement system, cytokines and immune-check-point inhibition provide renewed opportunity, using a drug combination therapy approach, for targeting host pathways to curatively adjust the response to infection in sepsis.
- Understanding perturbation in homeostasis set-points and the dynamics of an adverse host response to infection is urgently needed.
- Combination therapy should consider a stratified approach targeting patient-specific maladapted innate and adaptive immune response pathways.
- Mathematical models for describing the first order effects in the resulting immune dynamics will be required to guide precision medicine and identify the 'right' patient for combinatory therapeutic intervention.

This box summarizes key points contained in the article.

important signals for B cell maturation and induction of T-effector cell functions.

Over the last 30 years, a wide range of sepsis clinical trials targeting immunity have been undertaken, following promising results reported in animal models [4]. However, these results failed to translate in a clinical setting which has raised many unanswered questions, including the validity of animal models, consideration of patient heterogeneity, and interventions that are applied too late for reversing the disease course or fail to account for the multifactorial nature based on a single therapeutic target [2,4,12–15].

Currently, high acuity physiologic parameters are used to stratify an at risk population, assuming the resultant mortality will be high, and fail to take into account the heterogeneity within the groups, including the patients molecular, cellular and genetic traits, comorbidities, and preferences for care [2,12]. The consequences of this practice are two-fold, first the inclusion of patients that will not benefit from treatment (the very frail) and second an absolute requirement for a much larger sample size to compensate for patient heterogeneity.

We contend that there is an undeniable need for a completely new approach to sepsis research and medical treatment. New systems biology methodologies are beginning to help better delineate disease pathways and patient stratification; however, a systems medicine approach enabling precision diagnostics and treatment is lagging behind.

Here, we will not cover in detail the many emerging systems biology investigations but will highlight key areas with a particular focus given to sepsis target validation for biologic therapeutics with emphasis on the possibility of repurposing drugs used for complement and immune checkpoint targeted therapies. We first discuss the complement system followed by immune checkpoint inhibition and highlight the use of host-directed pathway modeling for precision combinatory therapy.

2. Complement system

The complement system is one of the first line responders to infection orchestrating defense and host protection pathways from the innate to the adaptive immune systems [16–18]. Although it is primarily perceived as a host defense mechanism, it plays a much broader functions in immune surveillance and homeostasis [16,18,19]. However, aberrant activation of the complement system can cause tissue damage and organ failure [20,21]. The three interconnected activation pathways (CP, LP, and AP) are triggered immediately after encountering a pathogen by **pattern recognition molecules (PRMs)**. These three pathways all converge on the activation of C3 by C3 convertases, leading to the release of the C3 split products, C3a and C3b [22]. C3b participates in the formation of C5 convertase, which activates C5 to C5a and C5b, the latter initiating formation of the membrane attack complex (MAC). Both C3a and C5a are **anaphylatoxins** that critically promote acute inflammation, including recruiting and activating leukocytes, endothelial cells and platelets, as well as inducing platelet aggregation, smooth muscle contraction, capillary leakage and, potentially, anaphylactic shock [23–25]. The amplitude and duration of complement activation impacts downstream immune intensity at multiple levels.

2.1. Pattern recognition molecules (PRMs)

For detection of tissue damage or microbial infection, immune cells express a set of receptors known as PRMs, which recognize pathogen-associated molecular patterns (PAMPs) expressed by invading and innocuous microorganisms alike [26,27].

PRMs can be divided based on their location into cell associated and fluid phase molecules [28]. The latter function as the ancestors of antibodies and have a variety of roles, including complement activation, opsonization, agglutination, neutralization and regulation of inflammation [29–32]. Soluble PRMs include lectins of the ficolin, collectin and pentraxin (PTX) families and are expressed by different cell types including myeloid, epithelial and endothelial cells [28,33–36].

2.2. Lectins and C1q

The members of the lectin family have two common structural characteristics, a collagen-like extended triple helix structure coupled to a compact recognition structure [34]. The latter defines the complement proteins as C-type lectins (Mannose Binding Lectin (MBL), Collectin-10 (CL-10), and Collectin-11 (CL-11)) that express a carbohydrate recognition domain (CRD) or ficolins (ficolin-1, ficolin-2, and ficolin-3) that have a C-terminal fibrinogen-like domain. The effector functions of collectins and ficolins are mediated via a set of proteases (MASP-1, MASP-2, and MASP-3) [37]. All three ficolins are able to forming complexes with MASPs to generate LP-activating complexes, though with varying degrees of efficiency [34].

2.3. Pentraxins

Pentraxins are a superfamily of phylogenetically conserved proteins divided into short and long pentraxins. The first

group includes C-reactive protein (CRP; a widely measured nonspecific inflammatory biomarker) and serum amyloid P (SAP), while PTX3, PTX4, neuronal pentraxin 1 (NP1) and NP2 belong to the latter group [27,33]. PTXs interact with complement activating PRMs and regulatory molecules.

CRP was the first PRM identified, as an antibody-like molecule recognizing the C-type polysaccharide of pneumococcus, in the 1930s[32]. Subsequently SAP was identified through homology to CRP (amino acid sequence identity of 51%) [38]. Both CRP and SAP are major acute-phase reactants in humans, with low basal levels that increase markedly during the acute phase response [33]. For these reasons CRP has been extensively used clinically for over half a century as a nonspecific systemic marker of infection, inflammation, and tissue damage [33].

Regarding long pentraxins, PTX3 is the most well studied and has served as a tool to study humoral innate immunity [32]. PTX3 has complex roles in pathophysiology that range from essential homeostatic functions, to defense against infectious agents, tissue repair and regulation of carcinogenesis [39,40]. Serum PTX3 levels have been associated with sepsis severity and mortality [41–43]. PTX3 can be released by a several cell types, including neutrophils and activated endothelial cells [44]. It recognizes and binds pathogens, leading to the activation and modulation of the complement system [45,46].

2.4. C1q

C1q has a similar structure and function to collectins; it comprises a collagen-like stalk or six intertwining chains that end in six globular heads that are the antibody (and other ligand) recognition domains. There are numerous receptors for C1q on a variety of cell types, suggesting direct roles in opsonization and other processes, but for complement activation, C1q must bind its effector molecules C1r and C1s to form the C1 complex. The classical and lectin pathways respectively are activated when C1q and MBL/ficolins bind to an activating structure. C1q also has important roles in maintaining immune tolerance via labeling and facilitating clearance of apoptotic cells, in phagocytosis of bacteria, and in neutralization of viruses. Deficiency of C1q is associated with autoimmune disease and increased susceptibility to infections [21].

2.5. Anaphylatoxins

The two anaphylatoxins generated through complement activation (C3a and C5a) interact with their receptors expressed on various cells, thereby inducing changes characteristic of an acute inflammatory response and are further suspected to act in the intracellular space to shape T cell fates. C5a is a potent agonist of myeloid cells which express high levels of C5aR. Research over the past three decades has shown that C5a has an important role in acute inflammatory diseases and in sepsis in particular [47]. There is now a much more in-depth understanding of the molecular and cellular mechanisms involved in C5a-induced harmful effects in sepsis. C3a interacts with C3a receptors (C3aR) on several cell types, thus promoting degranulation of basophils and mast cells, which causes edema and constriction of smooth muscle, especially in the gut and upper airways of the lungs [48]. Intracellularly, activated C3 may act as a 'chaperone' that guides the processing of an apoptotic cargo, likely modulating T cell responses to self-antigens displayed on dying cells [49]. Further, while little is known about the intracellularly complement system links between cellular metabolism during immune cell homeostasis and effector functions have been discussed [50].

2.6. Complement regulators in sepsis

The importance of complement system regulation is underscored by the large number of molecular players identified (Table 1). Malfunctioning complement regulation and deficiency of particular regulators acting early in the cascade can result in both host cell damage and accumulation of immunological debris. Conversely, tumor cells and pathogenic microorganisms can over-express or hijack host complement regulators and mimic the protective properties of the host organism, thus escaping complement surveillance, resulting in unrestricted growth and infections. Accordingly, in sepsis, complement can be both an asset and a liability. It acts as an asset in the defense against pathogens, by inducing opsonization and direct killing by the MAC, and by triggering inflammatory responses through C3a and C5a and its receptor [23]. While these activation products are not necessarily the initiating factors that lead to harmful effects, they are responsible for promoting and perpetuating inflammatory reactions [24]. For example, signaling of C5a receptors (C5aR) on phagocytes (neutrophils, macrophages) is as an important contributor to multiorgan dysfunction, apoptosis, deterioration of the coagulation/fibrinolytic system and contractile dysfunction of cardiomyocytes in sepsis [51–53]. Also notable, is the role of C3 activation pathways in promoting the development of myeloid derived suppressor cells (MDSCs) that are elevated in sepsis and contribute to neutrophil and T cell suppression [54,55].

Table 1. Complement regulators and receptors.

Regulator (alternative name)	Acts on
Soluble regulators	
Factor H	Alternative pathway
FHL1	Alternative pathway
Properdin	Alternative pathway
Carboxypeptidase N (anaphylatoxin inactivator)	Classical pathway and lectin pathway
C4BP	Classical pathway and lectin pathway
C1INH	Classical pathway and lectin pathway
CFHR1	Alternative pathway
Clusterin (SP-40,40; apolipoprotein J)	Terminal pathway
Vitronectin (S-protein)	Terminal pathway
Surface bound regulators	
CR1 (CD35)	C3 convertase
CRIg (VSIG4)	C3 convertase
CD46 (MCP)	C3 convertase
CD55 (DAF)	C3 convertase
CD59	MAC assembly
Receptors for complement effector proteins	
C3aR	C3a
C5aR (CD88)	C5a
C5L2	C5a
C1qR (CD93)	C1q
SIGNR1 (CD209)	Classical pathway

Fluid-phase complement regulators target both host and non-host surfaces and act at multiple levels of the complement cascade [56]. For instance, C1 inhibitor (C1INH) inhibits the CP and LP of the complement system by neutralization of C1r and C1s or MASP activities and is the main inhibitor of the contact phase system by inhibition of factor FXIIa, kallikrein, and FXIa [57].Due to the anti-inflammatory properties of C1INH, it has been considered as a potential therapy to treat inflammatory diseases such as sepsis [58]. Properdin is the only known positive regulator of complement activation. A serum protein, it increases the production of complement activation products in the alternative pathway by binding and stabilizing the convertase complex, C3bBb [59]. In sepsis patients, properdin concentrations at ICU admission were decreased in non-survivors of sepsis, suggesting that Properdin may be used as a predictive marker of outcome in the initial stage of sepsis. Factor H is a fluid phase negative regulator of amplification through the alternative pathway [56].

3. Targeting the complement pathways in sepsis

In humans complement plays a crucial role for the initiation and progression of sepsis and sepsis associated multiple organ dysfunction syndrome (MODS). Hence, we consider targeting complement proteins or molecules involved in complement activation as representing an early innate-immune targeting approach. As previously mentioned, the C5a/C5aR axis is strongly correlated with disease severity and mortality in sepsis. Keshari et al. tested RA101295, a 2-kDa macrocyclic peptide inhibitor of C5 cleavage, in an *in vivo* baboon model of *Escherichia coli* (*E. coli*) sepsis and concluded that treatment was associated with significantly improved survival, reduced inflammation and coagulopathy, as well as significantly improved organ function compared to controls, suggesting improvement of sepsis-induced MODS [60]. Notably, this baboon model promisingly shows the potential impact of complement blockade up to 36 hours after initiation of sepsis. Whether this holds in humans remains open and may only translate for bacterial infections acquired in the ICU.

In another baboon sepsis model study, a different group assessed the effect of systemic blockade of C3 using compstatin. They showed reduced complement activation, sepsis-induced coagulopathy and preserved anti-coagulatory features of the endothelium. C3 inhibition also improved hemodynamics and heart function and reduced biochemical damage markers of the kidney and liver, indicating protective effects in sepsis-induced MODS [52].

With regard to applicability in the clinical setting, research has shown that the inhibition of C5 activation by the inhibitory antibody eculizumab [61], might be compromised in the context of sepsis due to the overwhelming activation of the system and the interwoven nature of the complement cascade [9,10,62]. Furthermore, other serine proteases such as elastase, trypsin or thrombin, increased in tissues in sepsis, can in a redundant manner cleave and activate C5 and produce C5a [16,24,53]. For these reasons, a C5a-blocking rather than C5 blocking approach has been favored as a targeted approach in sepsis [63,64]. Blocking C5a in experimental models of sepsis has been shown to produce positive results [47]. Indeed, earlier studies in the 1980s, using rabbit polyclonal antibodies to inhibit C5a in a primate model of sepsis induced by infusion of live *E. coli*, indicated that C5a blockade could significantly attenuate acute sepsis induced lung injury and failure [65,66]. Likewise, the blockade of C5a with antibodies in rats and pigs was shown to be highly effective in diminishing severity of sepsis and improving outcome [67–72]. C5a/C5aR targeted drugs such as IFX-1, Avacopan and ALXN1007, have shown potential for therapy of a wide panel of diseases, including sepsis [73,74].

Plasma-derived C1INH was developed for treatment of hereditary angioedema, caused by a partial deficiency of C1INH. Administration of C1INH in septic baboons had a beneficial effect on sepsis progression, via inhibiting complement activation and reducing cytokine release [58].

3.1. Clinical trials

Over the years, several complement interventions have been tested in preclinical models of sepsis in nonhuman primates with positive results as noted above [60,75]. However, few have entered human clinical trials to date and, like many other monotherapy approaches in sepsis, none have to date shown sucess [76,77]. While the precise reasons for failure are unclear, these interventional trials failed to account for the dynamic behavior of the pathway and the relative levels of components. For example, an important consequence of complement activation, as with all excitable systems, is a period of refractoriness post-activation and this period therefore may represent an unregulated state of the system. It is also notable that complement depletion often occurs during sepsis [11,70,71,78]. In this connection, a prospective observational study revealed that depletion of C3 is associated with poor prognosis in severe abdominal sepsis involving dysregulated coagulation and increased susceptibility to infections [11].

In regard to interventional trials, there have been two attempted so far. One study utilized C1INH in a double-blind randomized placebo-controlled trial in trauma patients with a femur fracture (CAESAR; NCT01275976); however, this was terminated early due to challenges in recruitment [77]. The second trial used a monoclonal antibody against C5a, to prevent septic organ dysfunction (CIENS; NCT02246595), the outcome of this study is yet to be made available. It should be noted that there remain concerns for potential side effects of C5a blockade in compromising its neuroprotective effects [79,80]. Notwithstanding these complications there remains an abundance of evidence that complement is activated or dysregulated in the human disease and is therefore perhaps the most compelling reason to maintain exploring complement blockade.

Critically, sepsis is multifactorial disease involving many immune and metabolic pathways. Accordingly, just targeting one pathway may not in itself be sufficient for an intervention therapy. The complement pathway represents an upstream early acute response pathway and it could be that, further downstream, other immune homeostasis pathways should

also be taken into consideration. Key downstream immune modulatory therapeutics could involve inhibitors of inflammatory cytokines, such as anti-TNF, anti-IL1, however in large multicentre randomized control trials these approaches have also failed as monotherapies. Another and perhaps more central homeostatic link between the innate and adaptive arms of the immune system is via immune-check point control; this describes the co-stimulatory and co-inhibitory pathways of communication between myeloid antigen presenting cells and adaptive immune T-cells. In this connection, it has recently been demonstrated that opsonization of apoptotic cells by C1q induces an increased expression of the immune checkpoint regulators Programmed Death-Ligand 1 (PD-L1) and Programmed death-ligand 2 (PD- L2), and reduced CD40 expression at the surface of macrophages [81].

4. T cell dysfunction and immune checkpoint control in sepsis

4.1. Co-stimulatory and Co-inhibitory pathways

The innate and adaptive arms of the immune system physically communicate through bi-directional signaling via the immunological synapse. This exchange is tightly regulated by a large array of co-signaling molecules that can act as stimulators and/or inhibitors [82]. These key regulators serve a central hub for regulating the state of immune reaction termed immune checkpoint control. The immune-check point controls are crucial for the activation and resolution of an immune response and have critical roles in the maintenance of self-tolerance, preventing autoimmunity and protection from damage during infection. The response of the immune system in severe sepsis is characterized by a dysfunctional T-cell inhibitory state and prolongation of this state is thought to be a contributing factor for sepsis-induced mortality and morbidity [83–85]. In particular, and similar to many cancers, there is a dominance of co-inhibitory over activating receptors, expansion of suppressive cell types, immune cell depletion, T cell dysfunction, and induction of inhibitory ligands on both antigen presenting cells and tissue parenchymal cells [86].

T cell dysfunction ultimately culminates in apoptosis of the cell and is considered an altered differentiation state, often characterized by features such as loss of effector functions, continuous upregulation of several cell surface inhibitory receptors, downregulation of co-stimulatory receptors, reduced production of cytokines (IFN-γ, IL-2, TNF-α), altered expression of key transcription factors, and metabolic derangements [87].

During normal immune activation response, inhibitory receptors are transiently expressed in functional T cells, however a continuously higher expression is a hallmark of T cell dysfunction [87]. There are well over 160 characterized co-inhibitory and co-stimulatory molecules reported to date. Notably, dysfunctional T cells are known to express a range of cell surface inhibitors (Table 2 and Table 3), and the higher the frequency of co-inhibitors expressed by T cells, the more severe the dysfunction [88].

Co-stimulatory and co-inhibitory pathways are now recognized as the main component in modulating host response in acquired diseases ranging from cancer to infectious diseases [109]. While co-stimulation is indispensable for boosting and molding the initial response following signaling through the antigen receptor, inhibitory pathways are also essential for modulating the immune response by controlling autoreactivity and immunopathology [87,109,110].

One of the best characterized inhibitory pathway is mediated by PD-1 in response to binding PD-L1 and/or PD-L2 and helps elucidate some of the mechanisms by which inhibitory receptors may control T cell function: sequestering of target receptors or ligands and/or preventing the optimal formation of microclusters and lipid rafts; modulation of intracellular mediators; induction of inhibitory genes [110,111]. However, co-stimulatory receptors also play crucial roles in T cell dysfunction. The loss of adaptor molecules can lead to the desensitization of co-stimulatory pathways thus serving as a mechanism of T cell dysfunction during infection.

4.2. Existing Immune checkpoint mediators implicated in sepsis

The immune system response in sepsis exhibits multiple states of immunosuppression that range from a variety of innate and adaptive processes. Notably, immune checkpoint co-inhibitors such as PD-1, PD-L1, CTLA-4 and BTLA display an upregulation on immune cells during sepsis and have been hypothesized to be among the key contributors causing sepsis-induced immune cell dysfunction [112].

The role of expression levels of these inhibitors in sepsis has been extensively researched both in pre-clinical models and clinical trials and is summarized in Tables 2 and 3. The PD-1/PD-L1 axis is the most well studied immune checkpoint interaction in sepsis immunopathology and has been shown to be involved in intestinal and liver injury during sepsis. However, additional studies are required to reveal the exact role of PD-L1 in various organ injuries such as kidney, brain, lung, heart and others during sepsis [23,82,113–117].

A comprehensive and first systems biology analysis highlighting immune checkpoint co-stimulatory and co-inhibitory pathways described the clinical investigation of neonatal sepsis [118]. Here a systematic profiling of all known (>160) immune checkpoint regulators identified 41 immune checkpoint regulators statistically altered in expression levels in blood-culture positive sepsis patients. Most notably, co-stimulatory molecules such as CD28, ICOS, CD40L, CD27, CD2 were significantly down-regulated in expression, while co-inhibitory genes such as PDL1, LGALS9, CD85A (LILRB3), CD85K (LILRB4) were significantly up-regulated in expression (Figure 1) (Table 3). It is worth noting that the LILRBs have been shown in mice not to be involved in hematopoiesis or normal development [119] and therefore represent ideal potential targets for treating sepsis in early life. It remains to be determined whether these molecules are involved in older populations or exclusive to neonatal sepsis.

Table 2. Pre-clinical studies showing alterations in expression of immune various checkpoints during sepsis.

Immune checkpoint	Alteration in expression	Location	Model	Reference
PD-1	Increased	Peritoneal macrophages	CLP	Huang et al., 2009 [89]
		Splenic T and B cells and monocytes	CLP	Zhang et al., 2010 [90]
		Kupffer cells	CLP	Hutchins et al., 2013 [91]; Wang et al., 2016 [92]
		CD4+ and CD8+ splenic T cells	CLP	Brahmamdam et al., 2010 [93]; Chen et al., 2017 [94]
			Candida fungal sepsis, and Two hit model (CLP + fungal sepsis)	Chang et al., 2013 [95]
		Splenic CD4+, NKT and NK cells	Two hit model (CLP + fungal sepsis)	Shindo et al., 2017 [96]
	No Change	Splenic T cells	Burn wound sepsis (Pseudomonas aeruginosa)	Patil et al., 2016 [112]
PD-L1	Increased	Splenic B cells and monocytes	CLP	Zhang et al., 2010 [90]
		Liver tissue	CLP	Zhu et al., 2013 [97]
		Liver sinusoidal endothelial cells	CLP	Hutchins et al., 2013 [91]
		Increased PD-L1 on macrophages, monocytes, T and Natural Killer T (NKT) cells and neutrophils	CLP	Huang et al., 2014 [98]
		intestinal epithelial cells	CLP	Wu et al., 2016 [99]
		Splenic dendritic cells, macrophages and monocytes	Burn wound sepsis (Pseudomonas aeruginosa)	Patil et al., 2016 [112]
		CD4+ cells, NKT and Natural Killer (NK) cells	Two hit model (CLP + fungal sepsis)	Shindo et al., 2017 [96]
CTLA-4	Increased	Splenic CD4+ and CD8 + T cells	CLP	Inoue et al., 2011 [100]
BTLA	Increased	Macrophages, monocytes, dendritic cells and neutrophils in peritoneum	CLP	Shubin et al., 2012 [101]
		Splenic CD4+ and CD8 + T cells	CLP	Chen et al., 2017 [94]
		Peritoneal macrophages and dendritic cells; and in tissues- kidney, lung, liver and spleen	Two hit model (hemorrhage + CLP)	Cheng et al., 2016 [102]
HVEM	Increased	Macrophages, monocytes, dendritic cells and neutrophils in peritoneum	CLP	Shubin et al., 2012 [105]
2B4	Increased	Splenic CD4+ and CD8 + T cells	CLP	Chen et al., 2017 [94]

5. Targeting immune checkpoint pathways in sepsis

The levels of inhibitory immune checkpoint receptors such as PD-1, CTLA-4 and BTLA are increased during sepsis and are important contributors to sepsis-induced immune cell dysfunction [85,87,112]. The current view is that these inhibitory immune regulators hinder the immune responses needed to clear invading pathogens, or perhaps more importantly prevent the resolution phase of the immune response. However, it is possible that depleted T-cells may confer beneficial effects [120]. Thus, while therapies targeting immunosuppression are currently of great interest for the development of new sepsis treatments, caution in this enthusiasm should be noted until we understand better the precise role and function of T-cell subsets in sepsis. This is especially the case for tissue versus systemic T-cells. In principle, therapeutic applications of monoclonal antibodies of decoy receptors for blockade of co-inhibitory pathway antagonists would lead to the augmentation of T cell responses. This strategy could be employed to promote T cell immunity in sepsis, although in certain models tissue resident T-cells but not infiltrating T-cells appear less affected during sepsis which might impact the potentially beneficial role of anti-PD1/PD-L1 therapies [121,122]. While other models have highlighted the importance of homing to niche environments, in particular bone-marrow, for resolving T-cell homeostasis in response to systemic antigens, suggesting therapies should also account for relevant tissue localization[123].

Nevertheless, numerous pre-clinical studies using immunotherapeutic agents such as IL-7, anti-PD-1 have been able to reverse T cell dysfunction and improve survival [112]. Several pre-clinical studies have also shown that targeting PD-1 and PD-L1 during sepsis improves host resistance to infection [84]. Several experimental medicine studies have evaluated *ex-vivo* the potential therapeutic benefit of targeting the PD-1/PD-L1 axis in line with reversal of immunosuppression [9,124,125]. These investigations primarily tested anti-PD-L1 antibody upon treatment of isolated immune cells from septic patients indicating reduced T-cell apoptosis, increased T-cell IFN-γ and IL-12 levels, elevated monocyte cytokine production, as well as neutrophil and NK cell functions

6. Repurposing and combinatory therapies

In the last two decades several highly effective and specific complement therapies targeting different parts of the complement cascade (Figure 2) have been developed and introduced to the clinics, and many more are currently under development (Table 4) [126,127]. Numerous complement-related pathologies share several common factors; hence, a complement-targeting drug approved for one disease may be repurposed for different ones. However, no complement intervention strategies have been implemented to effectively address the complex immune response observed during sepsis [9,10,128], and only a select few have been used in sepsis trials (Figure 2 orange crosses). Thus, it is highly important to look at the currently available drugs as a therapeutic 'toolbox' with a diverse panel of possible candidates for use in sepsis therapies. Besides complement activation products, such as anaphylatoxins, other molecules including CRP and PTX3 play crucial roles in contributing to complement dysregulation in sepsis and trauma, thus profoundly influencing secondary outcomes. Therefore, it is possible that they have potential as both sepsis diagnostics and therapeutic targets.

Table 3. Clinical studies showing alterations in expression of various immune checkpoints during sepsis.

Immune checkpoint	Alteration in expression	Location	sample size	Study type	Correlated outcome	Reference
PD-1	Increased	CD4 + T cells	64 Patients	Prospective study	Impaired lymphocyte proliferation	Guignant et al., 2011 [103]
			14 Patients	Prospective study	Decreased costimulatory ICOS and CD28	Chen et al., 2017 [94]
		CD8 + T cells	43 Patients	Prospective study	Increased rate of secondary infections	Chang et al., 2014 [124]
		CD4+ and CD8 + T cells	19 Patients	Prospective study	Increased apoptosis	Zhang et al., 2011 [104]
			40 patients	Postmortem study	Decreased IL-7 receptor alpha on splenic T cells	Boomer et al., 2011 [85]
		Monocytes	64 Patients	Prospective study	Increased occurrence of secondary nosocomial infections after septic shock.	Guignant et al., 2011 [103]
			59 Patients	Prospective study	Increased severity of sepsis and predictor of 28 day mortality	Shao et al., 2016 [105]
PD-L1	Increased	Monocytes	64 Patients	Prospective study	Increased mortality	Guignant et al., 2011 [103]
			19 Patients	Prospective study	Decreased the ability of monocytes to produce proinflammatory cytokines *in vitro*.	Zhang et al., 2011109
			43 Patients	Prospective study	Decreased IFN-γ and Il-12 production	Chang et al., 2014 [124]
			59 Patients	Prospective study	Independent prognostic marker	Shao et al., 2016 [105]
		Lung tissue	40 patients	Postmortem study	Localized inhibition of T cells thereby predisposing to infection.	Boomer et al., 2011 [85]
		Splenic dendritic cells	40 patients	Postmortem study	Promotes a tolerogenic phenotype, resulting in T- cell suppression.	Boomer et al., 2011 [85]
			24 patients	Prospective study	Early stage of immune cell exhaustion and predisposition to nosocomial infection or poor outcome.	Boomer et al., 2012 [106]
		Suppressor neutrophils	17 patients	Prospective study	Impaired neutrophil function.	Patera et al., 2016 [125]
		NK cells	17 patients	Prospective study	Impaired NK cell function.	Patera et al., 2016 [125]
		Epithelial cells of colon		Retrospective analysis	Mediates the pathophysiology of sepsis-induced intestinal barrier dysfunction.	Wu et al., 2016 [99]
		CD4 + T cells	17 patients	Prospective study	Impaired CD4 + T cell function.	Patera et al., 2016 [125]
		Whole blood	62 patients	Prospective study	Disease severity.	Smith et al., 2014 [118]
	Decreased	CD8 + T cells	43 Patients	Prospective study	-	Chang et al., 2014 [124]
PD-L2	Increased	Monocytes	64 Patients	Prospective study	Increased occurrence of secondary nosocomial infections after septic shock.	Guignant et al., 2011 [103]
		Splenic dendritic cells	40 patients	Postmortem study	Promotes a tolerogenic phenotype, resulting in T- cell suppression	Boomer et al., 2011 [85]
HVEM	Increased	Lung tissue	40 patients	Postmortem study	Expression of important immunoregulatory proteins.	Boomer et al., 2011 [85]
CTLA-4	Increased	CD4 + T cells	24 patients	Prospective study	Early stage of immune cell exhaustion and predisposition to nosocomial infection or poor outcome.	Boomer et al., 2012 [106]
		CD8 + T cells	24 patients	Prospective study		Boomer et al., 2012 [106]
TIM-3	Increased	CD4 + T cells	24 patients	Prospective study		Boomer et al., 2012 [106]
LAG-3	Increased	CD4 + T cells	24 patients	Prospective study		Boomer et al., 2012 [106]
BTLA	Increased	CD4 + T cells	24 patients	Prospective study	Increased mortality	Shubin et al., 2013 [107]
		Plasma	101 Patients	Prospective study	Sepsis severity	Lange et al., 2017 [108]
2B4	Increased	CD4 + T cells	14 Patients	Prospective study	Decreased T cell functionality and macrophage activation	Chen et al., 2017 [94]
CD28	Decreased	Whole blood	62 Patients	Prospective study	Disease severity.	Smith et al., 2014 [118]
ICOS	Decreased					
CD40L	Decreased					
CD27	Decreased					
CD2	Decreased					
LGALS9	Increased					
CD85A (LILRB3)	Increased					
CD85K (LILRB4)	Increased					

On the other hand, co-inhibitory receptor ligand pathways are central to tolerance mechanisms; their control of innate and adaptive immunity is an emerging and promising area of study for new sepsis therapies. Immune-checkpoint inhibitors have caused a seismic revolution in the treatment of cancer showing remarkable efficacy with 100% long-term remission. Cancer is an acquired disease, similar to infection, and perhaps an underlying chronic maladapted immune response in a cancer patient may have some of level of convergence with an acute sepsis condition in the context of functional T-cell exhaustion. Defining the role of immune checkpoint regulators in sepsis should provide important insights into the new avenues of immune intervention in disease. In oncology, there is clearly a consensus to move away from monotherapies to combination therapies of immune-checkpoint inhibitors. Here, we would propose a similar strategy should be considered for sepsis. However, unlike cancer, sepsis is a result of an acute extreme systemic immune response and therefore combinatory therapy for sepsis should accountant for moderating the overactive inflammatory state. In this scenario, we propose a combination of complement and immune-checkpoint inhibitors as a promising therapeutic modality.

7. Mathematical and predictive computational models

In this section, we do not discuss the many excellent systems biology studies in sepsis that can help in target discovery. Instead, as part of a computational systems approach for precision medicine, we believe that it is critical that early consideration is given to co-developing a formal framework that can guide patient stratification and optimization of therapeutic modalities. Notably, the key mechanisms involved in the immune response to sepsis determine a complex system characterized by non-linear, time-dependent, interactions. Target validation and design of effective therapeutic interventions require us to understand, and consequently control, the dynamics characterizing the onset and late stages of sepsis. The language of mathematics can describe, in an elegant and precise manner, the complex interactions underpinning the time course of the dynamics. This description, formalized in a mathematical model, and parameterized on an individual patient, allows testable predictions on the behavior of an individual's response to a particular treatment.

Characteristically, in the immune system we can identify a duality in mechanisms of control, where key regulators orchestrate an immune response characterized by stimulatory and inhibitory effects acting in a reciprocally balancing fashion to ensure a measured response, limited in time. For example, in infection activation of the complement pathway triggers neutrophil activation (A) which leads to an amplification of the inflammatory response and T-cell activation (I) but can also cause the expansion of a subset of myeloid derived suppressor cells (MDSCs) that are anti-inflammatory and suppress neutrophil activation. When we formalize this system, specifying a negative feedback loop between A (the activator or response) and I (the antagonist or counter-response), together with upstream production and clearance, we obtain a minimal model, depicted in Figure 3 and described by the following set of ordinary differential equations:

$$\begin{cases} \frac{dA}{dt} = \lambda - \mu A - \beta A I \\ \frac{dI}{dt} = \tau A I - \sigma I \end{cases} \quad (1)$$

where t is time, $\lambda = \begin{cases} \lambda_H & health \\ \lambda_I & infection \end{cases}$, $\mu = \begin{cases} \mu_H & health \\ \mu_I & infection \end{cases}$, with $\lambda_I > \lambda_H$ and $\mu_I < \mu_H$,

i.e. we assume that neutrophil activation and half-life are increased in infection, compared to healthy baselines.

This simple model can describe a number of different states, depending on the parameter regime. Analysis of the equations reveals the existence of two steady states (unchanging in time),

$$\mathrm{P}: \begin{cases} \mathrm{A}^*_\mathrm{P} = \frac{\sigma}{\tau} \\ \mathrm{I}^*_\mathrm{P} = \frac{1}{\beta}\left(\frac{\tau\lambda}{\sigma} - \mu\right) \end{cases} \text{ and } \mathrm{Q}: \begin{cases} \mathrm{A}^*_\mathrm{Q} = \frac{\lambda}{\mu} \\ \mathrm{I}^*_\mathrm{Q} = 0 \end{cases} \quad (2)$$

where the * notation indicates steady state values for the cell populations.

Additionally, we find a threshold $\bar{\sigma} = \frac{\tau\lambda}{\mu}$, below which P is stable, and above which Q is stable. Figure 4, illustrates the concept of stability for steady states. Because of noise present in nature, unstable steady states cannot be observed: any perturbation is amplified over time driving the biological system away from that state.

Therefore, we expect that – after an initial transient phase – the dynamics will always drive the system to a stable steady state. Crucially, an infection triggering the immune response determines a change in the parameter regimes (in this example λ and μ), ultimately shifting both the threshold $\bar{\sigma}$, and the steady state values. Note, in fact, that the T cell population at P and the neutrophil population at Q attain values that will vary in health compared to infection.

From such models we can identify distinct parameter regimes, corresponding to possible transitions that can occur from health to disease (Figure 5). In this example the model predicts that an infection can trigger three possible outcomes, corresponding to three distinct regimes, with post-infection: increased T cells ($\sigma < \frac{\tau\lambda_H}{\mu_H}$), increased neutrophils ($\sigma > \frac{\tau\lambda_I}{\mu_I}$), or both increased neutrophils and T cells ($\frac{\tau\lambda_H}{\mu_H} < \sigma < \frac{\tau\lambda_I}{\mu_I}$).

This is a powerful example of how mathematical modeling can rigorously describe complex non-linear systems of interactions and obtain predictions which can be ultimately utilized to extract guidelines on possible interventions. For instance, in the above system we can envision a clinical intervention which aims at shifting the patient's specific parameters toward the required steady state regime, i.e. the required level of activation and inhibition. In this particular example, this can be accomplished by acting on the T cell population, through the use of checkpoint inhibitors that alter their clearance σ, or their recruitment by neutrophilsτ. Alternatively, we could intervene to modulate complement activation thereby altering neutrophil inflammatory response λ, or their clearance μ. Notably, the model predicts that alteringn β alone (checkpoint inhibition by T cells), will not shift the system to a different regime of stability, i.e. it will not change the qualitative asymptotic behavior of the system. Additionally, if a patient is in the regime $\sigma > \frac{\tau\lambda_I}{\mu_I}$, altering β will not change the quantitative asymptotic behavior of the system altogether, because the system will always fall in steady state Q. This model can further be used to model combinatory treatment regimes.

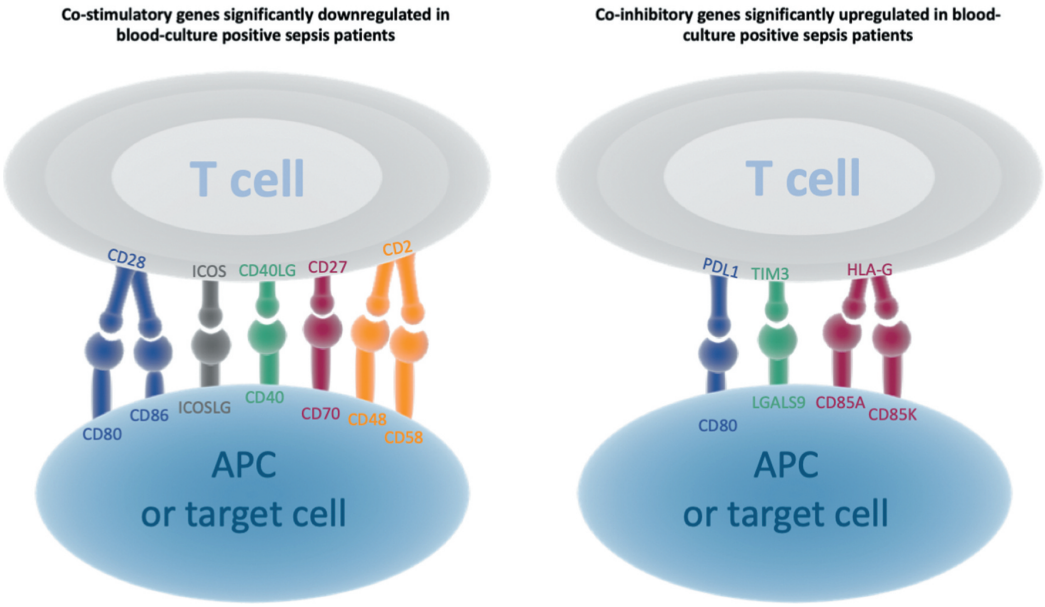

Figure 1. Checkpoint regulators on immune cells.[118]

Nevertheless, this exemplar model elegantly shows how multiple combined therapies need to be considered and can be 'tuned' (personalized) in terms of timing of treatment and combination of treatment for a given patient.

Generally, the immune response is a collection of mechanisms acting as dualities, where a process, cell type, or mechanism is accompanied by its own antagonist in a negative feedback loop. The resulting dynamics are non-trivial. The basic system of interactions considered above illustrates the potential for acting on the tunability characteristic of such systems. Employing the rigorous language of mathematics to build a minimal description of the interactions, we can highlight the first order effects in the resulting dynamics and identify targets for intervention. This modeling approach prioritizes the retention of key interactions as identified by the current experimental evidence. It is, therefore, inherently subject to continuous refinement as a new understanding emerges from experimental investigation and model prediction.

8. Expert opinion

8.1. Final remarks

Sepsis is at the same time one of the best known yet most poorly understood medical diseases. It is a common and lethal condition, and even though outcomes have improved, mortality remains high. There is evidence in sepsis, that activation of the complement system results in excessive production of anaphylatoxins, which prompt a series of events leading to septic shock, multiorgan failure, and lethality. Activation of sepsis in non-human primate models has been shown to occur in a biphasic pattern, the initial phase mediated by the bacteria and the later phase mediated by an endogenous mechanism possibly involving PRMs [129]. Increase of complement activation during the first phase of sepsis may relate to bacterial opsonization and is thus beneficial to the host defense response [52]. Conversely, complement activation during the second stage of sepsis via CRP, MBL or other PRMs could be a major contributor to tissue injury and death [69]. Whilst the complement system is the initial driver, immune checkpoint regulation is the 'master switch' in charge of the immune response in sepsis; development of a personalized therapeutic strategy capable of targeting patients suffering from a dysregulation of either of these two mechanisms in a timely fashion would likely lead to an improvement in the chances of survival.

In the past decades, over 100 randomized clinical trials have tested the hypothesis that immunomodulatory compounds modulating the septic response to infection can improve survival of patients with sepsis [12,130]. Clinical trials blocking C3 during the development of sepsis-caused MODS are often considered with caution or disregarded because of perceived enhanced infection risk; however, recent studies in primates have revealed that long term inhibition of C3 is potentially safe [131]. Nevertheless, these trials are still on hold and require further consideration of the impact of sepsis in cognitive functions [9]. Regarding trials using immune checkpoint regulation, despite promising results in preclinical and ex-vivo clinical trials, only one clinical study has been performed for evaluating the dose safety of anti-PD-L1 in sepsis patients. The study has been completed but results have yet to be published (ClinicalTrial.gov# NCT02576457).

However, it is now acknowledged that acute preclinical sepsis models do not represent accurately the disease progression observed in sepsis patients. It is important to acknowledge that significant differences exist between the animals used for sepsis models and humans, not only in

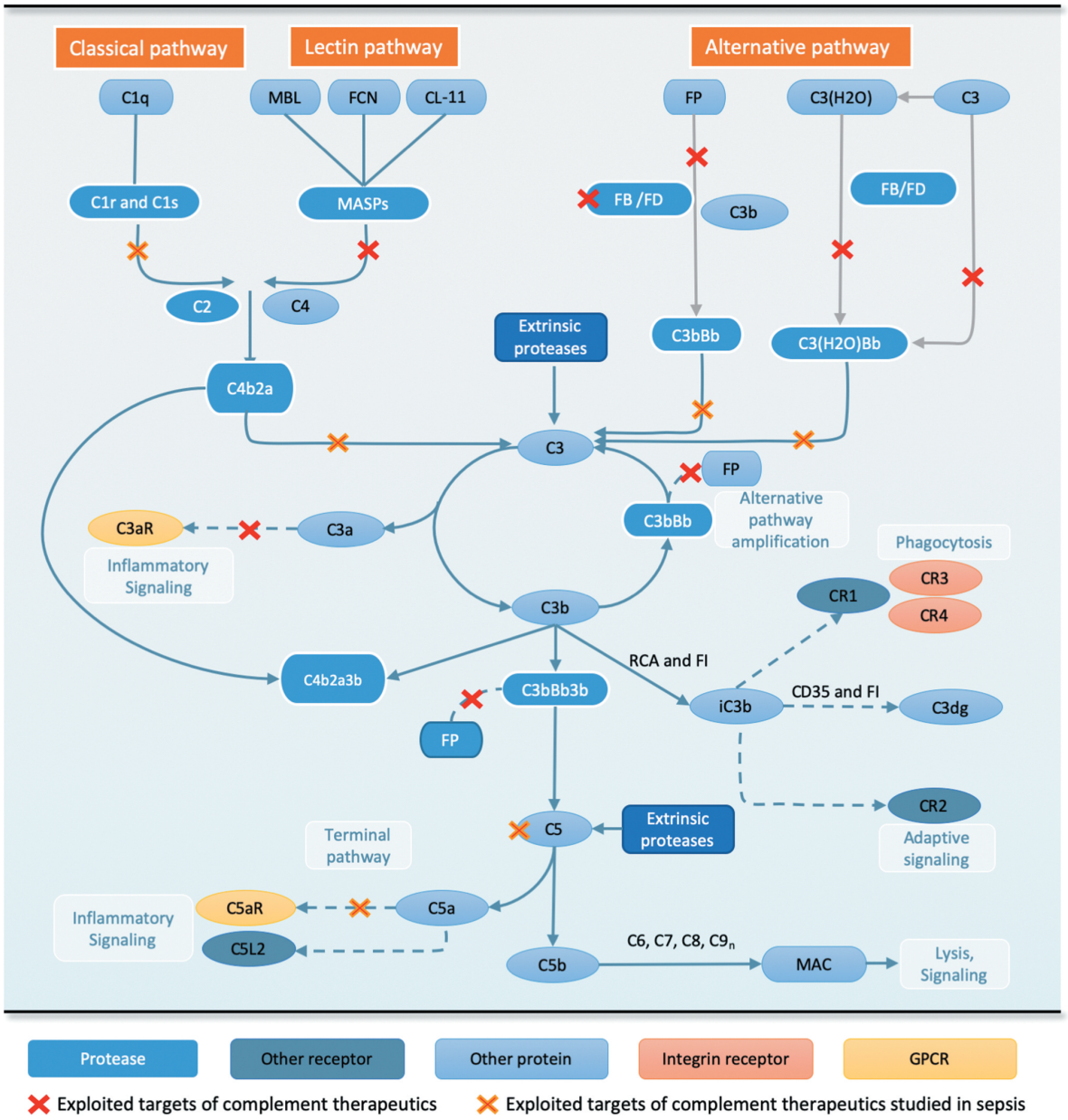

Figure 2. Simplified scheme of the complement system with presently exploited targets of complement-directed therapeutic intervention highlighting the approaches thought to be of interest in sepsis. C3(H2O), hydrolyzed C3; C1-INH, C1 inhibitor; C5L2, C5a receptor-like 2; CP, classical pathway; CR, complement receptor; FB, factor B; Fcn, ficolins; FD, factor D; FH, factor H; FP, factor P (properdin); GPCR, G protein–coupled receptor; LP, lectin pathway; MAC, membrane attack complex; MASP, mannose-binding lectin–associated protease; MBL, mannose-binding lectin.

terms of physiology but also the response to septic insult [4]. Thus, preclinical studies on novel sepsis therapies should aspire to better reproduce what is observed in the clinics by incorporating aged animals with various co-morbidities and subject to various interventions (e.g. antibiotic therapy). Additionally, computer-simulated models of sepsis can help predict how some complement therapies currently used for other diseases would impact the prognosis of sepsis patients.

We believe, sepsis therapeutics cannot target every disease status, it is important to individually evaluate the different immune stages, their relevance, and target them in a patient-specific manner. In particular, when designing therapeutic measures using complement strategies it is crucial to accurately measure the levels of the target complement factor or activation product in order to determine the exact status of complement activation, before any intervention can be carried out. This approach would allow a precise and timely intervention tailored to the progression of sepsis, for each individual patient, by inhibiting or supporting the complement system in a way that enables the immune system to counteract the negative effects of the hosts

Table 4. Targets of complement therapeutics and drugs currently under clinical trial [126]. Some drugs are being used in different trials, in those cases the phase represented corresponds to the most advanced.

Target	Drug	Conditions	Phase 1	Phase 2	Phase 3
C1r/s; MASPs	Berinert	Hereditary angioedema and organ transplant	✓	✓	✓
	Cinryze	Neuromyelitis optica, Hereditary angioedema and organ transplant rejection	✓		
	Ruconest	Hereditary angioedema	✓		
C1s	Sutimlimab	Agglutinin Disease, Cold	✓	✓	✓
C3	AMY-101	Complement Mediated Diseases	✓		
	APL-2	Paroxysmal Nocturnal Hemoglobinuria, Geographic Atrophy	✓	✓	✓
	APL-9	Coronavirus	✓		
C5	Cemdisiran	Atypical Hemolytic Uremic Syndrome, Berger Disease, Paroxysmal Nocturnal Hemoglobinuria	✓	✓	
	Crovalimab (SK59)	Paroxysmal Nocturnal Hemoglobinuria	✓		
	Eculizumab	Atypical Hemolytic Uremic Syndrome, organ transplant rejection	✓	✓	✓
	Nomacopan	Paroxysmal Nocturnal Hemoglobinuria	✓	✓	✓
	Pozelimab	Paroxysmal Nocturnal Hemoglobinuria	✓		
	Ravulizumab	Paroxysmal Nocturnal Hemoglobinuria, Neuromyelitis Optica Spectrum Disorder	✓	✓	✓
	Tesidolumab	Paroxysmal Nocturnal Hemoglobinuria	✓	✓	
	Zilucoplan	Paroxysmal Nocturnal Hemoglobinuria, Myasthenia Gravis	✓	✓	
	Zimura	Idiopathic Polypoidal Choroidal Vasculopathy, Geographic Atrophy, Macular Degeneration	✓	✓	
	ABP 959 (eculizumab biosimilar)	Paroxysmal Nocturnal Hemoglobinuria	✓		✓
C5a	IFX-1	Pyoderma Gangrenosum	✓	✓	
C5aR1	Avacopan	ANCA-Associated Vasculitis, C3 Glomerulopathy	✓	✓	✓
CR1 (Functional domains of CR1 targeted to endothelium via lipid 'tail')	Mirococept	Ischemia reperfusion injury in the kidney allograft	✓	✓	
Expression of soluble CD-59	AAVCAGsCD59	Dry Age-related Macular Degeneration	✓		
Factor B	IONIS-FB-L_{RX}	Geographic Atrophy, Age Related Macular Degeneration	✓	✓	
	LNP023	C3 Glomerulopathy, Paroxysmal Nocturnal Hemoglobinuria	✓	✓	
Factor D	Danicopan	C3 Glomerulopathy, Paroxysmal Nocturnal Hemoglobinuria	✓	✓	
	ACH-5228	Paroxysmal Nocturnal Hemoglobinuria	✓		
MASP2	Narsoplimab	Lupus Nephritis, C3 Glomerulopathy	✓	✓	✓

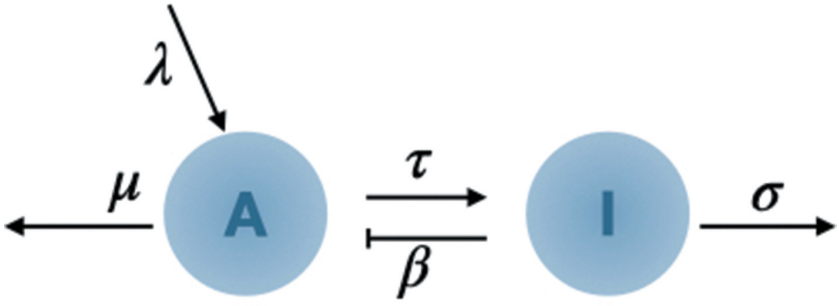

Figure 3. Example of duality mechanism in the immune system. Complement activation in Neutrophils (A) induces inflammation and activates T cells (I), but also activates inhibitory MDSCs that curtail further neutrophil activation. Additionally, we assume upstream production of neutrophils (this includes activation by complement) and clearance by apoptosis of both cell types. Annotated parameters indicate the rate of a given interaction, and are positive constants. The flat ended arrow indicates a negative interaction.

dysregulated immune response to infection. Furthermore, it is likely that combinations of several immunotherapeutic agents that target different pathways will hold significant potential for sepsis therapy [112,132,133]. Due to the variation in individual immune responses to a septic insult, combinations of immunomodulatory agents offer better odds of success than standalone therapy with any individual agent. Moreover, individual therapies could be adapted over the course of sepsis based on the temporal changes in immune responses [112,134]. However, it is not yet known what would be the best way to characterize the extent of the immune response for each individual patient. Here, we propose that validated predictive mathematical models need to be co-developed alongside therapeutics. These models, similar to modeling pharmacodynamics of drugs, minimally capture the first order dynamics of the immune response and can be parameterized to an individual.

Lastly, the burdens faced by the survivors of sepsis include long-term physical and neurocognitive impairments [135]. Studies have shown that admission to hospital with sepsis is associated with new functional disabilities, long-term cognitive decline and increased health-care use and it is possible

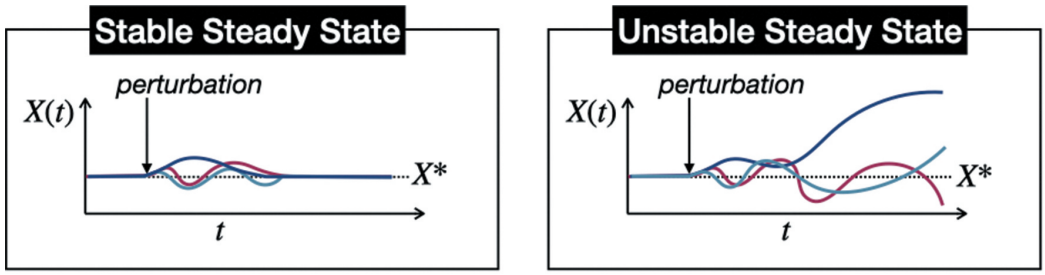

Figure 4. In dynamical systems a steady state X^* can be: i) stable, when any small perturbation resolves with time, and the system returns to the pre-perturbation value; ii) unstable, when a small perturbation results in amplifying instabilities driving the system away from the pre-perturbation value.

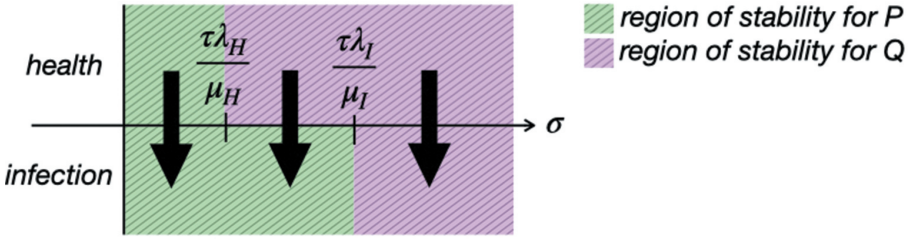

Figure 5. Parameter regimes determining different transitions from health to infection. The system is always expected to converge to the steady state which is stable for the specific condition (health or infection) and parameter values (λ, μ, τ and σ).

that targeting multiple -mechanisms might aid in addressing the underlying trajectory of the persistent inflammation endured by sepsis survivors [7,135].

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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