· 专家论坛 ·

抗凝治疗应成为细菌感染所致严重脓毒症的标准治疗方案

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Anticoagulant therapy should be suggested as a standard therapeutic measure for patients with severe sepsis induced by bacterial infection

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在脓毒症（sepsis）发病机制中，凝血功能障碍是导致疾病发生发展的一个重要因素，其既是疾病进展的一个动因，也是疾病发展的一个结果[1-2]。在脓毒症病理生理改变过程中，凝血功能障碍是非常重要的一个方面，与炎症反应、内皮功能损伤、免疫功能状态改变等其他因素互相交叉、互为因果，共同构成了脓毒症发病的病理生理机制[3-5]。

不同病原微生物引发的脓毒症，其凝血功能障碍程度、表现形式各不相同。无论是革兰阴性（G^-）杆菌抑或革兰阳性（G^+）球菌感染均产生大量内毒素及外毒素，可引起内皮损伤和凝血功能障碍[6]。内皮功能损伤在严重脓毒症早期即已存在，并促进了微循环功能障碍的发生发展[7-8]。微循环内微血栓的形成消耗了大量血小板及凝血因子，以血小板下降、纤维蛋白原下降及 D- 二聚体升高为主[9-10]。严重脓毒症的凝血功能紊乱以发病早期凝血功能亢进、血液呈现高凝状态，但生理性抗凝不足及相对性纤溶抑制为特征[11]。在凝血与抗凝、纤溶的动态平衡中，促凝机制上调而抗凝机制下调[3]。与有效血液成分丢失和凝血因子功能障碍所致凝血病不同，脓毒症所致凝血病为消耗性凝血病，而前二者又称稀释性凝血病和功能性凝血病。凝血功能障碍可以导致微循环功能障碍及多器官功能障碍综合征（MODS）[12]。严重脓毒症并发的器官功能障碍，如急性呼吸窘迫综合征（ARDS）或急性肾损伤（AKI）等，其微循环功能改变既是全身病理改变的一部分，又具有独特的器官特异性[9,13]。

在脓毒症早期凝血功能障碍即已出现。液体复苏、升压药物等集束化治疗针对的是大循环功能而不是微循环血液瘀滞及功能障碍。遗憾的是，无论是 2012 版国际脓毒症指南[14]还是《中国严重脓毒症 / 脓毒性休克治疗指南（2014）》[15]，均未论述严重脓毒症的凝血问题，也未提出相关治疗策略，仅在预防深静脉血栓栓塞方面提及抗凝治疗的重要性，但这是远远不够的。如此，临床容易出现抗凝治疗延迟，导致微循环障碍不能及早获得纠正，重症加强治疗病房（ICU）住院时间延长，甚至增加病死率。

分析目前关于严重脓毒症抗凝治疗的研究发现，肝素较早用于脓毒症致凝血功能障碍的治疗。Wang 等[16]进行的 Meta 分析纳入了 9 项研究（其中 8 项为随机对照试验），共 3 603 例患者，结果显示肝素能降低严重脓毒症患者 28 d 病死率，且并不增加出血事件发生率。低分子肝素使用方便，无须特殊监测，效果等同于普通肝素，且出血并发症发生率低，在深静脉血栓预防、急性冠脉综合征（ACS）治疗等方面已广泛应用[17]，更值得在脓毒症凝血病治疗中大力推广。既往开展的低分子肝素治疗脓毒症凝血病的研究已取得满意效果[18]。但目前尚无大样本随机对照试验提供有力的循证医学证据。

应改变目前重症医学领域对疾病早期血液高凝及严重脓毒症凝血功能障碍的忽视，改变“不认识、不理解、不重视”的现状，顺应脓毒症早期的病理生

理变化，将脓毒症抗凝治疗提高到与 ACS 或缺血性脑血管病抗凝治疗同等重要的地位[19]，而不能只停留在疾病的中后期针对深静脉血栓预防开展抗凝治疗，应在观念上将抗凝治疗作为一种必须的治疗措施。不同病菌种类、不同感染器官及感染的不同阶段，其凝血纤溶状态不同，因此需开展脓毒症凝血病的分层研究[20]，运用特异性生物标志物及其他综合评分体系[21]，尽早识别获得性凝血病 / 弥散性血管内凝血（DIC）的高危人群；强调开展大规模的循证医学研究，完善抗凝治疗适应证、禁忌证、治疗时机、药物选择、治疗剂量等技术环节，最终将抗凝治疗作为细菌感染所致脓毒症的标准治疗[22]。

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