

A narrative review of the role of the complement system in sepsis

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Abstract

Sepsis is a common syndrome with a high mortality rate worldwide, characterized by complex physiological, pathological, and biochemical abnormalities. The complement system, an essential component of innate immunity, consists of approximately 30 proteins that undergo a series of cascading enzymatic reactions to form a membrane attack complex, leading to cell lysis. Sepsis-induced complement activation drives endothelial cells toward a proinflammatory and prothrombotic phenotype. This review highlights the complex interactions among the complement, coagulation, and inflammatory systems, examines the prognostic significance of complement activation in patients with sepsis, and discusses the potential clinical applications of complement inhibitors.

Keywords: Coagulation, Complement system, Endothelial cells, Sepsis

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.^[1] The complement system, a crucial part of innate immunity, provides early protection against infection; however, excessive complement activation can be detrimental.^[2–4] Increasing evidence indicates crosstalk between the complement system, coagulation, and inflammatory response pathways. For example, several complement components and coagulation factors share structural similarities and can activate one another.^[5] The complement split products C3a and C5a act as potent chemoattractants that recruit neutrophils and macrophages to infection sites, promoting phagocytosis. Therefore, the overactivation of these pathways contributes significantly to the pathophysiology of sepsis.^[6]

Endothelial dysfunction plays a central role in the pathogenesis of sepsis. When endothelial cells are damaged by exogenous or endogenous insults, they acquire proinflammatory and pro-coagulant properties. Complement activation contributes to this process by promoting tissue factor (TF) expression, platelet activation, and fibrinolysis inhibition. Among them, C3a and C5a act as potent anaphylatoxins that stimulate mast cells to release

vasoactive mediators, such as histamine. Notably, C5a is a strong chemokine that attracts inflammatory cells, such as neutrophils, monocytes, and eosinophils, to the activation site, leading to the release of inflammatory mediators. More importantly, the close crosstalk among the complement, coagulation, and inflammatory systems can create a vicious cycle of coagulation and inflammation, resulting in diffused microthrombi formation and, eventually, multiple organ failure.^[4, 7–9]

This review aimed to investigate the mechanisms by which the complement system induces endothelial cell injury and to explore the interactions among the complement, coagulation, and inflammatory pathways. Finally, we highlight the prognostic implications of complement activation in patients with sepsis and discuss the potential clinical applications of complement inhibitors.

Method

A systematic literature search was conducted to identify studies related to the complement system and sepsis using the PubMed database. The search strategy combined MeSH subject terms and free-text keywords, including “Sepsis,” “Complement System,” “Inflammation,” “Therapy,” and “Biomarkers.” The time frame covered January 2015 to June 2025. The inclusion criteria focused on clinical research studies, observational research, and review articles. Relevant references were further identified through citation tracking to ensure comprehensive coverage.

Complement system

The complement system is a key component of the host's innate defense, composed of multiple plasma and membrane-bound proteins, primarily C1–C9, along with several regulatory and activation molecules. Upon injury or pathogen invasion, the complement system is activated through a cascade of enzymatic reactions leading to the formation of the membrane attack complex (MAC), which directly lyses pathogens and damaged tissue cells. Complement activation occurs via 3 pathways: classical, lectin, and alternative. Among these, the lectin pathway plays a crucial role in sepsis and trauma.^[10–12] This pathway is initiated by pattern-recognition molecules (PRMs), including

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mannose-binding lectin (MBL), collectins (CL-10 and CL-11), and ficolins (ficolin-1, -2, and -3). Complement activation begins when PRMs bind to specific molecular patterns exposed on pathogens or damaged tissues, such as pathogen-associated molecular patterns and damage-associated molecular patterns.^[13, 14] MBL-associated serine proteases (MASP-1 and -2) initially trigger the activation of the lectin pathway, then cleave C4 and C2 to form C3 convertase (C4b2a).^[15] Furthermore, collectins and ficolins use MASP to activate the complement system.^[13] C3 is subsequently decomposed into C3a and C3b by the action of C3 convertase. C3a is released into the free liquid phase, and C3b forms a C5 convertase (C4b2a3b) with C4b2a. C5 is then cleaved by C5 convertase to form C5a and C5b.

C5a and C3a are potent inflammatory mediators that act as chemoattractants and cell activators that form an effective chemotactic gradient and recruit neutrophils and macrophages to the infection site to promote pathogen phagocytosis.^[15–17] Meanwhile, C5b recruits C6–C9 to activate C5b-9 formation, which lyses target cells. C3b deposition enhances opsonization, facilitating recognition and phagocytosis by macrophages and neutrophils (Fig. 1).^[18]

Complement levels are determined by the balance between synthesis and consumption. In humans, the liver serves as the primary site of complement protein biosynthesis, although adipose tissue and resident myeloid cells, such as macrophages, also contribute to local complement production. Conditions such as cirrhosis, hepatic failure, and malnutrition can reduce circulating complement proteins. Conversely, several complement proteins, including C3 and C4, act as acute-phase reactants and can increase by up to 50% in response to systemic inflammation.^[19]

Endothelial cells and the complement system

The vascular endothelium is the innermost layer lining the walls of arteries, capillaries, and veins, consisting of a single layer of endothelial cells. These cells serve as a barrier and function as secretory units, playing a crucial role in regulating platelet adhesion and aggregation, leukocyte activation, adhesion, and migration.^[20] During sepsis, various stimuli induce proinflammatory and proangiogenic responses in endothelial cells, leading to further immune dysregulation. According to the “endothelial activation theory,” activation of the complement system leads to 2 distinct types of endothelial dysfunction: (1) release of inflammatory cytokines that activate inflammatory pathways and (2) release of hemostatic factors that promote the microthrombus pathway.^[21] Consequently, increasing attention has been directed toward the role of the complement system in the pathogenesis of sepsis.

The complement system plays a pivotal role in driving phenotypic changes in endothelial cells during sepsis. In response to pathogenic invasion, endothelial cells adopt proapoptotic, proinflammatory, proadhesive, and procoagulant phenotypes to restrict bacterial dissemination. The formation of the MAC is a critical defense mechanism against bacteria; however, excessive MAC deposition on endothelial membranes can contribute to endothelial dysfunction. Activation of endothelial cells and induction of procoagulant and proinflammatory changes by the MAC are mediated indirectly through the transcription, production, and secretion of interleukin (IL)-1 α . Stimulation of endothelial cells by pore-forming proteins, such as the MAC, triggers calcium-dependent activation of calcineurin and binding of nuclear factor kappa-B to the IL-1 α gene promoter, leading to highly specific transcriptional activation. IL-1 α subsequently

induces endothelial activation via auto- or paracrine signaling. Therefore, complete endothelial activation by the complement system occurs primarily in damaged vascular segments directly targeted by the complement system, where blood flow is reduced. Under physiological conditions, IL-1 α is rapidly cleared, preventing endothelial activation.^[22, 23]

The vascular endothelial surface is coated with a glycocalyx, which is critical for regulating cell adhesion, preventing thrombosis, maintaining vascular permeability, and sensing mechanical stress. Oxidative stress represents a major mechanism underlying glycocalyx degradation, compromising its structural integrity both directly and indirectly through activation of enzymatic degradation pathways involving heparanase, hyaluronidase, and matrix metalloproteinases. Complement activation further contributes to glycocalyx breakdown. Heparan sulfate, a vital component of the glycocalyx of endothelial cells, decreases significantly in patients with renal thrombotic microangiopathy and is closely associated with local deposition of complement components C3b and C5b-9. In a mouse model of renal ischemia-reperfusion, anti-C5 treatment mitigated glycocalyx loss and complement activation, suggesting that complement activation directly contributes to glycocalyx damage.^[24] Shedding of glycocalyx exposes adhesion molecules, thereby promoting leukocyte and platelet recruitment and leading to microthrombus formation. Damage to the glycocalyx further exacerbates vascular tension dysfunction, leading to organ failure.

Another crucial mechanism of endothelial injury involves the imbalance between reactive oxygen species (ROS) production and antioxidant defenses, with ROS generation in monocytes and neutrophils depending on complement system activation.^[25] During sepsis, numerous neutrophils are mobilized from the bone marrow, accompanied by the release of proteolytic enzymes and ROS. Under normal conditions, neutrophils have the shortest lifespan among white blood cells; however, in sepsis, their apoptosis is delayed, resulting in prolonged inflammation. Proinflammatory factors such as C5a activate extracellular regulatory protein kinase 1/2 and phosphoinositol-3 kinase, leading to protein Kinase B phosphorylation and subsequent Bcl-2-associated death promoter phosphorylation. This ultimately prevents the formation of apoptotic bodies. C5a also upregulates the antiapoptotic protein Bcl-xL and downregulates Bim, further inhibiting caspase activity essential for apoptosis.^[26] Endothelial cells also produce large amounts of ROS through interactions between pathogen-associated molecular pattern, damage-associated molecular pattern, and pattern-recognition receptors.^[27]

Epithelial cells and the complement system

Epithelial tissues, such as those found in the gastrointestinal tract, skin, and lungs, establish a physical barrier between the body and the external environment and are frequently exposed to numerous inflammatory stimuli. Epithelial cells function as vigilant sentinels equipped with a multitude of pattern-recognition receptors that detect disturbances in the microenvironment, amplify signaling, and release defensins to combat bacterial threats.^[28] Therefore, the complement system plays a crucial role in the interaction of epithelial cells with the host and the external environment. For example, C3b deposited on the surface of *Listeria* can directly interact with the autophagy protein ATGL16L1 after entering epithelial cells, increasing autophagy targeting, thereby restricting intracellular bacterial growth.^[29] Moreover, viruses opsonized with C3b induce the innate immune response of human epithelial cells during infection by activating

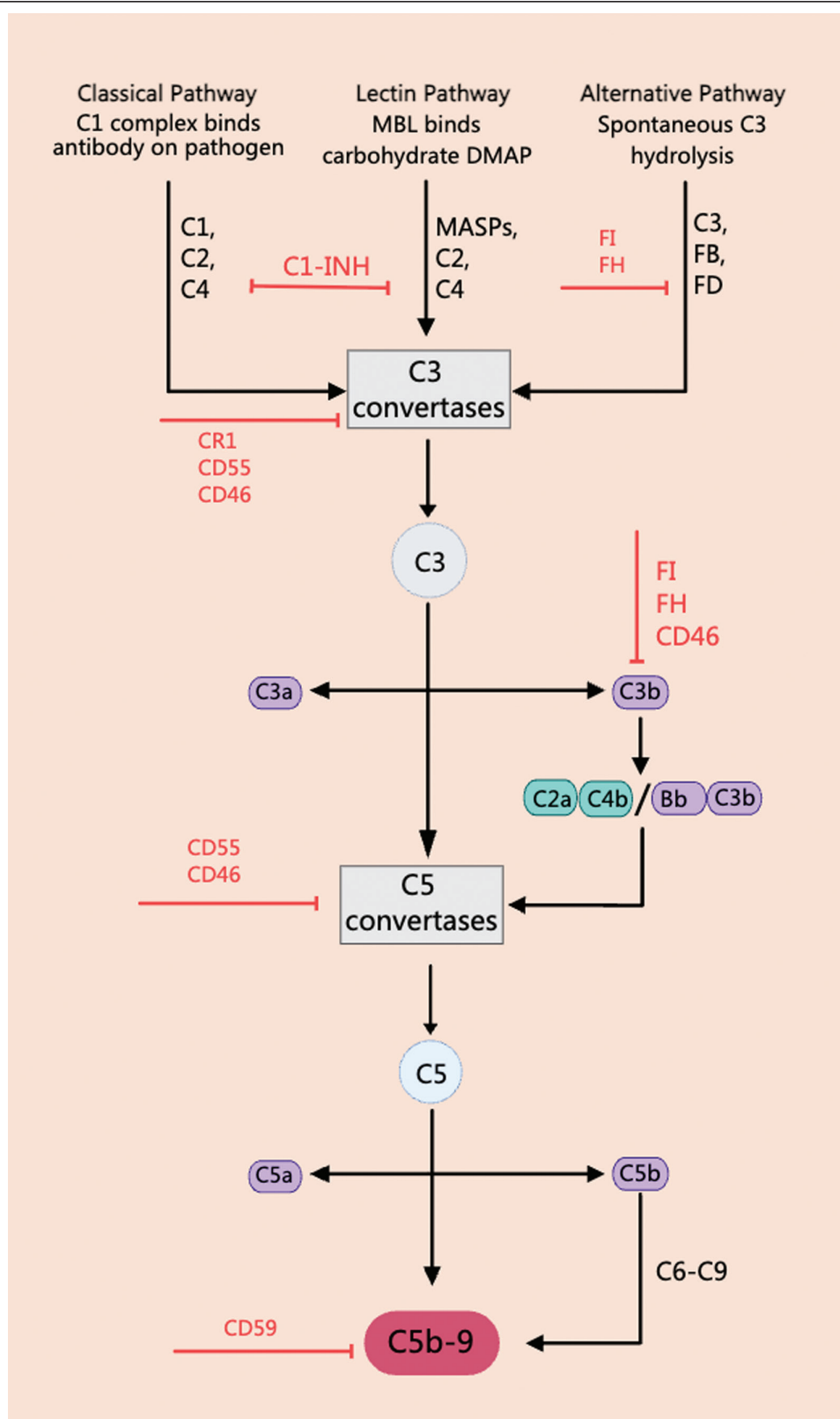


Figure 1. Three pathways of complement activation. The classical pathway is initiated by antigen–antibody complexes. The C1 complex binds via C1q to the Fc region of antibodies, triggering a conformational change that autoactivates C1r and subsequently C1s. Activated C1s cleaves C4 into C4a and C4b; C4b binds C2, which is then cleaved into C2a and C2b. The resulting C2a–C4b complex acts as a C3 convertase, cleaving C3 into C3a and C3b. C3b binds to the C2a–C4b complex to form the C5 convertase (C4b2a3b), initiating the terminal pathway. The lectin pathway is antibody-independent and utilizes pattern-recognition molecules, such as MBL, to identify PAMPs on microbial surfaces. MBL associates with MASPs, which cleave C4 and C2, leading to the same downstream cascade as the classical pathway. The alternative pathway operates continuously at a low level via spontaneous hydrolysis of C3 to C3b, which binds Factor B; Factor D then cleaves Factor B to generate the C3bBb. This enzyme amplifies C3 cleavage, rapidly depositing C3b on pathogen surfaces and forming the C5 convertase (C3bBbC3b). C1-INH, C1 esterase inhibitor; CR1, complement receptor 1; FB, Factor B; FD, Factor D; FH, Factor H; FI, Factor I; MASPs, MBL-associated serine proteases; MBL, mannose-binding lectin; PAMPs, pathogen-associated molecular patterns.

mitochondrial antiviral signaling pathways, thereby restricting viral replication.^[30] However, pathogens can also exploit the complement system to exacerbate infections. For example, CD46 serves as a receptor for various pathogens, allowing them to adhere to epithelial cells and triggering a cascade of downstream signals that facilitates the translocation of bacteria and viruses across the epithelial barrier.^[31]

The complement system plays a key role in epithelial cell damage. C5b-9, the terminal product of complement activation, exerts a cytotoxic effect that leads to cell dysfunction and cell lysis. In epithelial and endothelial cells, C5b-9 can induce intracellular Ca²⁺ fluxes. Additionally, the generation of C5a during sepsis leads to the activation of neutrophils and macrophages, ultimately causing damage to epithelial cells.^[32]

Interaction between complement and coagulation factors

The interaction between the complement and coagulation systems has been demonstrated in numerous studies, showing that complement inhibition is often accompanied by coagulation inhibition. For instance, C3-knockout mice exhibit longer hemostasis times after skin injury compared with wild-type mice.^[6, 33, 34] Although the complement and coagulation systems are distinct cascades, they share an evolutionary origin, with several proteins possessing highly conserved serine, histidine, and aspartic acid catalytic sites.^[5] Consequently, both systems can be activated or inhibited by similar mediators. For example, C1 esterase inhibitors not only suppress the classical and lectin complement pathways but also inactivate coagulation factor XII.^[35] Activated FXIIa can, in turn, activate complement factor C1r, initiating the classical complement pathway.^[36, 37] Thrombin can cleave C5 to generate C5aT and C5bT, which are structurally and functionally analogous to C5a. The C5bT-9 complex induced by C5bT exhibits higher cleavage activity than C5b-9. In addition to thrombin, other coagulation factors and factors of the fibrinolytic system, including FXa, FXIIa, plasminase, and kallikrein, can lyse the complement system.^[4, 15, 37, 38] Conversely, complement components can promote hemostasis. MASP is structurally similar to thrombin^[39, 40] and activates plasma FXIII in a dose-dependent manner independent of thrombin. MASP can further increase the clotting tendency by activating prothrombin to activate thrombin.^[36, 41–43] Moreover, C5a triggers the extrinsic coagulation pathway by inducing TF expression in endothelial cells and neutrophils.^[38, 44]

In addition to coagulation activation, the complement system also influences fibrinolysis. C5a induces mast cells to produce plasminogen activator inhibitor-1 through specific binding to C5aR, thereby inhibiting tissue-type plasminogen activator activity, which is coproduced by the cells.^[43, 45] MASP-1, a procoagulant protein, facilitates clot formation and activates thrombin-activated fibrinolysis inhibitor, albeit less efficiently than thrombin.^[42] However, MASP-1 can also accelerate fibrinolysis under certain conditions, thereby preventing excessive clot growth and vascular occlusion.^[40] The active form of thrombin-activated fibrinolysis inhibitor further inhibits C3a and C5a, contributing to the regulation of inflammatory responses.^[46]

Platelet aggregation, a key process in hemostasis, is also influenced by complement activation. Platelet activation results in the release of bioactive molecules encapsulated in platelet particles, including coagulation regulators, chemokines, growth factors, and adhesion molecules. These conditions are associated with sepsis-induced coagulation disorders and inflammatory

dysfunction. Platelets in patients with sepsis can be activated by multiple mechanisms, including thrombin overproduction, increased collagen exposure, and endothelial upregulation of von Willebrand factor and TF. The complement system plays an important role in this process. Studies have shown that platelet aggregation is inhibited by the collagen domain of C1q and by monoclonal antibodies against the C1q receptor, indicating direct involvement of C1q in platelet activation.^[47] Complement activation products (C3, C3a, and C5) can degranulate platelets. These particles contain abundant FVa receptors and exhibit high prothrombin activity, which enhances the thrombin-induced platelet secretion and aggregation.^[43, 48, 49] Additionally, C5b-9 can be directly deposited on the platelet surface, thereby inducing phosphatidylserine exposure and facilitating further aggregation.

Disseminated intravascular coagulation (DIC) is a fatal complication of sepsis. Beyond pathogen-induced coagulation activation, mechanisms, such as neutrophil extracellular traps (NET) and glycocalyx injury, contribute to sepsis-induced DIC, both of which are closely related to complement activation. The complement system also directly participates in the early formation of sepsis-associated microthrombi. In sepsis, C5b-9-mediated endothelial injury promotes a procoagulant endothelial phenotype, vasoconstriction, impaired antithrombotic function, platelet aggregation, and activation of the coagulation cascade, culminating in microthrombus formation. When blood flow decreases, IL-1 α produced by complement-activated endothelial cells continuously triggers endothelial activation in local and downstream blood vessels, leading to diffuse microthrombosis.^[22] Thus, the complement and coagulation systems appear to mutually activate one another, amplifying widespread microthrombus formation.

Interaction between the complement and inflammatory systems

Neutrophils and the complement system are crucial components of innate immunity. Both are regarded as among the earliest innate immune effectors that perceive incoming inflammatory signals and are promptly recruited to injury and inflammatory locations. Complement activation products, including C3a and C5a, and opsonins C3b and C4b, can activate neutrophils through their corresponding cell membrane receptors, inducing the release of proinflammatory factors, ROS production, and NET formation.^[17] Complement anaphylatoxin C5a induces TF expression in neutrophils and triggers exogenous clotting pathways. Moreover, the inhibition of C3 in the complement system can effectively reduce the amount of TF produced by neutrophils and weaken the induction of granulocyte colony-stimulating factors.^[44, 50] An in vitro experiment simulating air embolism found that TF-mRNA expression levels increased in blood incubated with air bubbles compared with those in blood incubated without air, and C3 inhibitors substantially reduced TF-mRNA virtually to baseline.^[51] C5a plays a proinflammatory role via the G protein-coupled receptor C5aR1. In tissues expressing C5aR1, the activation of C5aR1 induces the transformation of endothelial cells into a proinflammatory phenotype, which further leads to the production of ROS, activation of platelets, and the release of numerous cytokines from macrophages.^[52–54] In mice with a second-blow model of acute lung injury (complement activation simulated by recombinant C5a), neutrophils and NET formation have been shown to be more abundant than in a single stimulus environment, suggesting that complement activation can trigger NET formation in vitro.^[55] In addition, the capacity of neutrophil complement-dependent phagocytosis is

reduced at high levels of C5a, possibly due to the role of neutrophil proteases in cutting C5aR1.^[17] Direct evidence suggests that an increase in C5a levels leads to neutrophil microvesicle shedding, leading to the loss of C5aR1.^[56] Additionally, the action of C5a-C5aR1 on neutrophils can affect the basic function of the cells by increasing the pH of the cytoplasm.^[53] This suggests that excessive activation of C5a leads to an excessive release of inflammatory factors and impaired immune function of neutrophils, resulting in an inability to effectively remove pathogens from the blood.

Finally, NETs can activate the classical complement pathway by releasing pentraxin 3 (PTX3)^[17] and converting C5 into active C5a, independent of the plasma complement system. When isolated NETs were incubated with serum, the C5a levels increased, possibly because NETs provide a platform for complement activation (Fig. 2).^[57]

Prognostic effects of the complement system in sepsis

Initial activation of the complement system occurs after trauma and infection. Previous studies have shown that complement

component levels are closely related to sepsis severity. The innate immune system recognizes microbial components, causes tissue damage via PRMs, and activates the complement system. PRMs include MBL, collectins, ficolins, and pentraxins, which can be divided into short pentraxins (eg, cardiopulmonary resuscitation [CRP]) and long pentraxins (eg, PTX3). PRMs are significantly elevated in the early stages of sepsis,^[11, 12] and increased median PTX3 and CRP levels are independently associated with increased mortality in patients with sepsis, with PTX3 peaking earlier than CRP levels. Conversely, high median MBL levels are independently associated with increased survival rates. During the first 5 days in the intensive care unit, nonsurvivors had significantly lower MBL levels than survivors,^[58] which may be related to impaired blood clotting function.^[59] However, MBL levels vary greatly among individuals, partly because of impaired liver function in critically ill patients with sepsis, which results in reduced MBL synthesis.^[58]

Many studies have shown that in patients with severe infection, C3 and C4 are significantly decreased, C5a and C5b-9 are increased, and the prognosis is worse in complement-depleted groups.^[60] In a cecum ligation and puncture mouse model, mice with reduced C3 and C4 levels are more prone to septic shock.^[61]

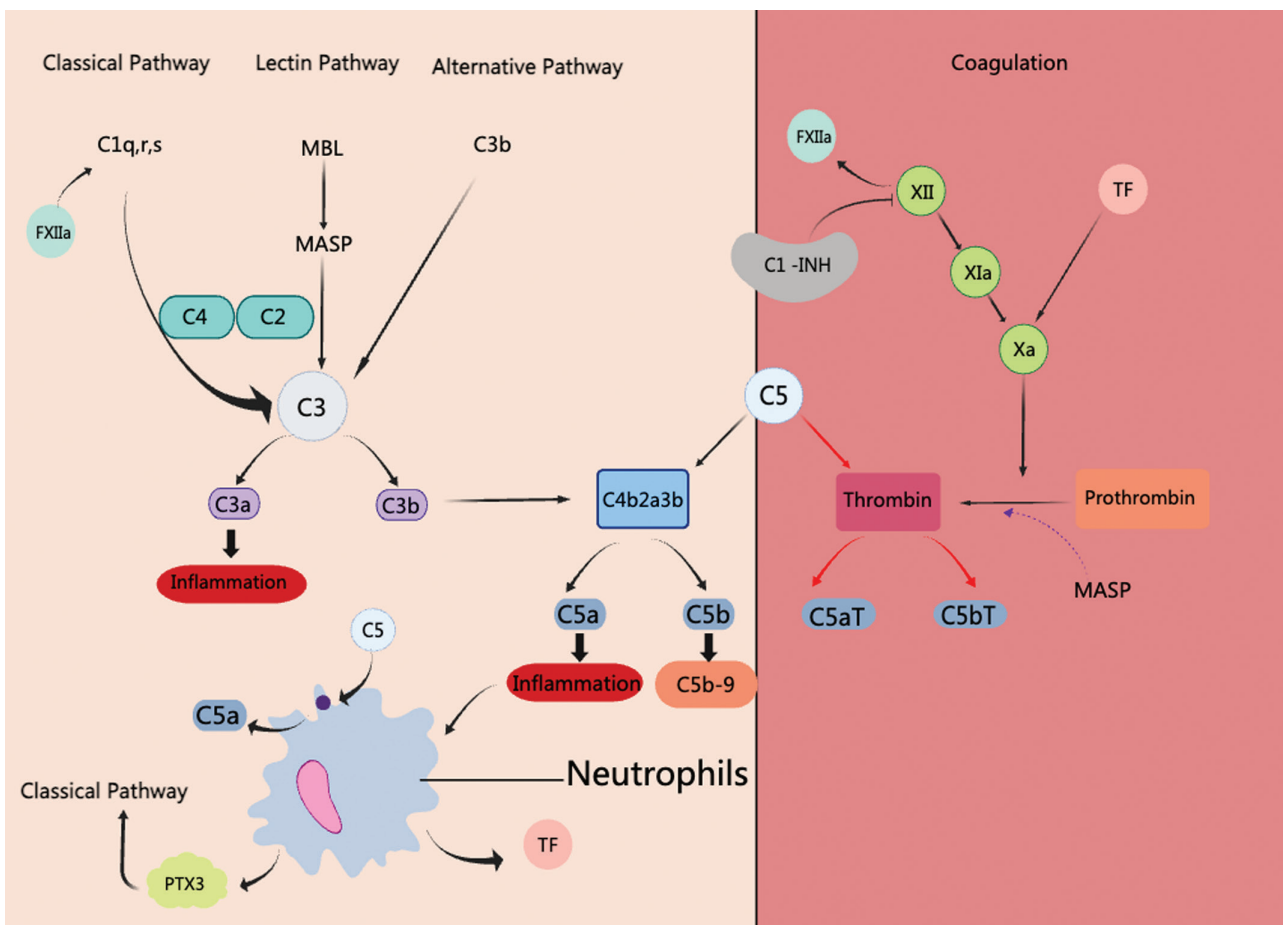


Figure 2. Crosstalk between the complement and coagulation systems. The complement system comprises 3 activation pathways that produce key cleavage products such as C3a, C3b, C5a, and C5b. Among these, C3a and C5a serve as potent inflammatory mediators. The coagulation cascade involves the TF-initiated extrinsic pathway and the Factor XII-triggered intrinsic pathway, which converge to activate Factor X. Factor Xa converts prothrombin to thrombin, while MASPs can also directly activate prothrombin to thrombin. Thrombin cleaves C5 into C5aT and C5bT. C1-INH inhibits the classical complement pathway and reduces Factor XII activity, whereas Factor XIa can activate C1q to trigger complement activation. C3a and C5a activate neutrophils, promoting NET formation. NETs, in turn, activate the classical pathway via PTX3 and provide a scaffold for C5 cleavage. TF within NETs further initiates coagulation. C1-INH, C1 esterase inhibitor; MASPs, MBL-associated serine proteases; MBL, mannose-binding lectin; NETs, neutrophil extracellular traps; PTX3, pentraxin 3; TF, tissue factor.

C3 and C4 levels were significantly lower than those in a control group in patients with septic shock caused by Gram-negative bacteria.^[62] Hecke et al. observed that C3a levels increased dramatically in patients with trauma before the onset of clinical symptoms of sepsis and suggested that C3a/C3 measurements could complement existing trauma scoring systems.^[63]

Additionally, sC5b-9 levels were increased in patients with septic symptoms, and sC5b-9 was higher in patients with septic shock than in those without septic shock.^[60] Patients with elevated sC5b-9 levels have increased fibrin degradation products, prolonged prothrombin time in the acute phase, and higher DIC scores.^[48]

Generally, the depletion of complement C4 and C3 reflects increased complement activation products, including the systemic anaphylatoxin C5a, which is associated with sepsis severity and mortality. However, no significant association was observed between the C5a levels and septic shock or 30-day mortality rates.^[62] This may be due to the rapid elimination of allergic toxins from the circulation; therefore, the use of C5a as a predictor of sepsis prognosis is questionable.^[60] C5a acts as a proinflammatory agent by binding to its receptor, C5aR. However, excessive inflammatory activation leads to immunosuppression of neutrophils, resulting in decreased surface expression of C5aR.^[56] The expression level of C5aR was significantly reduced in patients with sepsis compared with that in healthy participants.^[64]

Several previous clinical studies and animal experiments have confirmed the activation of the complement system in sepsis and the correlation between changes in complement component levels and severity and prognosis of sepsis (Table 1). However, recent studies have indicated that although patients with sepsis have significant reductions in C3 and C5 as well as increases in C3a, C5a, and the final product C5b-9, complement concentration is not correlated with the severity of the disease. This may be because the complement pathway is already profoundly activated.^[65] The differences in the research results before and

after might be due to the different diagnostic criteria for sepsis. Therefore, it cannot be ruled out that complement can serve as a prognostic marker in patients with mild sepsis. Another study quantifying the functions of the classical complement pathway and the alternative pathway found that although the function of the classical pathway was not associated with intensive care unit mortality, an increase in the function of the alternative pathway was associated with a reduced risk of bloodstream infection and an improved survival rate.^[66] Meanwhile, the level of change in complement concentration during the disease process may be another aspect that needs to be explored.

Complement inhibition therapy

Previous studies have focused on the anticoagulation and anti-inflammatory effects of sepsis treatment. With increasing research on the complement system, complement inhibition has shown great potential in treating sepsis. However, the complement system is complex, and as part of the innate immunity of the body, it may not be able to eliminate pathogens through opsonization, cytotoxicity, or mediation of local inflammatory responses after excessive immunosuppression, which is harmful to clinical treatment. Therefore, it is particularly important to select the appropriate complement inhibitors during sepsis. Eculizumab, the most commonly used complement inhibitor, prevents the cleavage of C5 into C5a and C5b and blocks the formation of the terminal complement complex C5b-9. Ravulizumab is a second-generation eculizumab with the same site of action as eculizumab; however, it has a longer half-life. Eculizumab is effective in treating paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, transplant-associated thrombotic microangiopathy, and autoimmune neuromuscular diseases.^[67] In severe cases of COVID-19, patients recovered after eculizumab treatment.^[68] However, it has not yet been approved for use in sepsis, and its clinical application in sepsis remains

Table 1
Complement Molecules for Predicting Prognosis in Patients With Sepsis

Complement Molecule	Mechanism	Relevant Experimental Outcome	References
C3	In the complement activation pathway, C3 is broken down into C3a and C3b by C3 converting enzymes.	Mice with reduced C3 were more likely to go into septic shock. C3 levels decreased significantly in patients with Gram-negative septic shock.	[61] [62]
C4	C4 is decomposed into C4b and C4a under the action of C1s and MASP, and the decomposition of C4 by MASP is the initial stage of the lectin pathway.	Mice with reduced C4 were more likely to go into septic shock. C4 levels are reduced in patients with Gram-negative bacteria-induced septic shock.	[61] [62]
C3a	C3a is a product of C3 breakdown that forms a chemical gradient to recruit neutrophils and macrophages to the site of infection.	C3a levels were elevated in trauma patients before the onset of sepsis.	[63]
C5a	C5a is a product of the breakdown of C5 and, similar to C3a, is involved in the inflammatory response.	No significant correlation between the level of C5a and the incidence and prognosis of sepsis.	[60]
C5aR	C5aR is a receptor for C5a, and C5a binding results in decreased surface expression of C5aR.	Expression levels of C5aR were significantly reduced in patients with sepsis compared with healthy participants.	[64]
sC5b-9/ C5b-9	C5b-9 is the end product of the complement pathway, which causes lysis of the cell. sC5b-9 is the non-cytolytic soluble terminal complement complex.	Patients with septic shock had higher levels of sC5b-9. Patients with elevated C5b-9 levels had increased fibrin degradation products and a higher incidence of DIC.	[60] [48]
Pentaxins	Pentaxins are a type of PRMs that can be divided into short (such as CRP) and long pentaxins (such as PTX3).	Increased median levels of PTX3 and CRP were independently associated with increased mortality in patients with sepsis.	[11, 12]
MBL	MBL can directly recognize the sugar structures presented on the pathogens and thus initiate the lectin pathway.	Nonsurvivors had significantly lower MBL levels than survivors.	[58]

CRP, cardiopulmonary resuscitation; DIC, disseminated intravascular coagulation; MASPs, MBL-associated serine proteases; MBL, mannose-binding lectin; PRMs, pattern-recognition molecules.

under investigation. RA101295, a 2-kDa macrocyclic peptide inhibitor of C5 cleavage, markedly inhibited complement activation *in vivo* and *in vitro* by blocking the production of C5a and sC5b-9. RA101295 significantly reduces the mortality of baboons with sepsis.^[69] However, its therapeutic effect on human sepsis is yet to be confirmed. RA101295 is clinically used under the name zilucoplan to treat myasthenia gravis.

Early clinical trials discovered that patients treated with C5 inhibitors have an increased risk of secondary infections, particularly those caused by *Neisseria meningitidis*.^[70] This is because the MAC of the complement system is a key immune mechanism for defense against encapsulated Gram-negative bacteria. Therefore, compared with C5 inhibition, the application of C5a inhibitors in sepsis may be more appropriate.^[54] Blocking the C5a–C5aR1 interaction inhibits neutrophil recruitment and the subsequent lung inflammatory response and significantly reduces the bacterial load in the lungs and other organs.^[17] Multiple animal experiments have shown that blocking C5a is beneficial for improving the survival rates. Blocking C5a with polyclonal rabbit anti-mouse antibodies significantly improves cecum ligation and puncture survival in both rat and primate models.^[2] Blocking C5aR1 with PMX205 in a mouse model of meningococcal septicemia significantly improved survival (pre- and postattack administration).^[17] Another study showed that although the survival rate of C5R1-deficient mice showed no significant difference compared with the wild type in the severe sepsis group, it was significantly improved in the mild sepsis group.^[72] Moreover, blocking C5aR improved the inflammatory cytokine response in human whole blood.^[73]

C1 inhibitors are a broad class of serine protease inhibitors capable of regulating the complement system (inhibiting the classical and lectin pathways of the complement system by blocking C1r and C1s activation and MASP) and the kinin, fibrinolytic, and coagulation systems.^[74] C1 esterase inhibitor can effectively inhibit the expression of TF and coagulation activation induced by *Escherichia coli*.^[75] Although its use in human sepsis is experimental and not supported by major clinical trials, in a large number of animal models of sepsis, the use of C1 esterase inhibitor has significantly improved outcomes.^[76]

Conclusion

Sepsis is a life-threatening syndrome involving multiple organ dysfunction caused by a dysregulated immune response to infection, with a high mortality rate. Although extensive studies have examined the pathophysiology of sepsis, the role of the complement system in disease progression remains unclear. Complement activation contributes to endothelial dysfunction, excessive inflammation, coagulation abnormalities, and poor clinical outcomes. The complement system circulates throughout the bloodstream, facilitating the progression of sepsis from localized infection to systemic organ failure. Despite its critical role in the pathophysiology of sepsis, complement-targeted therapies have not yet been integrated into routine clinical practice. Further research is warranted to clarify its potential as a prognostic marker and therapeutic target in sepsis.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Zhu L wrote the original draft. Both authors contributed to writing, reviewing, and editing.

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