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Mechanism and treatment progress of disseminated intravascular coagulation in sepsis

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Abstract: Sepsis is the main cause of death in critically ill patients in clinic, with high incidence and complicated pathogenesis. Coagulation system is an important factor of the pathogenesis and lethal mechanism of sepsis, especially sepsis complicated with disseminated intravascular coagulation (DIC), which is the dual effect of coagulation cascade reaction and inflammatory immune response. This paper describes the molecular mechanism of DIC in sepsis and the latest treatment research progress, in order to provide new ideas and methods for clinical work.

Keywords: Sepsis; Coagulation system; Disseminated intravascular coagulation; Tissue factor; Neutrophil extracellular trap
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1 Introduction

In 2016, the definition of sepsis was updated to describe it as a life-threatening organ dysfunction caused by an excessive host response to infection. During the development of sepsis, the inflammatory immune response triggered by infection can lead to multiple organ dysfunction and disturbances in various systems, including the coagulation system. Coagulation system dysfunction is a critical factor influencing the mortality rate in sepsis. After the immune system is stimulated by cytokines during sepsis, the coagulation cascade is inevitably activated to respond to the damage caused to the body by sepsis [1]. Regarding the coagulation cascade, the inherent ability of platelets to be activated and aggregated provides a perfect stage for the initiation of the coagulation cascade.

Studies have showed that the mortality rate in sepsis patients with disseminated intravascular coagulation (DIC) is significantly higher than in those without DIC. Furthermore, correction of coagulation dysfunction can notably improve the prognosis of sepsis patients [2]. The core molecular mechanism of DIC is the dual effect of the coagulation cascade and the inflammatory immune response. However, the exact mechanism of the coagulation cascade triggered by DIC in sepsis remains unclear. This paper aims to elucidate the latest research progress on the pathogenesis and treatment of DIC in sepsis, hoping to provide references for future studies.

2 Molecular Mechanism of DIC in Sepsis

2.1 Initiation of the Coagulation System in Sepsis: The Tissue Factor Pathway

Tissue factor is a membrane glycoprotein receptor that forms a high-affinity complex with coagulation factors VII/VIIa, activating factors IX to IXa and X to Xa through proteolysis, leading to thrombin generation and fibrin formation, and platelet activation. According to current research and perspectives, tissue factor is a central element in the initiation of DIC.

Firstly, when inflammation and immune responses cause endothelial cell damage, the membrane-bound proteoglycans and side chains in endothelial cells are exposed, leading to the loss of their antithrombotic properties. This results in the release of platelet recruitment and thrombus formation signals into the coagulation system, namely, tissue factor. Secondly, tissue factor is also present in inflammatory cells, mainly monocytes and macrophages. Upon infection, these cells recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), Fcγ receptors, and G-protein-coupled receptors [3-4]. Upon recognition of PAMPs and DAMPs by PRRs on the surfaces of monocytes and macrophages, these cells are activated to release inflammatory cytokines and chemokines, which in turn activate neutrophils, platelets, and endothelial cells. Activated monocytes can also release extracellular vesicles that express tissue factor and phosphatidylserine on their surfaces. Therefore, tissue factor and phosphatidylserine are released into circulation, activating both exogenous and endogenous coagulation pathways. Neutrophils play an important role in the activation of the coagulation cascade through the expression of tissue factor and the release of chemical mediators and proteins. Thus, the expression and release of tissue factor in endothelial cells and inflammatory cells is the key to initiating the coagulation cascade.

2.2 The Pro-coagulant Effect of the Inflammatory Response on the Coagulation System in Sepsis

After the release of tissue factor, neutrophils and platelets jointly mediate the next step in the immune response. First, it is important to recognize the existence of "nets" formed by neutrophils in the vasculature, called neutrophil extracellular traps (NETs), which are a bactericidal mechanism used by neutrophils in response to infection. NETs are DNA fibers composed of histones and antimicrobial proteins. Infecting microorganisms, such as bacteria, are trapped within these nets and are killed by locally concentrated and lethal effector proteins [5]. Studies have shown that NETs can influence microorganisms and inflammatory stimuli *in vitro* [6-7]. This is one of the mechanisms of the inflammatory immune response for pathogen elimination. However, at the same time, NETs provide a scaffold for platelet binding and aggregation, directing the development of coagulation reactions [8]. NETs induce the formation of thrombi rich in red blood cells, and these thrombi also interact with plasma proteins critical to thrombus stability [9].

As previously mentioned, after monocytes and macrophages release inflammatory cytokines and chemokines, upregulating tissue factor and phosphatidylserine expression [10], they also activate neutrophils to release NETs. Additionally, they induce cell apoptosis to further limit and kill pathogens. Fuchs *et al.* confirmed in their experimental model that under the influence of NETs, DNA and histones released from apoptotic immune cells can attract platelet aggregation and thrombus formation [11]. The apoptosis induced by NETs can generate damage-associated molecular patterns, which in turn enhance the inflammatory immune response and coagulation cascade, creating a localized positive feedback loop.

2.3 The Promoting Role of Platelets in Inflammatory Response in Sepsis

Platelet activation is characteristically increased in sepsis patients. Studies have shown that pathogen-induced activation of the endothelium and leukocytes, complement activation triggered by inflammation, and other inflammatory processes are significant factors in mediating platelet activation [12-13]. In this regard, platelet activation is an unavoidable factor to focus on in sepsis, as platelets not only possess coagulation properties but also play a role in promoting the inflammatory immune response.

Activated platelets mediate pathogen recognition and immune complex formation through the expression of various receptors such as TLRs, Fc receptors, and CD40 ligand (CD40L) [14-16]. Studies have shown that activated platelets interact directly with leukocytes or endothelial cells through surface expression of CD62P, promoting the formation of platelet-neutrophil aggregates in the circulation of septic mice, which assists in neutrophil infiltration in the lungs, thereby limiting bacterial spread [17-18]. However, this can also lead to conditions such as septic pneumonia or cecal perforation [19]. Additionally, activated platelets release chemokines like CCL5 (C-C motif ligand 5) and platelet factor 4 (PF4), which stimulate macrophages to produce chemokines such as macrophage inhibitory protein-2 (MIP-2) and KC (CXCL1; homologous to human IL-8/CXCL8), thus promoting neutrophil recruitment, but also facilitating edema formation [20-22]. The serotonin released from dense granules during platelet activation promotes the adhesion and extravasation of neutrophils in sepsis [23]. Moreover, the high-mobility group box protein 1 (HMGB1) secreted by platelets not only activates platelets but has also been associated with leukocyte recruitment and bacterial clearance in experimental mouse models [24].

In summary, various receptors and secreted factors such as TLRs, Fc receptors, CD40L, CD62P, CCL5, PF4, MIP-2, serotonin, and HMGB1 can collectively aid in the aggregation of neutrophils and other inflammatory cells, thereby promoting the inflammatory immune response. Platelet activation induced by pathogens and inflammatory mediators promotes thrombosis formation while enhancing immune responses, making platelets' role in sepsis particularly significant.

2.4 The Development of DIC in Sepsis

In sepsis, the continuous interplay between inflammatory immune responses and coagulation cascades gradually leads to the development of DIC, accompanied by a disruption of the fibrinolytic system. Under normal conditions, the fibrinolytic system is balanced between tissue plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1). t-PA promotes fibrinolysis, while PAI-1 inhibits it. In the early stages of sepsis, following thrombus formation in blood vessels, the effect of t-PA is enhanced, thereby promoting fibrinolysis and ensuring timely removal of the thrombus to prevent vessel blockage. As sepsis progresses and severe inflammation takes hold, the body shifts its focus to controlling and eliminating the infection, leading to an increase in PAI-1 activity, enhanced fibrinolysis inhibition, and a hypercoagulable state in the vascular system. Fibrin networks form to limit the spread of pathogens such as bacteria, preventing their dissemination to other organs and tissues, which could lead to more severe infections. The inhibition of fibrinolysis causes a hypercoagulable state, depleting coagulation factors throughout the body, and the balance of fibrinolysis is completely disrupted [25].

In addition, the interaction between protease-activated receptor-1 (PAR-1) and thrombin upregulates both inflammatory and coagulation responses. Endothelial cells lose their anticoagulant glycocalyx, releasing thrombomodulin, von Willebrand factor (VWF), and adhesion molecules. Anticoagulants like antithrombin and protein C also leak out due to increased vascular permeability mediated by inflammation, making it difficult

to regulate coagulation in the vessels. A combination of factors leads to the massive formation of microvascular thrombi, causing the onset of DIC [26].

3 Latest Treatments for Sepsis

3.1 Heparin

Heparin is commonly used in sepsis patients. Analytical reports indicate that heparin can improve the prognosis of sepsis, particularly in reducing the mortality of severely ill patients [27]. Clinically, heparin can also be used as a control measure in patients with sepsis complicated by disseminated intravascular coagulation (DIC). Additionally, recent clinical reviews have found that low molecular weight heparin (LMWH) shows potential life-saving effects, reducing inflammation and coagulation disorders in sepsis patients. It is especially beneficial in patients under 60 years of age, those diagnosed with sepsis-induced coagulopathy (SIC), ISTH-defined DIC, non-infectious shock, or non-diabetic patients, and those in moderate-risk groups (APACHE II score 20-35 or SOFA score 8-12) [28]. Thus, its use can be further explored in clinical treatment. However, LMWH is preferred over standard heparin due to its superior treatment outcomes and prognosis in current evidence [29].

3.2 Antithrombin

Antithrombin is a serine protease inhibitor (SPI) that inactivates factors VIIa, IXa, Xa, and IIa. It is one of the most abundant physiological anticoagulants in plasma. In addition to its anticoagulant properties, antithrombin also exhibits anti-inflammatory effects by stimulating the production of prostacyclin in endothelial cells, thereby inhibiting the production of cytokines and tissue factors in endothelial and monocyte cells [30].

Antithrombin is highly suitable for treating sepsis patients with DIC. Several randomized controlled trials have compared the effects of antithrombin on the prognosis of sepsis-related DIC [31]. It is clear that antithrombin significantly improves mortality rates in such patients. However, sepsis patients with DIC should not be treated in the same way as those without DIC. A study by Kienast *et al.* [32] on 563 septic patients with DIC but no heparin treatment showed a 14.6% reduction in 28-day mortality in the antithrombin group, while no such effect was seen in non-DIC sepsis patients. Nevertheless, as current studies do not provide a uniform standard for antithrombin dosages, longitudinal comparative research is needed to better determine the benefit of antithrombin treatment in different dosages.

At present, the timing and dosage of antithrombin use remain areas that require further investigation. Recent studies have explored the potential beneficial effects of combining antithrombin with recombinant thrombomodulin (rTM), particularly in severe cases [33]. The efficacy of this combination therapy should be further tested in future trials.

3.3 rTM

rTM binds to thrombin, promoting protein C activation and inhibiting thrombin formation, thus exhibiting anticoagulant effects [33]. Additionally, its lectin-like domain provides anti-inflammatory and cell-protective activities [34-35]. Related research has shown that rTM is effective in treating DIC and alleviate the condition [36].

Several randomized controlled trials have indicated that rTM improves the prognosis of sepsis, particularly reducing mortality rates. One study found that rTM reduced the 28-day mortality of sepsis and suspected DIC patients from 21.6% to 17.8% [37]. However, subsequent studies showed no significant difference in outcomes when patients had at least one organ dysfunction, prolonged INR>1.4, and decreased platelet counts [38]. Still, most randomized controlled trials support the use of rTM to significantly reduce mortality in sepsis-related DIC patients [39]. Thus Therefore, the Japanese sepsis guidelines recommend rTM for sepsis-related DIC [40].

3.4 Activated Protein C

Protein C is a natural anticoagulant that exhibits anticoagulant properties by inactivating factor Va and factor VIIIa. Recombinant human activated protein C (rhAPC) was once considered a specific anticoagulant in the treatment of sepsis. However, in multiple randomized controlled trials, we were unable to conclusively demonstrate its significant impact on reducing mortality rates [41-43]. Although one randomized controlled trial indicated that the reduction of rhAPC was a significant marker for poor prognosis [44], there is no compelling evidence or clear mechanism to support this. Therefore, the use of rhAPC for the treatment of sepsis-related DIC remains highly controversial. We hope that newly developed rhAPC will prove to be more effective.

3.5 Berberine

Studies have found that berberine can block Msr1 to inhibit bacterial sepsis-induced caspase-11-dependent coagulation, thereby preventing coagulopathy [45]. Berberine and its main metabolite M2 inhibit platelet activation by suppressing Class I PI3Kβ and Rasa3 membrane translocation, then inhibiting Rap1 activation. Moreover, berberine can effectively convert antiplatelet activity into antithrombotic activity in vivo without increasing the risk of bleeding [46].

3.6 Interferon-β

Interferon-β has antiviral activity. Research shows that interferon-β combined with nicotinamide riboside (NR) alleviates sepsis during bacterial septicemia by enhancing

endothelial SIRT1. Interferon-β combined with nitrate reductase protects endothelial integrity via SIRT1. Additionally, interferon-β combined with nitrate reductase repairs CLP-induced endothelial glycocalyx damage through the SIRT1/heparanase-1 pathway [47]. As discussed earlier in the mechanisms of sepsis-induced DIC, endothelial cell damage and glycocalyx disruption are key steps in triggering DIC and releasing tissue factor. Therefore, IFN-β's protective and reparative effects on endothelial cells theoretically make it an effective treatment to block DIC. However, the actual clinical efficacy still requires further research and trials to verify.

3.7 Ketoconazole

Ketoconazole is used as an anticoagulant in clinical treatment of vascular diseases. A study in Egypt showed that ketoconazole had a protective effect against microcirculatory dysfunction induced by neonatal sepsis. It significantly reduced the incidence of DIC and multiple organ dysfunction, resulting in better prognosis [48].

4 Conclusion

At present, although the mechanisms of sepsis-induced DIC are still not fully clear, our understanding of sepsis-related DIC has advanced significantly. Preventive measures for DIC caused by coagulopathy in sepsis, which ultimately leads to death, have also progressed. Treatment options and medications for sepsis-related DIC are continually evolving. However, there remains much room for improvement, particularly in determining the optimal timing for anticoagulation, the dosing of anticoagulants, and the monitoring of anticoagulation markers. It is hoped that future research will lead to more definitive and effective treatments to save more sepsis patients.

The authors report no conflict of interest

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· 研究进展 ·

脓毒症中弥散血管内凝血的机制及最新治疗进展

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摘要：脓毒症发病率高且致病机制复杂，是临床上危重症患者死亡的主要原因。凝血系统是脓毒症发病及致死机制中的重要组成部分，尤其是脓毒症并发弥散血管内凝血（DIC），是凝血级联反应和炎症免疫反应的双重作用结果。本文通过综述脓毒症 DIC 的分子机制及最新治疗研究进展，以期望为临床治疗提供新的思路和方法。

关键词：脓毒症；凝血系统；弥散血管内凝血；组织因子；中性粒细胞细胞外陷阱

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Mechanism and treatment progress of disseminated intravascular coagulation in sepsis

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Abstract: Sepsis is the main cause of death in critically ill patients in clinic, with high incidence and complicated pathogenesis. Coagulation system is an important factor of the pathogenesis and lethal mechanism of sepsis, especially sepsis complicated with disseminated intravascular coagulation (DIC), which is the dual effect of coagulation cascade reaction and inflammatory immune response. This paper describes the molecular mechanism and the latest treatment research progress of DIC in sepsis, in order to provide new ideas and methods for clinical work.

Keywords: Sepsis; Coagulation system; Disseminated intravascular coagulation; Tissue factor; Neutrophil extracellular trap

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1　引　言

2016 年脓毒症的定义更新为由宿主对感染的过度反应引起的危及生命的器官功能障碍。脓毒症发病过程中，感染所引发的炎症免疫反应可造成多器官的功能障碍及多系统的功能紊乱，自然也包括凝血系统的紊乱。凝血系统障碍是影响脓毒症死亡率的重要因素。当免疫系统被脓毒症中的细胞因子刺激后，凝血级联反应必然会被启动，以应答脓毒症对于机体所造成的损伤[1]。而对于凝血级联反应而言，血小板本身所具有可以被激活、聚集的特性，为凝血级联反应的产生提供了相当完美的舞台。

研究报道，脓毒症中弥散血管内凝血（DIC）患者的死亡率远超非 DIC 患者的死亡率，同时，凝血功能的纠正可明显改善脓毒症患者的预后[2]。DIC 分子机制的核心是凝血级联反应和炎症免疫反应的双重作用结果。目前脓毒症中 DIC 所造成的凝血级联反应的机制尚不十分清楚。本文通过对脓毒症中 DIC 的最新发病机制以及治疗的研究进展进行阐述，希望能为后续的研究提供参考。

2　脓毒症中 DIC 的分子机制

2.1　脓毒症中凝血系统的启动——组织因子途径　组织因子是一种跨膜糖蛋白受体，与凝血因子Ⅶ/Ⅶa 形成高亲和力复合物，以蛋白水解方式激活因子Ⅸ至Ⅸa 和Ⅹ至Ⅹa，产生凝血酶并导致纤维蛋白形成和血小板活化。根据现有的研究及观点，组织因子是 DIC 启动的核心物质。

其一，当炎症免疫反应导致内皮细胞受损后，内皮细胞中的膜结合蛋白聚糖和侧链暴露，导致了内皮细胞的抗血栓性丧失，从而向凝血系统释放出血小板募集和血栓形成的信号，

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即为组织因子。其二,组织因子也存在于炎症细胞中,主要是单核细胞和巨噬细胞。感染发生后,这些细胞通过表达 Toll 样受体(TLRs)、Fcγ 受体和 G 蛋白偶联受体等模式识别受体(PRRs),识别病原体相关分子模式(PAMPs)和损伤相关分子模式(DAMPs)[3-4]。单核细胞和巨噬细胞表面的 PRRs 识别 PAMPs 和 DAMPs 后,这些细胞被激活并释放炎症因子和趋化因子,随后激活中性粒细胞、血小板和内皮细胞。已被激活的单核细胞还可释放细胞外囊泡,在其表面表达组织因子和磷脂酰丝氨酸。因此,组织因子和磷脂酰丝氨酸被释放到循环中,外源性和内源性凝血途径被激活。中性粒细胞通过组织因子的表达及化学介质和蛋白质的释放在凝血级联的激活中发挥重要作用。因此,组织因子在血管内皮细胞和炎症细胞中的表达和释放,是凝血级联的启动。

2.2　*脓毒症中炎症反应对凝血系统的促进作用*　在组织因子释放后,中性粒细胞和血小板共同发挥了下一步免疫反应的介导作用。首先,要明确中性粒细胞在脉管系统中所构建的“网”的存在,即中性粒细胞细胞外陷阱(NETs),其为中性粒细胞应对感染的一种杀菌机制。NETs 是由组蛋白和抗菌蛋白组成的 DNA 纤维网。细菌等感染物被固定在网中,由局部高浓度和致命浓度的效应蛋白进行杀菌[5]。有研究表明,NETs 在体外环境中可以影响微生物以及炎症刺激因素[6-7]。这是炎症免疫反应杀灭病原体的机制之一,但同时,NETs 为血小板结合和聚集提供了支架和刺激,引导凝血反应的发展[8]。NETs 诱导富含红细胞的血栓形成,同时结合对血栓稳定性重要的血浆蛋白[9]。

上文中阐述的单核细胞和巨噬细胞在产生炎症因子和趋化因子,上调了组织因子和磷脂酰丝氨酸的表达同时[10],也激活了中性粒细胞释放 NETs,同时诱导细胞凋亡来进一步限制和杀灭病原体。Fuchs 等[11]的实验模型也证实,在 NETs 作用下,免疫细胞凋亡所产生的 DNA 和组蛋白也能吸引血小板聚集和血栓的形成。NETs 所造成细胞凋亡可产生 DAMPs,又能反过来增强炎症免疫反应和凝血级联反应,形成一种局部的正反馈现象。

2.3　*脓毒症中血小板对炎症反应的促进作用*　脓毒症患者中血小板的活化呈现特征性的增加。研究表明,病原体、机体炎症反应引发的内皮细胞和白细胞活化、炎症引发的补体活化,都是可以介导血小板活化的重要因素[12-13]。以此观之,血小板的活化是脓毒症中不可避免要关注的因素。因为除了血小板自身的凝血特性外,血小板对于炎症免疫反应也有促进作用。

活化的血小板通过血小板上 TLRs、Fc 受体、CD40 配体(CD40L)等多种受体的表达,来介导病原体识别、免疫复合物的形成等[14-16]。研究发现,活化的血小板和白细胞或内皮细胞通过表面表达的 CD62P 直接相互作用,促进脓毒症小鼠循环中血小板-嗜中性粒细胞聚集体的形成,可以辅助肺部嗜中性粒细胞浸润,从而限制细菌传播[17-18],但也会导致肺败血症或盲肠穿孔等[19]。同时,活化的血小板也可以释放趋化因子(C-C 基元)配体 5(CCL5)和血小板因子 4(PF4),刺激巨噬细胞产生趋化因子巨噬细胞抑制蛋白-2(MIP-2)和 KC(cxcl 1;与人 IL-8/CXCL8 同源),从而促进嗜中性粒细胞募集,但也促进水肿形成[20-22]。血小板活化时致密颗粒中释放的血清素可以促进脓毒症中性粒细胞的黏附和外渗[23]。此外,血小板分泌的高迁移率族蛋白 B1(HMGB1)除了可以活化血小板外,在实验鼠的模型中也与白细胞募集和细菌清除有关[24]。

综上所述,TLRs、Fc 受体、CD40L、CD62P、CCL5、PF4、MIP-2、血清素、HMGB1 等多种受体及分泌物,都可以通过辅助促进中性粒细胞等炎症细胞的聚集,从而达到促进炎症免疫反应的作用。血小板被病原体及炎症介质所刺激活化,促进了血栓的形成,同时也增强了免疫反应,所以脓毒症中血小板的作用也尤为显著。

2.4　*脓毒症中 DIC 的产生*　脓毒症在炎症免疫反应和凝血级联反应的不断相互升级激活中,渐渐向 DIC 的方向发展,而纤溶系统此时也出现紊乱。纤溶系统正常状态下处于组织纤溶酶原激活物(t-PA)和组织纤溶酶原激活物抑制剂(PAI-1)之间的平衡。t-PA 促进纤维溶解,PAI-1 抑制纤维溶解。脓毒症早期,血管中血栓形成后,t-PA 作用增强,纤溶作用增强,保证了血栓的及时清除,避免了血管的阻塞。随着脓毒症的进展,当机体的炎症感染严重,机体的中心偏移至对脓毒症的控制和杀灭时,PAI-1 的作用增强,纤溶抑制作用增强,脉管系统呈现高凝状态,以纤维蛋白网限制细菌等病原体,避免其扩散入全身其他器官和组织,引发更严重的感染。纤维蛋白溶解抑制,导致高凝状态,全身的消耗凝血因子难以补充,纤溶平衡被彻底打破[25]。

除此之外,蛋白酶激活受体-1(PAR-1)和凝血酶的结合,可上调炎症和凝血反应;内皮细胞释放出血栓调节蛋白、血管性血友病因子(vWF)和黏附分子;抗凝血酶和蛋白 C 等抗凝因子,在炎症介导下由于血管通透性的增加而外渗,难以调节血管中的凝血反应。多种因素共同作用,导致微血管中的血栓大量形成,导致了 DIC 的发生[26]。

3　脓毒症的最新治疗

3.1　*肝素*　肝素通常可用于治疗脓毒症患者。有研究指出,肝素可改善脓毒症的预后,特别是能降低病情较重患者的死亡率[27]。临床上,对于脓毒症并发 DIC 的患者,应用肝素也不失为一种控制手段。另外,有临床回顾性研究发现,低分子肝素(LMWH)在脓毒症患者中表现出潜在的挽救生命的作用,并可减轻炎症反应和凝血功能障碍。肝素与年龄<60 岁,诊断为脓毒症诱导凝血障碍(SIC),ISTH 显性 DIC,非感染性休克或非糖尿病患者以及中度风险组(APACHEⅡ评分 20~35 或 SOFA 评分 8~12)患者的良好预后相关[28],可在临床治疗中进一步应用。但是,相比较而言,临床上更偏向 LMWH,因为根据目前的证据来看,LMWH 的治疗效果和预后要优于肝素[29]。

3.2　*抗凝血酶*　抗凝血酶是一种丝氨酸蛋白酶抑制剂,可使因子Ⅶa、Ⅸa、Ⅹa、Ⅺa 和Ⅱa 失活,是血浆中循环的最丰富的生理性抗凝剂之一。除了其抗凝血特性,抗凝血酶还通过刺激内皮细胞中前列环素的产生而具有抗炎特性,从而抑制内

皮细胞和单核细胞中细胞因子和组织因子的产生[30]。

抗凝血酶本身的特性非常符合脓毒症并发 DIC 患者的治疗。目前为止,已有多项随机对照试验研究分析抗凝血酶对脓毒症 DIC 患者预后的影响[31]。基本可以明确,抗凝血酶对于死亡率的改善是有显著益处的。但是,要注意的是,脓毒症患者和脓毒症并发 DIC 的患者并不能混为一谈。Kienast 等[32]对 563 例脓毒症并发 DIC 且未同时接受肝素治疗的患者研究发现,抗凝血酶组的 28 d 死亡率降低了 14.6%,而在未并发 DIC 的患者中没有观察到这种作用。另外,就目前的多项研究来看,抗凝血酶的使用剂量尚无统一标准,暂无对于抗凝血酶使用剂量的纵向对比研究。因此,并不能确定在不同剂量下脓毒症并发 DIC 患者的收益是相同的。

但就目前来看,抗凝血酶的使用时机、使用剂量仍需要进一步研究。此外最近有研究分析报道了抗凝血酶和重组血栓调节蛋白(rTM)联合治疗的潜在益处,特别是在严重病例中[33]。这种药物联合治疗的效果如何,应该在未来的试验中进一步探讨。

3.3　rTM　rTM 可与凝血酶结合,促进蛋白 C 的活化,抑制凝血酶的生成而起到抗凝的作用[33];同时,它本身具有凝集素样结构域,故具备抗炎作用和细胞保护活性[34-35]。相关研究表明,rTM 用于治疗 DIC,可有效缓解病情[36]。

有随机对照试验研究表明,rTM 对脓毒症的预后,尤其是死亡率有所改善,表明 rTM 能降低脓毒症和疑似 DIC 患者的 28 d 死亡率[37]。然而,后续的研究中,当研究对象的筛选标准提升到至少一种脓毒症相关的器官功能障碍,INR 延长>1.4,以及血小板计数减少时,rTM 并没有显示出明显的差异性结果[38]。但是,不能就此否认在绝大多数的随机对照试验中 rTM 对脓毒症并发 DIC 患者死亡率的显著改善[39]。且日本脓毒症指南推荐 rTM 用于脓毒症相关的 DIC[40]。

3.4　*活化蛋白 C*　蛋白 C 是一种天然抗凝血剂,通过灭活蛋白因子Ⅴa 和因子Ⅷa 表现出抗凝血特性。重组人活化蛋白 C(rhAPC)曾作为明确的抗凝剂出现于脓毒症的治疗中。但是,在多项随机对照试验中,无法明确地通过数据证实其对于死亡率的降低有明显的作用[41-43]。尽管有一项随机对照试验表明 rhAPC 的降低对于预后不良有明显预测意义[44],但却并没有令人信服的证据与机制阐述。所以,目前 rhAPC 是否用于脓毒症 DIC 的相关治疗,仍存在相当大的争议。期待新研发的 rhAPC 能起到更好的作用。

3.5　*黄连素*　研究发现,黄连素可以阻断 Msr1 抑制细菌脓毒症中胱天蛋白酶-11 依赖性凝血,从而预防凝血综合征[45]。黄连素及其主要代谢物 M2 通过抑制Ⅰ类 PI3Kβ、Rasa3 膜转位,然后抑制 Rap1 活化来抑制血小板活化,并且黄连素可在活体中将抗血小板活性有效地转化为抗血栓活性,且不会增加出血的风险[46]。

3.6　*干扰素-β*　干扰素-β 具有抗病毒活性。研究发现,干扰素-β 联合烟酰胺核苷通过内皮 SIRT1 减轻脓毒症,干扰素-β 加硝酸还原酶通过 SIRT1 保护内皮完整性,通过调节 SIRT1/肝素酶 1 通路修复 CLP 诱导的内皮糖萼损伤[47]。在前文对于脓毒症引发 DIC 机制的阐述中,提出内皮细胞的破坏和内皮糖萼的损伤是引发 DIC 的重要步骤,可引发组织因子释放。由此可见,干扰素-β 对于内皮细胞的保护和修复作用理论上是阻断 DIC 的根本原因,但对于临床上的实际效果,还是需要进一步的研究。

3.7　*己酮可可碱*　己酮可可碱在外科血管疾病的临床治疗中用作抗凝剂。埃及的一项研究表明,己酮可可碱对新生儿脓毒症诱导的微循环障碍有保护作用,可显著降低 DIC 和多器官功能障碍的发生率,有更好的预后[48]。

4　总　结

目前来看,虽然仍无法明确脓毒症 DIC 的机制,但对于脓毒症 DIC 的认识已经前进了一大步。脓毒症 DIC 的治疗药物及方法也在不断革新。但仍有很大的前进空间,对于抗凝的时机、抗凝药物的剂量、抗凝指标的监测仍是需要进一步研究的问题。希望能有更明确有效的治疗方式,以挽救更多脓毒症患者的生命。

利益冲突　无

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