· 综述 ·

细菌和病毒感染导致血瘀证的机制及血必净的多靶点治疗作用

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【摘要】 细菌和病毒是造成人体感染性疾病最常见的病原微生物，两者导致的疾病临床症状和严重程度差异很大。严重感染过程中，机体出现氧化应激、免疫失调及凝血功能紊乱，且各系统间相互作用，级联放大，最终导致机体微循环功能障碍，组织器官缺血缺氧，若得不到及时有效的治疗，则容易发展为重症肺炎、脓毒症，甚至死亡。凝血功能紊乱及微循环障碍属于中医“血瘀证”范畴，具有活血化瘀作用的血必净注射液在治疗重症肺炎和脓毒症中发挥了多靶点的作用，其机制可能与阻断氧化应激、免疫失衡与凝血紊乱之间的“交汇作用”，遏制三者相互促进的恶性循环有关。本文从细菌和病毒等感染诱发氧化应激损伤、免疫功能失衡、凝血功能紊乱和血必净注射液的多靶点治疗作用 4 个方面进行综述。

【关键词】 细菌；　病毒；　感染；　血瘀证；　血必净注射液；　多靶点作用

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Mechanism of blood stasis syndrome induced by bacteria and virus infection and multi-target treatment effect of Xuebijing

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【Abstract】 Bacteria and virus are the most common pathogenic microbes of human infectious disease. The clinical symptoms and severity of disease caused by bacteria and virus differ greatly among patients. Oxidative stress, immune dysfunction and coagulation disorder may occur in organisms during severe infection. The interaction among various systems and the cascade-amplification effects result in microcirculation dysfunction and lead to ischemia and hypoxia of tissues and organs. Under the above situation, if no timely and effective treatment can be applied, it could easily develop into severe pneumonia, sepsis, and even death. Coagulation disorder and microcirculation dysfunction belong to the category of "blood stasis syndrome" in traditional Chinese medicine. Xuebijing injection, which has the function of promoting blood circulation and removing blood stasis, has played a multi-target role in the treatment of severe pneumonia and sepsis. The mechanism may be related to blocking the "crosstalk" among oxidative stress, immune dysfunction and coagulation disorder, leading to curbing the vicious circle of mutual promotion. This article reviews the four aspects such as oxidative stress injury, immune function imbalance, blood coagulation disorders induced by bacterial and viral infection, and multi-target therapeutic effect of Xuebijing injection.

【Key words】 Bacteria; Virus; Infection; Blood stasis syndrome; Xuebijing injection; Multi-target effect

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外来抗原入侵感染是人类生存面临的巨大挑战。细菌和病毒是最常见的外来抗原，细菌和病毒等感染常引起多种炎症反应，炎症反应诱发的氧化应激又可作用于免疫细胞，若机体免疫功能失衡，则触发形成“炎症风暴”。“炎症风暴”可波及凝血系统，引起凝血功能异常和微循环障碍，最终导致组织器官缺血缺氧，出现多器官功能障碍，进而发展为脓毒症[1]。因此，氧化应激、免疫失衡和凝血功能紊乱在从一般感染向脓毒症过渡的过程中扮演着重要角色，其中凝血功能改变和微循环障碍与脓毒症的严重程度及病死率密切相关[2-3]。

中医学将感染导致的凝血功能紊乱和微循环障碍归属于血瘀证范畴。王今达教授曾提出著名的“三证三法”理论，其中“血瘀证”是脓毒症中最为重要的证型，并采用活血化瘀注射剂血必净治疗[4]。本研究通过总结机体感染细菌和病毒等后出现氧化应激、免疫失衡与血瘀证之间的相互关系和血必净注射液的多靶点治疗作用，旨在揭示病原体感染机体后发展为脓毒症的复杂病理学机制，以期为血必净注射液防治脓毒症提供一定的理论依据。

1　氧化应激损伤

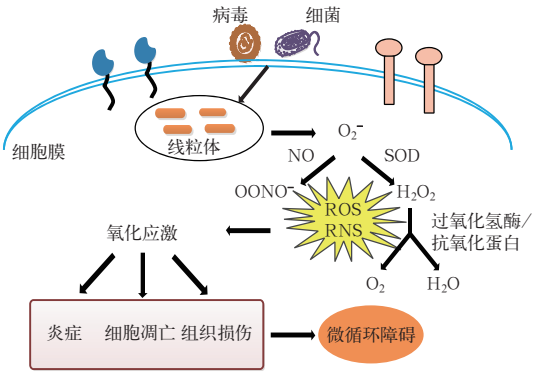
1.1　细菌和病毒感染诱发氧化应激损伤的机制：越来越多的研究证明，氧化应激在感染性疾病中发挥了重要的作用[5-6]。活性氧自由基（ROS）是线粒体的代谢产物，在生理情况下，体内的抗氧化系统能清除 ROS，当细菌和病毒侵入机体后，宿主细胞的三磷酸腺苷（ATP）被大量消耗，导致线粒体呼吸链改变和能量通路不平衡，释放出大量 ROS[7-8]。线粒体功能紊乱引起的细胞缺血缺氧、抗氧化能力下降、ROS 累积造成氧化-还原失衡，即氧化应激状态[9-10]。ROS 水平轻度升高，通过激活免疫细胞增强机体的免疫功能；而

在严重感染的情况下，高水平ROS促进了“炎症风暴”的形成，导致组织器官损伤[11]。

研究证实，ROS在促进炎症因子释放的同时，还可以激活巨噬细胞，通过诱导型一氧化氮合酶（iNOS）催化产生大量一氧化氮（NO）[10]。NO与ROS很快耦联生成具有高氧化性的活性氮自由基（RNS）过氧化亚硝酸盐（$OONO^-$），共同造成氧化应激水平升高发挥细胞毒性作用[12]。这种分子间的“级联”反应将导致巨噬细胞和中性粒细胞的活化，增强炎症反应，加速细胞氧化应激损伤[13]。

1.2 氧化应激损伤形成血瘀证的机制：氧化应激可同时激活抗氧化/氧化信号通路，并可驱动核因子E2相关因子（Nrf2）转位进入细胞核，激活多种抗氧化保护基因表达，有助于保护细胞免受氧化应激损伤[14]。同时，丝裂素活化蛋白激酶（MAPK）通路对氧化应激敏感，激活的MAPK通路可促进ROS的产生，成为细胞凋亡的关键因素[15]。当ROS水平不断升高时，可激活核转录因子-κB（NF-κB）通路，驱动促炎细胞因子释放，形成“炎症风暴”[16-17]。“炎症风暴”波及凝血系统导致凝血功能异常和微循环障碍，进而形成中医学中的血瘀证。

自由基由于活性较强可直接攻击线粒体膜蛋白和核苷酸，破坏线粒体膜的完整性及生物酶活性，使线粒体功能紊乱，导致细胞损伤、死亡。若自由基直接攻击内皮细胞，则可促进血管内皮退化，增加血管通透性[10]；若直接攻击心肌细胞，则导致心肌细胞氧化损伤、死亡，诱导心肌收缩功能障碍[18]。同时，机体NO的积聚导致血管紧张素水平降低，形成低血压，最终使血管扩张，血管通透性增加，心肌收缩无力，循环功能障碍，加速了血瘀证的形成（图1）。



注：O_2^-为氧自由基，NO为一氧化氮，SOD为超氧化物歧化酶，$OONO^-$为过氧亚硝酸盐，H_2O_2为过氧化氢，ROS为活性氧自由基，RNS为活性氮自由基

图1 细菌和病毒感染诱发的氧化应激与血瘀证形成的关系

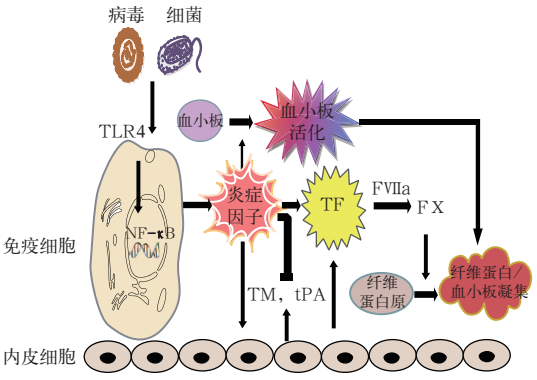
2 免疫功能失衡

2.1 细菌和病毒感染导致免疫功能失衡的机制：细菌和病毒一旦进入宿主，病原体表面抗原被免疫细胞的模式识别受体Toll样受体4（TLR4）识别，触发一系列的细胞信号，激活NF-κB，导致炎症因子快速大量产生。炎症因子趋化白细胞向感染部位聚集、浸润，清除入侵的病原体[19]。在此基础上，通过活化抗原呈递细胞，促进淋巴细胞的成熟、分化，释放大量炎症因子参与调节免疫反应。同时，促炎反应反馈性地激活抗炎机制，促炎反应与抗炎反应相互制约，防止炎症反应过度活化对机体造成损伤[20]。

当病原体清除失败时，宿主免疫反应失衡，炎症因子过度表达造成组织损伤。来源于损伤细胞和单核/巨噬细胞的晚期炎症因子高迁移率族蛋白B1（HMGB1）通过介导多种信号转导通路，如TLR4和MAPK等，进一步促进细胞产生炎症因子，加剧炎症损伤[21]。当促炎反应占据主导时，机体炎症反应过度激活导致组织器官损伤，严重者可引起多器官功能损害；当抗炎反应起主要作用时，机体免疫应答受到过度抑制，增加继发性感染的风险[22]。

2.2 免疫功能失衡形成血瘀证的机制：细菌和病毒等感染后，宿主同时激活炎症和凝血反应，组织因子（TF）在两者的相互促进作用中起到了关键作用[23]。TF主要由血管内皮细胞表达，正常情况下，TF不与循环血液接触，无法激活经典凝血途径[24]，在病原体感染机体免疫失衡时释放大量炎症因子，损伤血管内皮细胞，导致TF表达增加，TF进入血液循环，激活外源性凝血途径[25]。凝血系统形成的血栓促进炎症因子的释放，炎症系统则呈正反馈调节细胞因子、趋化因子维持TF的表达[23]。

血管内皮受损时，TF暴露于血液循环中，与凝血因子Ⅶa（FⅦa）结合，激活凝血因子X（FX），将纤维蛋白原转化为纤维蛋白，进而导致血栓的形成[26]。生理状态下，血管内皮表面可表达血栓调节蛋白（TM）、组织型纤溶酶原激活物（tPA）等抗凝成分，以抑制血栓的形成[27]。严重感染时，内皮细胞抗凝成分受到破坏不能发挥抗凝功能[28]。同时，血小板被促炎细胞因子活化，导致血小板凝集，促进凝血反应，形成血瘀证[29]（图2）。



注：TLR4为Toll样受体4，NF-κB为核转录因子-κB，TM为血栓调节蛋白，tPA为组织型纤溶酶原激活物，TF为组织因子，FⅦa为凝血因子Ⅶa，FX为凝血因子X

图2 细菌和病毒感染诱发的免疫功能失衡与血瘀证形成的关系

3 凝血功能紊乱

3.1 细菌激活外源性凝血系统：在细菌感染过程中，凝血与炎症系统协同作用清除入侵的病原体。在化脓性链球菌感染的早期阶段，内源性途径被激活，最终导致细菌滞留在纤

维蛋白凝块中被固定并杀死。细菌感染严重时，Ⅰ型干扰素（IFNs）使血液中 HMGB1 的释放增加，HMGB1 通过促进磷脂酰丝氨酸（PS）外化到细胞表面而显著提高了 TF 的促凝血活性，凝血系统的过度激活导致弥散性血管内凝血（DIC）。抑制 IFNs 的表达，阻断 α/β-IFN 受体（IFN-α/βR）或下游效应物（如 HMGB1）均能降低革兰阴性菌诱导的 DIC[30]。

3.2 细菌激活内源性凝血途径：内源性途径是通过凝血因子Ⅻ（FⅫ）与带负电荷的细菌结合而启动，当发生凝血时，FⅫ被自动激活为FⅫa，FⅫa 可触发激肽释放酶-激肽系统，或触发凝血级联反应。FⅫa 将与相对分子质量较大的激肽原复合循环的激肽释放酶原转化为有活性的激肽释放酶，激肽释放酶切割相对分子质量较大的激肽原释放促炎肽缓激肽，激活 FⅫ，放大接触系统。FⅫa 切割 FⅪ，FⅪ也与激肽原复合循环，FⅪa 随后将 FⅨ转换为 FⅨa，FⅨa 通过将 FⅩ转化为 FⅩa 来触发凝血的共同途径，将凝血酶原转化为凝血酶，从而分解纤维蛋白原，导致纤维蛋白凝块的形成。活化凝血酶将纤维蛋白原分解成纤维蛋白单体，这些单体能与相邻的纤维蛋白分子相互作用，从而形成长纤维，最后形成纤维蛋白凝块[31]。

3.3 病毒与凝血功能的相互作用：凝血级联反应在病毒感染期间被激活。凝血系统可对例如人类免疫缺陷病毒（HIV）、B3 型柯萨奇病毒（CVB3）、登革热病毒和埃博拉病毒等多种不同病毒感染产生反应[32-35]。感染 H7N9 病毒或高致病性 H5N1 病毒的患者出现活化部分凝血活酶时间（APTT）、凝血酶原时间（PT）、凝血酶时间（TT）和血小板计数（PLT）减少[36-38]。流感病毒可利用血凝素的纤溶酶原依赖性裂解来提高其复制率和传染性[39]。有研究显示，H1N1 流感患者可出现血栓栓塞、肺动脉血栓等[32]。

因此，细菌可通过激活外源性和内源性凝血系统促进凝血功能紊乱，形成血瘀证。病毒可激活凝血级联反应加重瘀血的形成。

4 血必净的多靶点治疗作用

血必净由红花、赤芍、川芎、丹参和当归 5 味中药提取精制而成，每味中药含有多种有效组分，每种组分又具有多个靶点，通过药物与药物之间、组分与组分之间、靶点与靶点之间、靶点群与靶点群之间的相互作用，配伍协同，整合构成了血必净系统化的治疗作用。研究显示，血必净注射液可通过降低 ROS 的活性，上调超氧化物歧化酶（SOD）的表达，改善急性肺损伤（ALI）大鼠的氧化应激状态[40]；通过下调 TLR4 及 NF-κB 的表达[41-42]，抑制 p38MAPK 的激活[43]，增加 Janus 激酶/信号转导和转录激活因子（JAK-STAT）通路负反馈调节因子细胞因子信号转导抑制因子（SOCS）的表达[44]，改善免疫细胞的失控性炎症反应；通过抑制炎症因子白细胞介素-1（IL-1）、肿瘤坏死因子-α（TNF-α）、HMGB1 的分泌[41, 45-46]，阻断炎症因子与凝血因子之间的“交汇作用”，遏制相互促进的恶性循环。

但是，单个靶点或通路并不能全面而具体地表征中药复方“系统整合式”的作用机制，也无法发掘不同生物进程之间是如何协同进而产生治疗作用逆转病理进程的。因此血必净的作用机制仍有待于进一步从系统整体的角度进行深层次地阐释。在新的多组学背景下，利用药物基因（蛋白）组学、系统生物学、网络药理学等方法系统阐释血必净治疗血瘀证的药理学机制，将单靶点（通路）转化到多个生物进程的整合，符合中医整体论的理念，有望揭示其系统整合式的作用机制，以期为临床用药提供科学依据。

5 结 语

细菌和病毒等感染引起机体氧化应激、免疫失调和凝血功能紊乱，三者协同作用，导致全身微循环功能障碍，形成血瘀证，使组织器官缺血缺氧，进一步发展为重症肺炎、脓毒症，甚至导致患者死亡。因此，血瘀证在重症感染性疾病中扮演着极其重要的角色[47]。血必净具有活血化瘀、溃散毒邪的作用，是治疗因感染引起的重症肺炎、脓毒症的一线临床用药。既往研究表明，血必净有抗氧化应激[40]、抑制炎症反应[45]、改善凝血平衡[48]、调节免疫功能[49]、促进纤溶系统激活[50]等的作用，从多种生物学功能、多个病理环节改善机体内环境，阻断氧化应激、免疫失衡与凝血紊乱之间的“交汇作用”，遏制三者相互促进的恶性循环。

利益冲突 所有作者均声明不存在利益冲突

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