脓毒血症合并既往心力衰竭的液体管理

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【摘要】脓毒血症作为致残率和死亡率较高的疾病,治疗上液体管理环节极为重要,其中包括液体复苏。心力衰竭作为迁延反复和难以逆转的综合征,治疗则以限液为特点,降低心血管负荷。二者共病时可对机体血流动力学稳态产生严重影响,对于既往心力衰竭患者出现脓毒血症的情况,最新版相关指南并未作出与液体管理相关的规范指导,现对二者的病理内环境特点及液体管理现状进行浅析。

【关键词】脓毒血症;心力衰竭;液体管理
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Fluid Management of Sepsis with Preexisting Heart Failure

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【**Abstract**】Sepsis is a disease with high morbidity and mortality. Fluid management is very important in treatment, including fluid resuscitation. Heart failure is a persistent and difficult to reverse syndrome, and its treatment is characterized by fluid limitation to reduce cardiovascular burden. When the two diseases coexist, it can have a serious impact on the hemodynamic stability of the body. For the sepsis of patients with preexisting heart failure, the latest version of the relevant guidelines does not make the normative guidance related to fluid management. This paper analyzes the characteristics of the pathological internal environment and the current situation of fluid management of the two.

【**Key words**】Sepsis; Heart failure; Fluid management

2017 年关于全球负担性疾病的报道显示,脓毒血症患者估测数量为 4 890 万,其中脓毒血症相关死亡病例占比约 23%[1];全球心力衰竭(心衰)患者数量估测为 6 430 万[2],一项 meta 分析纳入超过 150 万心衰患者,1、2、5 和 10 年估测生存率分别为 87%、73%、57%和 35%[3]。二者共存状况从临床鉴别、指标监测到治疗及预后都相对棘手。

1　病理生理内环境特点

1.1　脓毒血症

脓毒血症被定义为宿主对感染的反应失调并引起危及生命的器官功能障碍[4]。脓毒血症始于病原体直接入侵时的毒素释放,如 G^-菌的脂多糖、G^+菌的脂磷壁酸以及真菌的甘露聚糖,毒素与单核细胞 Toll 样受体结合,从而介导促炎因子释放(肿瘤坏死因子-α、白介素-1 和白介素-6 等)[5-6],激活淋巴细胞和补体系统,该链式过程在脓毒血症中反应过度,从而开启失控的促炎及抗炎反应,此时血管内皮细胞功能障碍,毛细血管通透性增加,液体由血管渗漏进间质,有效循环血量明显下降,各器官及组织出现低灌注,当血管内有效循环血量难以维持稳态时,可出现持续性低血压[7],低血容量和低血压均可引起肾素前体的释放,肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)得以激活,该系统中主要因子血管紧张素Ⅱ(angiotensin Ⅱ, AngⅡ)的生成旨在收缩血管,维持血管张力以代偿性提升血压,然而,RAAS 过度激活却可成为不良临床后果的原因,AngⅡ可增加超氧化物产生,诱导凝血过程,促进单核细胞血管浸润,从而导致内皮功能障碍,还能增加促炎因子、趋

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化因子及 NO 生成，AngⅡ受体因此可出现下调，实际上其代偿性收缩血管的生物学效应有所降低，NO 又可诱发血管瘫痪，从而出现微循环障碍甚至多器官功能障碍[8-11]。在此需提及自 2019 年 12 月起至今已在全球出现暴发流行的新型冠状病毒肺炎（COVID-19），目前 COVID-19 的发病机制尚未被完全阐明，但其诸多表现与脓毒血症类似，免疫应答失调是 COVID-19 重症感染发生级联事件的原因，炎症因子在 COVID-19 重症感染中明显激增，表现出极端的细胞因子风暴[12]；COVID-19 患者中可见 AngⅡ水平显著升高，表明 RAAS 有激活[13]，RAAS 中血管紧张素转换酶 2（angiotensin-converting enzyme 2，ACE2）是 RAAS 调节因子，本身可减轻 AngⅡ介导的不良效应，但与其他病原菌所致脓毒血症的不同在于 ACE2 可介导 COVID-19 直接感染[14-15]，对于 COVID-19 病例中促进还是抑制 ACE2 这一问题，应用 RAAS 调节剂的支持与否证据均有限[16]。

1.2 心衰

心衰是一组因心脏结构和/或功能异常，心输出量减少和/或心室舒张压升高，以活动性呼吸困难、疲劳乏力和液体潴留等特殊症状为表现的临床综合征[17]。因心功能不全致心输出量不足，交感神经系统激活，高浓度儿茶酚胺可引起肾脏球旁细胞释放肾素，RAAS 被激活，AngⅡ浓度升高，促进全身和肾小动脉血管收缩，促进醛固酮分泌，肾小管重吸收水钠，引起水盐潴留，此时水钠蓄积于静脉系统及细胞外间质，因静脉回流不佳，心输出量降低，实际动脉有效循环血量明显减少，同时受损的心脏泵功能难以通过增加前负荷补偿心输出量（Frank-Starling 机制）[18-21]，滞留于静脉及细胞外间质的液体成为心衰急性发作的因素，其中最紧急情况即进入肺间质及肺泡内[22]。

1.3 脓毒血症合并既往心衰

大量证据表明心衰与慢性炎症状态和免疫反应激活有关，有研究发现，如白介素-1β 和可溶性生长刺激表达基因 2 蛋白（白介素反应轴内重要因子）之间的相互作用可能局限于急性失代偿性心衰，且有全身性炎症的参与，进展性心衰状态中促炎介质明显更高，而在慢性心衰患者中，全身性炎症的参与程度有限，在既往心衰基础上出现脓毒血症，炎症反应则对心衰起到推波助澜的作用[23-26]，且 RAAS 可被进一步激活，此时高 AngⅡ水平又可增加炎症因子和趋化因子，钝化心肌细胞反应性，降低肌质网钙负荷，减少腺苷三磷酸的合成，增加氧氮自由基活性物质，引起心肌细胞氧化损伤，加重脂多糖诱导的心肌抑制效应等[27-28]；另脓毒血症时液体分布不均，微循环代谢障碍，冠状动脉毛细血管内皮受损可引起心肌缺血缺氧，且交感神经系统持续激活，β 肾上腺素受体反馈性下调，心功能进一步下降[20]，故对于心衰患者，脓毒血症将会是严重的打击。至于当下对全球人类健康产生严重威胁的 COVID-19 感染，其介导的心肌损害不容忽视，多项尸检报告发现 COVID-19 患者心肌中有巨噬细胞和 $CD4^+$T 淋巴细胞浸润[29]，在心肌巨噬细胞中亦发现了病毒颗粒，提示病毒可直接感染细胞，系统地传播到多个组织[30]，巨噬细胞和 $CD4^+$T 淋巴细胞可促进成纤维细胞的激活，这可能导致心脏重构及纤维化，成为心衰进展的基础[31]。

2 脓毒血症合并既往心衰的液体管理

目前对于脓毒血症的治疗主要是支持性的，基于液体复苏、血管活性药物及抗生素等，对于心衰的治疗基于限液、促进心功能、预防或抗感染等，但二者的指南均未明确提及当心衰患者出现脓毒血症时该如何调整液体管理方案。

2.1 液体反应性

液体反应良好是指快速补液后，每搏输出量随之增加至少 10%以上[32]，提示心脏处于心功能曲线上升段。在对重症、外伤及手术患者的异质组中进行的研究一致证明，仅有一半血流动力学状态不稳的患者对液体具有反应性[33]。脓毒血症相关指南强调，为防止液体过载，有必要在液体复苏前后评估液体反应性[34]。既往评估液体反应性的传统指标多有生命体征、胸部 X 线检查和中心静脉压等，但目前被后续研究质疑不具有可靠性[35-39]。愈发受关注的被动抬腿试验（passive leg raising，PLR），即通过抬高下肢，快速、短暂和可逆地增加静脉回流，增加心脏前负荷，从而提升每搏输出量，被指是当前可靠的液体反应性评估方法[33]。在对患者进行 PLR 的同时监测心功能，每搏输出量若提升≥10%，则认为 500 mL 液体可将心输出量提升 15%[40]。一项 meta 分析结果显示使用 PLR 预测急性循环衰竭患者液体反应性具有高度可靠性[36]，随后 Douglas 等[41]以感染性休克患者为研究对象，以 PLR 为干预措施，结果提示经 PLR 指导的液体复苏治疗可降低肾衰竭（5.1% vs 17.5%，$P=0.04$）及呼吸衰竭风险（17.7% vs 34.1%，$P=0.04$），并具有实践安全性。Toppen 等[42]亦报道 PLR 在血流动力学不稳定的患者中仅引起极少较严重不良反应，提示 PLR 具有安全性。

2.2　液体复苏

脓毒血症可引起组织低灌注以及感染性休克，对于低灌注状态且同时具有液体反应性的患者，静脉液体复苏是极为重要的一环，脓毒血症相关指南推荐前 3 h 内液体入量≥30 mL/kg[4]，而心衰患者对液体出入则尤为敏感，那么脓毒血症低灌注状态合并既往心衰时液体复苏量是否需调整？目前可获得的文献观点不一。Liu 等[43]以脓毒血症合并中等程度血乳酸值（2 mmol/L≤乳酸值<4 mmol/L）且血流动力学稳定的患者为研究对象，评估了“复合策略”对死亡率的影响，该策略纳入了 3 h 补液 30 mL/kg 的标准，在合并心衰的亚组中，“复合策略”实施率越高，患者院内及 30 d 死亡率越低（P<0.01），且不影响住院时长或增加对重症监护的需求；而在未合并心衰的亚组中，死亡率则与策略依从性无明显关联（P≥0.4）。Leisman 等[44]对来自 3 个中心的脓毒血症患者（n=14 755）进行了观察研究，该研究亦对脓毒血症治疗相关的“复合策略”进行了评估，不同的是，该策略补液标准是 30 min内补入 30 mL/kg，结果显示“复合策略”依从性越高，死亡率越低（P<0.05），且该特点在合并心衰时更明显。倾向于上调液体复苏量的研究以 Kuttab 等[45]的回顾性研究为代表，研究人群为 1 032 例脓毒血症患者（其中 245 例患者合并心衰），以前 3 h 内补液 30 mL/kg 为界值分为两组，结果显示患者住院死亡率的降低与 3 h 内补液量≥30 mL/kg 相关，补液量在 35~45 mL/kg 时前述关系达到峰效应，且无论是否合并心衰。另外亦有研究提示液体复苏量差异对特殊临床事件无明显影响，如 Khan 等[46]对脓毒血症合并心衰的患者进行回顾性分析，6 h 内补液量≥30 mL/kg 为标准组，<30 mL/kg 为限液组，结果显示两组间普通病房存活天数、机械通气时长或插管时间并无区别。综上，针对脓毒血症合并心衰患者的早期液体复苏问题，尚缺乏充足的前瞻性研究，但目前多数研究结果仍倾向于维持 3 h 内≥30 mL/kg 的复苏标准。

2.3　液体种类选择

无论液体复苏还是补液均涉及到液体种类的选择。平衡盐溶液中氯含量显著低于生理盐水，富含氯的液体会显著地影响电解质和酸碱状态，限氯可降低酸中毒和肾小球滤过率降低的发生率[47-48]，Yunos 等[49]的前后对照研究得出“限氯”策略可显著地降低重症监护病房中重症患者的急性肾损伤（14.0% vs 8.4%，P<0.001）和肾移植的发生率（10.0% vs 6.3%，P<0.05）；Semler 等将重症监护病房患者分为平衡晶体液组（n=217，使用液体类型为林格氏乳酸液或勃脉力复方电解质液）及生理盐水组（n=255），结论提示前者中全因死亡、肾移植或持续性肾功能不全的复合结局率较后者更低[50]；而一项 meta 分析结论则提示，与生理盐水相比，平衡盐溶液或白蛋白的使用与脓毒血症死亡率呈负相关[51]；一项以健康受试者为对象的双盲随机对照试验研究结果显示，与勃脉力复方电解质液相比，生理盐水可引起肾皮质血流减少[52]，故猜想生理盐水在容量敏感的重症患者如脓毒血症合并心衰状态则有致急性肾损伤的可能，但相关前瞻性研究仍不足。指南对平衡盐溶液或生理盐水的推荐并无选择倾向性。综上，从目前有限的研究结果中可看出平衡盐溶液似乎更具优势，且有必要重视血氯的动态变化，警惕高氯血症的出现加重肾功能损害，加速机体稳态失调。

2.4　乳酸监测

脓毒血症相关指南推荐使用乳酸作为判断脓毒血症伴低灌注状态的指标，并据此决定是否行液体复苏及判断微循环氧合是否恢复正常[4]。但脓毒血症低灌注状态及心衰均有引起乳酸增加的相关机制。器官灌注减低时，无氧循环可引起乳酸堆积[53]，且不论是脓毒血症或心衰，交感神经系统均为兴奋状态[18]，而 β2 受体的激活亦可介导乳酸增加[54]。在一组非休克状态的进展期心衰患者中，可观察到 25% 的患者合并高乳酸血症（>2.1 mmol/L）[55]，但该项回顾性研究的纳入对象左室射血分数<20% 且具有左室辅助装置植入指征，故 2.1 mmol/L 的标准并不代表多数心衰患者；一项以急性失代偿性心衰患者为对象的回顾性研究指出，乳酸>3.2 mmol/L 可使院内死亡率升高，不论是否合并急性冠脉综合征[56]。目前针对脓毒血症合并心衰时乳酸水平变化的实验分析较少，这使得在脓毒血症合并心衰时对乳酸的评估十分模糊，尚须更多研究将此环节细化。

3　总结

目前脓毒血症合并既往心衰时的治疗方案仍以脓毒血症指南为基础，由于此类患者血流动力学状态的特殊性，前瞻性随机对照试验研究甚少，液体管理极具挑战。而根据现有经验性临床数据分析，笔者认为，在液体复苏环节中，可以 PLR 结果评估患者是否具有液体反应性，同时确定是否处于低灌注状态，仍倾向以 3 h 内液体复苏≥30 mL/kg 为标准，液体类型可倾向选择平衡晶体液如乳酸林格氏液和勃脉力复方电解质液等，且对于该类特殊人群，补液时用于监

测微循环氧合的乳酸指标值范围尚需进一步循证研究证实。目前脓毒血症合并既往心衰的液体管理方案仍需在经验性和个体化治疗基础上,进行更多的前瞻性研究,以建立精准和系统化的指导方案。

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