

脓毒症合并急性肾损伤患者连续性肾脏替代治疗剂量的选择

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【摘要】 脓毒症是宿主对感染的反应失调,导致危及生命的器官功能损害,由脓毒症导致的急性肾损伤(AKI)发生率和病死率均较高,且预后不良。连续性肾脏替代治疗(CRRT)是目前治疗合并AKI的重症患者不可或缺的手段,但有关CRRT的合适治疗剂量目前尚无一致意见。通过回顾高容量血液滤过(HVHF)与标准剂量血液滤过(SVHF)的提出与应用历程,对两者的获益及风险进行对比,并对治疗方案提出可改进意见,为临床工作提供依据。

【关键词】 高容量血液滤过; 标准剂量血液滤过; 脓毒症

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Dose optimization of continuous renal replacement therapy in sepsis-induced acute kidney injury Cui Jun,

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【Abstract】 Sepsis is a life-threatening organ dysfunction caused by dys-regulated host response to infection. Acute kidney injury (AKI) caused by sepsis is one of the most common and severe clinical disease, which incidence and mortality remains high level, and has poor clinical outcomes. Continuous renal replacement therapy (CRRT) is an indispensable tool for the treatment of critically ill patients with severe AKI, but there is no consensus on the appropriate treatment dose of CRRT. By reviewing the process of high volume hemofiltration (HVHF) and standard volume hemofiltration (SVHF), comparing their benefits and risks, and making suggestions for therapeutic schedule improvement, reference for clinical work was provided.

【Key words】 High volume hemofiltration; Standard volume hemofiltration; Sepsis

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脓毒症是宿主对感染的反应失调,导致危及生命的器官功能损害^[1],尽管早期目标导向治疗(EGDT)在脓毒症患者的治疗中起到一定作用,但仍未达到较好的治疗效果^[2],其中脓毒症致急性肾损伤(AKI)的发生率较高^[3]。一项关于肾脏支持治疗开始与结局的研究(BEST Kidney研究)显示,脓毒症合并AKI患者的住院病死率高达70%^[4]。目前,连续性肾脏替代治疗(CRRT)已成为脓毒症患者的临床治疗方式之一,但有关CRRT的治疗剂量尚无一致意见;2012年国际严重脓毒症与感染性休克治疗指南指出,推荐肾脏替代治疗(RRT)使用标准剂量血液滤过(SVHF)^[5],即废液率为 $20 \sim 25 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ 的血液滤过(HF)治疗。现就CRRT时如何合理设定治疗剂量进行综述。

1 CRRT在脓毒症中的应用

脓毒症发病时,过度的炎症反应、免疫系统失衡导致大量炎性介质释放,对全身组织器官造成损伤,及早有效清除

体内炎性介质,阻断其作用机制,将直接影响患者的预后。临床发现,HF可明显降低体内炎性介质水平,调节促炎和抗炎平衡,稳定免疫平衡状态,已成为当前治疗脓毒症的主要手段。1977年Kramer首次将连续性动脉-静脉血液滤过(CAVH)技术用于治疗对利尿剂无反应、液体超负荷的肾衰竭患者,克服了传统间歇性血液透析存在的非生理性治疗缺陷,标志着CRRT技术的诞生。研究证实,对于感染性休克患者,清除血液中炎性介质或内毒素,有益于减轻过度的炎症反应,从而改善终末器官的损害^[6-8]。目前人们开始探索CRRT治疗剂量对脓毒症合并AKI患者预后的影响。

2 高容量血液滤过(HVHF)的提出

2.1 HVHF的定义: HVHF是在SVHF基础上发展起来的一项血液净化技术,其主要设想是通过增加置换液量进一步提高对中大分子溶质的清除。在HVHF提出的初期, HVHF的剂量标准并未统一^[9-10], 2008年、2009年两项大型随机

对照试验(RCT)^[11-12]及随后的系统综述^[13-15]显示,AKI患者CRRT合适的治疗剂量应为废液率 $25\sim 30\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$;这与2002年提出废液率 $>35\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 的HVHF有明确区别^[16]。先前研究显示,只有在更高的废液率时,才会存在有意义的血流动力学改善^[17-18],这意味着以 $35\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 标准界定HVHF可能太低^[10]。一项动物实验的系统综述显示, $25\sim 30\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ RRT剂量的HF对炎性介质的清除效果不明显^[19]。为了更加明确HVHF的定义,2012年在捷克帕尔杜比采进行的共识会议中,HVHF被定义为每日24h以 $50\sim 70\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 废液率进行持续HF,或间断4~8h以 $100\sim 120\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 废液率进行超高剂量HF,并继之以传统RRT剂量($25\sim 30\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$)的HF^[20]。这一定义随后被许多专家称为HVHF的帕尔杜比采共识定义。

2.2 HVHF的治疗假说:针对HVHF的治疗,包括Ronco^[8]、Honore^[21]等提出的峰值浓度假说;Honore^[7]、Klouche^[22]等提出的阈值免疫调节假说;Di Carlo和Alexander^[6]提出的介质传递假说;南京军区南京总医院全军肾脏病研究所提出的重建免疫内稳态理论^[23]等,这些假说在增大炎性介质清除方面理论上貌似可行,却存在明显的有效性不足及与HVHF相关的潜在危害。首先,脓毒症和脓毒症致AKI的特征是过度合成及释放促炎和抗炎介质^[8],而HVHF的滤器无法对介质进行有效充分或持续的清除,不能发挥其应有作用^[19]。由于脓毒症致AKI的病机复杂,研究者对HVHF的疗效理解不够^[8,21],导致部分研究容易依赖替代终点,而这些结果随后可能被证明无效^[24]。一项关于HVHF对脓毒症预后影响研究(RENAL研究)的事后分析发现,排除酸碱失衡和体温差异可能带来的影响,高剂量组($40\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$)较低剂量组($25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$)可改善血流动力学和减少血管活性药物用量^[25]。因此,要深入研究血流动力学改善的基础原理。

2.3 HVHF治疗脓毒症致AKI的局限性:近年来关于HVHF治疗脓毒症合并AKI的临床研究越来越多,几项大型RCT结果均偏向于HVHF不能明显改善脓毒症合并AKI患者的预后^[11-14,26]。而且,即使HVHF在脓毒症致AKI患者的治疗中可能发挥有利的作用,但任何形式的血液净化治疗都不可避免地造成各种并发症的风险,如对血流动力学的影响,营养物质、维生素、微量元素的消耗,抗菌药物水平的降低和其他治疗药物低于治疗剂量等。因此,考虑到目前高质量研究显示HVHF在脓毒症和感染性休克患者治疗中有效性的证据不足及潜在的副作用,HVHF的临床应用应该慎重。

3 SVHF的应用发展

3.1 SVHF的定义:目前在HF治疗中标准剂量的定义亦不明确,且有常规剂量、低剂量、低强度等概念混淆其中。如Tolwani等^[27]的研究中标准剂量组为 $20\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$;而2008年、2009年发表的两项CRRT治疗剂量对危重患者预后影响的大型多中心随机对照试验(ATN和RENAL)中以 $20\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 、 $25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 为低剂量组^[11-12]。尽管各项研究对于标准剂量的定义并不相同,但与2012年国际

指南推荐的CRRT标准剂量 $20\sim 25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ^[5]并不矛盾。目前对于脓毒症及脓毒症致AKI患者的推荐治疗剂量为 $20\sim 25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$,即SVHF。

3.2 脓毒症致AKI的SVHF治疗:Ronco等^[28]进行的一项单中心非双盲小样本RCT提示,与 $20\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 的较低剂量RRT比较, $35\sim 45\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 的较高剂量组患者绝对病死率降低了16%;两组HVHF能更好地维持血流动力学稳定,清除炎性介质,改善免疫功能,并纠正内环境、水电解质及酸碱平衡紊乱等^[29-32],因此,SVHF的临床疗效曾一度受到质疑,这是因为大多数文献为单中心小样本研究,且其中部分研究结果是倾向于HVHF不能明显改善预后的。2008年发表的多中心RCT研究(ATN研究)显示,废液率为 $20\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 较低剂量治疗组与 $35\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 较高剂量治疗组间60d病死率无明显差异(52%比54%)^[11];随后2009年发表的一项大型研究(RENAL研究)也显示,废液率为 $25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 与 $40\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 两个治疗组的90d病死率均为45%^[12]。两项研究结果均提示AKI病死率与CRRT治疗剂量间无联系。但由于这两项研究中的较高剂量组治疗剂量并未达到所谓的高剂量,且研究对象是单纯AKI而非脓毒症患者,在入选标准的针对性、治疗剂量的标准等方面具有一定局限性。2013年发表了一项针对脓毒症合并AKI患者的前瞻性随机开放多中心研究(IVOIRE研究),研究者纳入2005年10月至2010年3月在法国、比利时和荷兰的18个重症加强治疗病房(ICU)内140例脓毒症合并AKI患者,结果提示 $70\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 的高剂量组与 $35\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 的标准剂量组间28、60、90d病死率均无差异,机械通气时间、RRT时间、肾功能恢复时间等器官支持治疗时间也无统计学差异^[26]。为了评价HVHF与SVHF的治疗效果,Clark等^[33]对1966年至2013年发表的有关比较HVHF与SVHF的RCT进行了系统回顾和荟萃分析,结果亦显示,对于脓毒症合并AKI的危重患者,高剂量治疗(按帕尔杜比采共识定义给予HVHF)对28d病死率和血流动力学、器官功能改善的有效性证据不足,在肾功能恢复时间、ICU住院时间、总住院时间、血管活性药物使用剂量等方面均未见优势,且由于其低磷血症和低钾血症等不良反应发生率较高,不推荐其作为该类患者的辅助治疗。由此,在“与SVHF比较,HVHF不能降低脓毒症患者病死率”结论的引导下,SVHF才重新得到大众的认可。《中国严重脓毒症/脓毒性休克治疗指南(2014)》提出,不建议使用HVHF治疗脓毒症合并AKI(2B)^[34]。在2015年Perner和Myburgh^[35]列举的近年来十大“短命”理论中,甚至有“高强度RRT改善ICU肾功能衰竭患者存活率”这一项。

4 SVHF与HVHF的不良事件及经济效益的比较

4.1 不良事件比较:抗菌药物的早期合理应用在脓毒症治疗中起重要作用,HVHF时抗菌药物的过量清除可能导致血药浓度不足和治疗失败,或者导致预后不良^[26],因此大多药物剂量需要重新调整。与SVHF相比,HVHF可导致更高比例的电解质紊乱(如低磷血症、低钾血症)和微量元素的

过量清除,这些都可能进一步混淆疗效和预后的关系^[12,26]。还有研究显示,CRRT期间低磷血症的发生可能预示预后不良的风险增加^[36-38]。

4.2 经济效益比较:CRRT是治疗脓毒症及AKI的重要措施,许多患者从中获益,但同时CRRT是一项复杂的技术,需要付出更多的医疗护理干预行为,增加医疗费用,还有并发症的风险。按目前已发表的文献显示,推荐ICU内CRRT方案由废液率 $35\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 变为 $20\sim 25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$,为评估其在临床与经济上的收益,Paterson等^[39]进行了一项研究,结果显示 $20\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 组和 $35\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 组CRRT总天数相近,使用滤器数量相同,而较低剂量组置换液使用量每日减少了25%(从37.7 L降至28.2 L),1年内CRRT所需一次性用品(透析液、过滤器、导管等)整体支出降低了12%,提示较低剂量治疗组不仅有与较高剂量组相同的临床效果,而且可以显著节约成本。

5 SVHF治疗的改进

虽然目前认为 $20\sim 25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 的SVHF治疗剂量已充足,但由于临床应用中存在可预测的治疗中断(CRRT套装更换与护理等)和不可预测的治疗中断(中途手术治疗和凝血异常等),实际交换量将较预期降低10%~15%^[40],是否需要通过在一段时间内增加置换液量来补偿HF中止带来的影响,仍需要进一步的临床证据支持。CRRT的治疗模式多种多样,为提升SVHF临床疗效,可选择高截留血液滤过(HCOHF)、高吸附血液滤过(HAHF)、连续性血浆滤过吸附(CPFA)、生物人工肾小管辅助装置(RAD)等方式辅助治疗。其中,HCOHF采用大孔径的滤过膜以增强对流效应,可以滤过大分子物质,清除炎性介质的效应强于其他CRRT模式^[41];HAHF通过加快血液滤器的更换频率来增加炎性介质吸附,从而有效减少血管活性药物的使用^[42];CPFA是在传统CRRT基础上串联血浆吸附的治疗模式,其安全性和改善患者免疫抑制状态的作用更好^[43-44];RAD是一种含有约109个具备生物活性的人远端肾小管细胞的生物反应器,可串联于CRRT管路中,对脓毒症的血流动力学及生存时间有明显改善^[45-46]。

6 小结

综上,对脓毒症致AKI危重患者, $20\sim 25\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 的SVHF剂量已充足,其疗效不减,还可减少不良事件、节约医疗资源;高剂量RRT并不能改善脓毒症患者的预后。可使用HCOHF、HAHF或CPFA等辅助治疗来提升临床疗效。

参考文献

[1] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [J]. *JAMA*, 2016, 315 (8): 801-810. DOI: 10.1001/jama.2016.0287.

[2] 鹿兴,李彤,李军,等.早期目标导向治疗对严重脓毒症或脓毒性休克患者病死率影响的Meta分析[J].中华危重病急救医学,2015,27(9):735-738. DOI: 10.3760/cma.j.issn.2095-4352.2015.09.007.

Lu X, Li T, Li J, et al. Effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta

analysis [J]. *Chin Crit Care Med*, 2015, 27 (9): 735-738. DOI: 10.3760/cma.j.issn.2095-4352.2015.09.007.

[3] 赵平,郑瑞强.连续性肾脏替代治疗严重感染所致急性肾损伤的研究进展[J].中国中西医结合急救杂志,2013,20(2):118-120. DOI: 10.3969/j.issn.1008-9691.2013.02.023.

Zhao P, Zheng RQ. Continuous renal replacement therapy research progress of acute kidney injury caused by severe infection [J]. *Chin J TCM WM Crit Care*, 2013, 20 (2): 118-120. DOI: 10.3969/j.issn.1008-9691.2013.02.023.

[4] Bagshaw SM, Uchino S, Bellomo R, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes [J]. *Clin J Am Soc Nephrol*, 2007, 2 (3): 431-439. DOI: 10.2215/CJN.03681106.

[5] Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012 [J]. *Intensive Care Med*, 2013, 39 (2): 165-228. DOI: 10.1007/s00134-012-2769-8.

[6] Di Carlo JV, Alexander SR. Hemofiltration for cytokine-driven illnesses: the mediator delivery hypothesis [J]. *Int J Artif Organs*, 2005, 28 (8): 777-786.

[7] Honoré PM, Matson JR. Extracorporeal removal for sepsis: Acting at the tissue level—the beginning of a new era for this treatment modality in septic shock [J]. *Crit Care Med*, 2004, 32 (3): 896-897. DOI: 10.1097/01.CCM.0000115262.31804.46.

[8] Ronco C, Tetta C, Mariano F, et al. Interpreting the mechanisms of continuous renal replacement therapy in sepsis: the peak concentration hypothesis [J]. *Artif Organs*, 2003, 27 (9): 792-801. DOI: 10.1046/j.1525-1594.2003.07289.x.

[9] Rimmelé T, Kellum JA. Clinical review: blood purification for sepsis [J]. *Crit Care*, 2011, 15 (1): 205. DOI: 10.1186/cc9411.

[10] Cariou A, Vinsonneau C, Dhainaut JF. Adjunctive therapies in sepsis: an evidence-based review [J]. *Crit Care Med*, 2004, 32 (11 Suppl): S562-570. DOI: 10.1097/01.CCM.0000142910.01076.A5.

[11] Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury [J]. *N Engl J Med*, 2008, 359 (1): 7-20. DOI: 10.1056/NEJMoa0802639.

[12] Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients [J]. *N Engl J Med*, 2009, 361 (17): 1627-1638. DOI: 10.1056/NEJMoa0902413.

[13] Van Wert R, Friedrich JO, Scales DC, et al. High-dose renal replacement therapy for acute kidney injury: systematic review and meta-analysis [J]. *Crit Care Med*, 2010, 38 (5): 1360-1369. DOI: 10.1097/CCM.0b013e3181d9d912.

[14] Jun M, Heerspink HJ, Ninomiya T, et al. Intensities of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis [J]. *Clin J Am Soc Nephrol*, 2010, 5 (6): 956-963. DOI: 10.2215/CJN.09111209.

[15] Kellum JA, Ronco C. Dialysis: results of RENAL—what is the optimal CRRT target dose? [J]. *Nat Rev Nephrol*, 2010, 6 (4): 191-192. DOI: 10.1038/nrneph.2010.15.

[16] Kellum JA, Mehta RL, Angus DC, et al. The first international consensus conference on continuous renal replacement therapy [J]. *Kidney Int*, 2002, 62 (5): 1855-1863. DOI: 10.1046/j.1523-1755.2002.00613.x.

[17] Grootendorst AF, van Bommel EF, van der Hoven B, et al. High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig [J]. *Intensive Care Med*, 1992, 18 (4): 235-240. DOI: 10.1007/BF01709839.

[18] Rogiers P, Zhang H, Smail N, et al. Continuous venovenous hemofiltration improves cardiac performance by mechanisms other than tumor necrosis factor- α attenuation during endotoxic shock [J]. *Crit Care Med*, 1999, 27 (9): 1848-1855. DOI: 10.1097/00003246-199909000-00024.

[19] Atan R, Crosbie D, Bellomo R. Techniques of extracorporeal cytokine removal: a systematic review of the literature [J]. *Blood*

- Purif, 2012, 33 (1-3): 88-100. DOI: 10.1159/000333845.
- [20] Honoré PM, Jacobs R, Boer W, et al. New insights regarding rationale, therapeutic target and dose of hemofiltration and hybrid therapies in septic acute kidney injury [J]. *Blood Purif*, 2012, 33 (1-3): 44-51. DOI: 10.1159/000333837.
- [21] Honoré PM, Joannes-Boyau O. High volume hemofiltration (HVHF) in sepsis: a comprehensive review of rationale, clinical applicability, potential indications and recommendations for future research [J]. *Int J Artif Organs*, 2004, 27 (12): 1077-1082.
- [22] Klouche K, Cavadore P, Portales P, et al. Continuous veno-venous hemofiltration improves hemodynamics in septic shock with acute renal failure without modifying TNFalpha and IL6 plasma concentrations [J]. *J Nephrol*, 2002, 15 (2): 150-157.
- [23] Gong D, Zhang P, Ji D, et al. Improvement of immune dysfunction in patients with severe acute pancreatitis by high-volume hemofiltration: a preliminary report [J]. *Int J Artif Organs*, 2010, 33 (1): 22-29.
- [24] Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? [J]. *Ann Intern Med*, 1996, 125 (7): 605-613. DOI: 10.7326/0003-4819-125-7-199610010-00011.
- [25] Bellomo R, Lipcsey M, Calzavacca P, et al. Early acid-base and blood pressure effects of continuous renal replacement therapy intensity in patients with metabolic acidosis [J]. *Intensive Care Med*, 2013, 39 (3): 429-436. DOI: 10.1007/s00134-012-2800-0.
- [26] Joannes-Boyau O, Honoré PM, Perez P, et al. High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial [J]. *Intensive Care Med*, 2013, 39 (9): 1535-1546. DOI: 10.1007/s00134-013-2967-z.
- [27] Tolwani AJ, Campbell RC, Stofan BS, et al. Standard versus high-dose CVVHDF for ICU-related acute renal failure [J]. *J Am Soc Nephrol*, 2008, 19 (6): 1233-1238. DOI: 10.1681/ASN.2007111173.
- [28] Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial [J]. *Lancet*, 2000, 356 (9223): 26-30. DOI: 10.1016/S0140-6736(00)02430-2.
- [29] Cornejo R, Downey P, Castro R, et al. High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock [J]. *Intensive Care Med*, 2006, 32 (5): 713-722. DOI: 10.1007/s00134-006-0118-5.
- [30] Boussekey N, Chiche A, Faure K, et al. A pilot randomized study comparing high and low volume hemofiltration on vasopressor use in septic shock [J]. *Intensive Care Med*, 2008, 34 (9): 1646-1653. DOI: 10.1007/s00134-008-1127-3.
- [31] 刘君玲. 连续性血液净化技术在脓毒症中的应用进展 [J]. *中国血液净化*, 2011, 10 (1): 44-46. DOI: 10.3969/j.issn.1671-4091.2011.01.013.
- Liu JL. The application progress of continuous blood purification in sepsis [J]. *Chin J Blood Purif*, 2011, 10 (1): 44-46. DOI: 10.3969/j.issn.1671-4091.2011.01.013.
- [32] Rimmelé T, Kellum JA. High-volume hemofiltration in the intensive care unit: a blood purification therapy [J]. *Anesthesiology*, 2012, 116 (6): 1377-1387. DOI: 10.1097/ALN.0b013e318256f0c0.
- [33] Clark E, Molnar AO, Joannes-Boyau O, et al. High-volume hemofiltration for septic acute kidney injury: a systematic review and meta-analysis [J]. *Crit Care*, 2014, 18 (1): R7. DOI: 10.1186/cc13184.
- [34] 中华医学会重症医学分会. 中国严重脓毒症 / 脓毒性休克治疗指南 (2014) [J]. *中华危重病急救医学*, 2015, 27 (6): 401-426. DOI: 10.3760/j.issn.2095-4352.2015.06.001.
- Society of Critical Care Medicine, Chinese Medical Association. The treatment guidelines of severe sepsis/septic shock in china [J]. *Chin Crit Care Med*, 2015, 27 (6): 401-426. DOI: 10.3760/j.issn.2095-4352.2015.06.001.
- [35] Perner A, Myburgh J. Ten 'short-lived' beliefs in intensive care medicine [J]. *Intensive Care Med*, 2015, 41(9): 1703-1706. DOI: 10.1007/s00134-015-3733-1.
- [36] 唐万欣, 陶冶, 付平, 等. 连续性静脉-静脉血液滤过中低磷血症防治及与危重评分相关性研究 [J]. *华西医学*, 2007, 22 (1): 40-41. DOI: 10.3969/j.issn.1002-0179.2007.01.024.
- Tang WX, Tao Y, Fu P, et al. A correlative research of the prevention of hypophosphatemia and chronic health evaluation II (APACHE II) in continuous venovenous hemofiltration [J]. *West China Med J*, 2007, 22 (1): 40-41. DOI: 10.3969/j.issn.1002-0179.2007.01.024.
- [37] Demirjian S, Teo BW, Guzman JA, et al. Hypophosphatemia during continuous hemodialysis is associated with prolonged respiratory failure in patients with acute kidney injury [J]. *Nephrol Dial Transplant*, 2011, 26 (11): 3508-3514. DOI: 10.1093/ndt/gfr075.
- [38] Schiff H, Lang SM. Severe acute hypophosphatemia during renal replacement therapy adversely affects outcome of critically ill patients with acute kidney injury [J]. *Int Urol Nephrol*, 2013, 45 (1): 191-197. DOI: 10.1007/s11255-011-0112-x.
- [39] Paterson AL, Johnston AJ, Kingston D, et al. Clinical and economic impact of a switch from high- to low-volume renal replacement therapy in patients with acute kidney injury [J]. *Anaesthesia*, 2014, 69 (9): 977-982. DOI: 10.1111/anae.12706.
- [40] Prowle JR, Schneider A, Bellomo R. Clinical review: Optimal dose of continuous renal replacement therapy in acute kidney injury [J]. *Crit Care*, 2011, 15 (2): 207. DOI: 10.1186/cc9415.
- [41] Uchino S, Bellomo R, Goldsmith D, et al. Super high flux hemofiltration: a new technique for cytokine removal [J]. *Intensive Care Med*, 2002, 28 (5): 651-655. DOI: 10.1007/s00134-002-1261-2.
- [42] Haase M, Silvester W, Uchino S, et al. A pilot study of high-adsorption hemofiltration in human septic shock [J]. *Int J Artif Organs*, 2007, 30 (2): 108-117.
- [43] 燕朋波, 李国强, 孙亮, 等. 基于 Diapact 连续性肾脏替代治疗装置实现连续性血浆吸附滤过功能的临床安全性研究 [J]. *中国中西医结合急救杂志*, 2016, 23 (3): 303-306. DOI: 10.3969/j.issn.1008-9691.2016.03.020.
- Yan PB, Li GQ, Sun L, et al. A clinical security research on function of continuous plasma filtration adsorption therapy based on Diapact continuous renal replacement therapy device [J]. *Chin J TCM WM Crit Care*, 2016, 23 (3): 303-306. DOI: 10.3969/j.issn.1008-9691.2016.03.020.
- [44] 应利君, 吕铁, 严静. 血液滤过联合血液吸附对伴人白细胞 DR 抗原低表达脓毒症患者的免疫改善作用 [J]. *中华危重病急救医学*, 2015, 27 (9): 750-753. DOI: 10.3760/cma.j.issn.2095-4352.2015.09.010.
- Ying LJ, Lyu T, Yan J. Effect of hemofiltration combined with hemoabsorption on improvement of immune function in septic patients with low expression of human leukocyte antigen DR [J]. *Chin Crit Care Med*, 2015, 27 (9): 750-753. DOI: 10.3760/cma.j.issn.2095-4352.2015.09.010.
- [45] 王恒进, 王笑云, 应旭旻, 等. 肾脏组织工程研究: 生物人工肾小管对多器官功能障碍猪白细胞介素 10 水平及生存时间的影响 [J]. *中国临床康复*, 2005, 9 (7): 82-84. DOI: 10.3321/j.issn.1673-8225.2005.07.063.
- Wang HJ, Wang XY, Ying XM, et al. Kidney tissue engineering: Effect of bioartificial renal tubule on interleukin-10 level and survival time in pigs with multiple organ dysfunction syndrome [J]. *Chin J Clin Rehabil*, 2005, 9 (7): 82-84. DOI: 10.3321/j.issn.1673-8225.2005.07.063.
- [46] Tumlin J, Wali R, Williams W, et al. Efficacy and safety of renal tubule cell therapy for acute renal failure [J]. *J Am Soc Nephrol*, 2008, 19 (5): 1034-1040. DOI: 10.1681/ASN.2007080895.

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