

中国严重脓毒症 / 脓毒性休克治疗指南 (2014)

中华医学会重症医学分会



指南手机版电子书

脓毒症 (sepsis) 是由感染引起的全身炎症反应综合征 (SIRS), 可发展为严重脓毒症 (severe sepsis) 和脓毒性休克 (septic shock)。严重脓毒症和脓毒性休克是重症医学面临的重要临床问题, 随着人口的老齡化、肿瘤发病率上升以及侵入性医疗手段的增加, 脓毒症的发病率在不断上升, 每年全球新增数百万脓症患者, 其中超过 1/4 的患者死亡^[1-6]。中华医学会重症医学分会 2007 年组织编写了《成人严重脓毒症与脓毒性休克血流动力学监测与支持指南》, 为脓毒症的诊治提供了规范和指导, 但是随着近年来国内外该领域研究的不断深入, 为了更好地指导我国重症医学工作者对严重脓毒症和脓毒性休克的治疗, 中华医学会重症医学分会组织专家应用循证医学的方法制定了本指南。

1 定义

脓毒症是指明确或可疑的感染引起的 SIRS。严重脓毒症是指脓毒症伴由其导致的器官功能障碍和 / 或组织灌注不足。脓毒性休克是指脓毒症伴由其所致的低血压, 虽经液体治疗后仍无法逆转。

2 诊断标准

脓毒症、严重脓毒症、脓毒性休克诊断标准见表 1~2。

表 2 严重脓毒症和脓毒性休克诊断标准

严重脓毒症是脓毒症伴由其导致的器官功能障碍和 / 或组织灌注不足 (以下任意一项)

- 脓毒症所致低血压;
- 乳酸水平超过实验室检测正常水平上限;
- 即使给予足够的液体复苏, 尿量仍 < 0.5 mL·kg⁻¹·h⁻¹ 至少 2 h;
- 非肺炎所致的急性肺损伤且 PaO₂/FiO₂ < 250 mmHg;
- 肺炎所致急性肺损伤且 PaO₂/FiO₂ < 200 mmHg;
- 血肌酐水平 > 176.8 μmol/L (2.0 mg/dL);
- 胆红素 > 34.2 μmol/L (2 mg/dL);
- 血小板计数 < 100 × 10⁹/L (100 000 μL);
- 凝血障碍 (INR > 1.5)

脓毒性休克是指脓毒症伴由其所致的低血压, 虽经液体治疗后仍无法逆转

3 检索方法

本指南针对相关重要临床问题进行文献检索。文献检索时间为 1993 年 1 月到 2014 年 12 月。文献检索首先确定包括脓毒症、严重脓毒症、脓毒性休克及特定问题的合适关键词, 在 MEDLINE、EMBASE 和 Cochrane Library (Cochrane 系统评价数据库, CDSR)、万方数据库、中国知网等综合数据库中检索, 文献质量要求为 Jadad 评分大于等于 3 分, Jadad 评分标准见表 3。

表 1 脓毒症诊断标准

明确或可疑的感染, 具备以下临床特点:

一般临床特征: (1) 发热 (体温 > 38.3℃); (2) 低体温 (体温 < 36℃); (3) 心率 > 90 次/min, 或大于不同年龄正常值的 2 个标准差; (4) 气促; (5) 精神状态的变化; (6) 明显水肿或液体正平衡 (24 h 超过 20 mL/kg); (7) 高血糖症 [血糖 > 7.7 mmol/L (> 140 mg/dL)] 且无糖尿病史。

炎症反应指标: (1) 白细胞增多 [WBC 计数 > 12 × 10⁹/L (> 12 000/μL)]; (2) 白细胞减少 [WBC 计数 < 4 × 10⁹/L (< 4 000/μL)]; (3) WBC 计数正常但幼稚白细胞总数超过 10%; (4) 血浆 C-反应蛋白大于正常值的 2 个标准差; (5) 血浆降钙素原大于正常值的 2 个标准差。

血流动力学变量: 低血压 [SBP < 90 mmHg (1 mmHg = 0.133 kPa), MAP < 70 mmHg 或成人 SBP 下降超过 40 mmHg 或低于年龄段正常值的 2 个标准差]。

器官功能障碍指标: (1) 动脉低氧血症 (PaO₂/FiO₂ < 300 mmHg); (2) 急性少尿 (即使给予足够的液体复苏, 尿量仍然 < 0.5 mL·kg⁻¹·h⁻¹ 且至少持续 2 h 以上); (3) 血肌酐上升 > 44.2 μmol/L (> 0.5 mg/dL); (4) 凝血功能异常 (INR > 1.5 或 APTT > 60 s); (5) 肠梗阻 (肠鸣音消失); (6) 血小板减少 [血小板计数 < 100 × 10⁹/L (< 100 000/μL)]; (7) 高胆红素血症 [血浆总胆红素 > 70 μmol/L (> 4 mg/dL)]。

组织灌注指标: (1) 高乳酸血症 (> 1 mmol/L); (2) 毛细血管再灌注能力降低或瘀斑形成。

注: WBC 为白细胞, SBP 为收缩压, MAP 为平均动脉压, PaO₂/FiO₂ 为氧合指数, INR 为国际标准化比值, APTT 为活化部分凝血活酶时间

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表 3 Jadad 评分标准

随机分组序列的产生方法
2 分:通过计算机产生的随机序列或随机数表产生的序列; 1 分:试验提到随机分配,但产生随机序列的方法未予交待; 0 分:半随机或准随机试验,指采用交替分配病例的方法,如入院顺序、出生日期单双数。
随机化隐藏
2 分:恰当:中心或药房控制分配方案、或用序列编号一致的容器、现场计算机控制、密封不透光的信封或其他使临床医生和受试者无法预知分配序列的方法; 1 分:不清楚:只表明使用随机数字表或其他随机分配方案; 0 分:不恰当:交替分配、病例号、星期日数、开放式随机号码表、系列编码信封以及任何不能防止分组的可预测性的措施。
双盲法
2 分:描述了实施双盲的具体方法并且被认为是恰当的,如采用完全一致的安慰剂等; 1 分:试验仅提及采用双盲法; 0 分:试验提及采用双盲,但方法不恰当,如比较片剂与注射剂而未提及使用双盲法。
退出与失访
1 分:对退出与失访的病例数和退出理由进行了详细的描述; 0 分:没有提到退出与失访。

4 推荐等级

我们按照推荐等级的评估、制定与评价系统 (Grades of Recommendations Assessment, Development and Evaluation, GRADE) 的原则,指导证据质量评估 [从高 (A 级) 到极低 (D 级)], 确定推荐等级 (表 4 ~ 5) [7-9]。

GRADE 系统的建立首先需对证据质量进行连续评估, 然后评估疗效与风险之间的平衡、负担以及费用, 根据这些评估情况确定治疗推荐等级。证据质量和推荐强度的明确分级是 GRADE 系统评价方法的关键及典型特点。本系统将证据质量分为高 (A 级)、中 (B 级)、低 (C 级)、极低 (D 级)。随机试验最初为高质量证据, 但可能因试验实施过程的限制、结果的不一致或不精确、证据为间接证据以及可能的报告偏倚而造成证据质量下降 (表 4)。间接证据包括研究人群、干预措施、结果的评定以及这些因素与相关问题之间的关联情况。

表 4 证据质量的确定

基本方法
A 级 (高级): RCT; B 级 (中级): 降级的 RCT 或升级的观察研究; C 级 (低级): 进展顺利的观察研究与对照 RCT; D 级 (极低级): 降级的对照研究或基于其他证据的专家意见
削弱证据强度的因素
1. 低质量的计划与实施的随机对照试验, 意味着存在偏倚的可能性较大 2. 结果的不一致性, 包括子群分析的相关问题 3. 证据的间接性 (不同群体、干预性、对照、结果、比较) 4. 结果的不精确性 5. 报告偏倚的高可能性
可能会增加证据强度的主要因素
1. 大的作用的重要性 (直接证据、相关风险 > 2 无可信的混杂因素) 2. 非常大的作用的重要性 (相关风险 > 5 且不会影响有效性) (通过两个水平) 3. 剂量 - 反应梯度
注: RCT 为随机对照试验

GRADE 系统将推荐强度分为强 (1 级) 或弱 (2 级)。决定推荐强度的影响因素见表 5。将推荐等级分配为强或弱的临床意义比证据质量分级更大。我们评估推荐项目的有利效果是否优于其不良效果, 推荐强度反映该评估可信度及专家的意见: 推荐的有利效果 (有益健康、更低的医护人员和患者负担、节省的费用) 将明显优于不良效果 (有害健康、更高的医护人员和患者负担、更高的费用)。在低质量证据下进行强烈推荐时, 其潜在不利之处亦需进行斟酌。弱推荐等级表明推荐的有利效果很可能将超过不良效果, 不过专家对这些推荐的权衡把握不足——这是因为某些证据质量较低 (因此优势和风险仍存在不确定性) 或其优点和缺点接近平衡。强推荐等级用“推荐”表示, 而弱推荐等级用“建议”表示。

对于不宜按照 GRADE 分级进行推荐的意见, 本指南给予了单独列举的说明并且显示“未分级” (UG)。

表 5 确定强推荐和弱推荐的因素

考虑因素	推荐的过程
高质量或中等质量证据 (是否存在高质量或中等质量的证据?)	证据的质量越高, 越可能采用强推荐
获益与伤害和负担之间平衡的确定 (是否存在确定性?)	理想后果与不良后果之间的差异确定性越大, 越可能采用强推荐。 净效益越小和该效益确定性越低, 越可能采用弱推荐
价值的确定性或相似性 (是否存在确定性或相似性?)	价值和偏好的确定性或相似性越大, 越可能采用强推荐
来源的含义	与备选或其他相关决定的成本相比, 干预成本越低 (即是消耗的资源越少), 越可能采用强推荐

意见不一致时,采用下述投票程序:(1)对持续存在分歧的部分,推荐或反对某一干预措施(和特定的替代措施相比较)至少需要50%的参与者认可,少于20%选择替代措施(选择认为是平等的)。未满足此项标准将不产生推荐意见。(2)一个推荐意见被列为强推荐而非弱推荐,则需要得到至少70%的参与者认可^[10]。

初始复苏

推荐意见1:推荐对脓毒症导致组织低灌注(经过最初的液体冲击后持续低血压或血乳酸 ≥ 4 mmol/L)的患者采取早期目标导向的液体复苏。在进行初始复苏的最初6 h内,下述复苏目标可以作为规范化治疗的一部分:(1)中心静脉压8~12 mmHg;(2)平均动脉压(MAP) ≥ 65 mmHg;(3)尿量 ≥ 0.5 mL \cdot kg⁻¹ \cdot h⁻¹;(4)上腔静脉血氧饱和度或混合静脉血氧饱和度 ≥ 0.70 或0.65。(1B)

Rivers等^[11]研究发现,早期定量液体复苏可提高急诊科脓毒性休克患者的存活率。最初6 h达到以上推荐中的生理标准,可使患者28 d病死率降低15.9%,此治疗策略称为早期目标导向治疗(early goal-directed therapy, EGDT)。我国8家重症加强治疗病房(ICU)314例脓毒症患者的多中心随机对照试验显示,EGDT组28 d病死率(75.2%)较对照组(57.5%)降低17.7%^[12]。然而,ARISE研究将51个临床研究中心的1600例脓毒性休克患者随机分为EGDT组和常规治疗组,并未发现两组间28 d病死率、ICU病死率、院内病死率存在统计学差异^[13]。我们对6项RCT^[11-16]研究进行Meta分析显示,EGDT可降低脓毒症患者的短期(院内、ICU或28 d)病死率。

然而,两项大规模多中心随机对照研究(ProCESS研究和ARISE研究)显示,EGDT组严重脓毒症和脓毒性休克的远期(60 d或90 d)病死率并无明显改善。ProCESS研究将美国31个急诊中心的1341例脓症患者随机分为程序化EGDT组、程序化标准治疗组(不置入中心静脉导管,但可应用升压药物和/或输血)和常规治疗组,结果显示,3组间60 d病死率无显著差异(21.0%、18.2%、18.9%;程序化标准治疗组比常规治疗组:相对危险度(RR)=1.04,95%可信区间(95%CI)=0.82~1.31, $P=0.83$;程序化EGDT组比程序化标准治疗组:RR=1.15,95%CI=0.88~1.51, $P=0.31$),3组间90 d病死率、1年病死率和呼吸支持治疗率也无显著差异^[17]。ARISE研究发现,EGDT组

(18.6%)和常规治疗组(18.8%)90 d病死率差异无统计学意义(RR=0.98,95%CI=0.80~1.21, $P=0.09$)^[13,18]。而Rivers等^[11]的研究发现,EGDT组60 d病死率(56.9%)较标准治疗组(44.3%)降低12.6%(RR=0.67,95%CI=0.46~0.96, $P=0.03$),差异有统计学意义。我们对以上3项RCT研究^[11,13,17]进行Meta分析显示,EGDT组和对照组对脓症患者远期(60 d或90 d)病死率无差异。

另外,由于ProCESS研究和ARISE研究涉及到常规治疗(Usual Care)的概念,即由实施治疗的临床医生自主决定复苏目标及监测方法。我们对目前为止设立EGDT组和常规治疗组的3项RCT研究^[14-15,17]进行Meta分析发现,两组间患者的病死率无差异。然而,由于多年来EGDT的广泛推广,常规治疗组的临床医生可能已经接受了较好的脓毒性休克的培训,掌握了治疗技术并且明确了有效的复苏目标^[18]。

综上所述,现有的循证医学证据支持EGDT可降低脓毒症患者的短期病死率(院内病死率、ICU病死率或28 d病死率),尚无证据显示EGDT增加脓毒症患者的远期(60 d或90 d)病死率。因此推荐,对脓毒症诱发组织低灌注的患者可采用EGDT进行液体复苏。

推荐意见2:推荐在严重脓毒症和脓毒性休克患者液体复苏过程中,乳酸和乳酸清除率可作为判断预后的指标。(1D)

研究表明,血清乳酸水平与患者的病情严重程度和预后密切相关,是组织低灌注的标志之一^[11,19-20]。而脓毒症诱发持续低血压但无高乳酸血症的患者病死率并不高^[21]。研究表明,血清乳酸水平 >1.5 mmol/L的脓症患者病死率有所增加^[22],是独立于临床体征和器官功能障碍之外的脓毒症预后因素^[23]。血清乳酸水平的降低标志着全身组织缺氧情况的改善,与病死率降低相关^[24],是较准确的预后指标之一^[25]。Jansen等^[26]研究发现,对入住ICU的高乳酸血症(>3.0 mmol/L)患者进行以乳酸为导向的治疗(lactate-guided therapy,在初始8 h内使血清乳酸水平每2 h下降 $\geq 20\%$),其院内病死率较对照组(无乳酸测量值)明显降低[风险比(HR)=-0.61,95%CI=0.43~0.87, $P=-0.006$],并建议在初始8 h内每2 h监测血清乳酸水平,之后每8~12 h监测血清乳酸水平。

然而,由于患者不同的机体基础状态(如肝脏、肾脏基础,及既往药物使用史),单纯监测某一时刻的血清乳酸水平不能准确反映组织氧供、氧耗

的动态变化。因此,临床为了准确评估机体组织细胞的灌注和氧代谢情况,以及患者对治疗的反应,动态监测血清乳酸水平的变化,将乳酸清除率作为评估预后的一个重要指标。美国急诊医学休克研究网络协作组(Emergency Medicine Shock Research Network, EMSHOCKNET)对166例脓毒症患者进行液体复苏的观察性研究发现,复苏6h内乳酸清除率 $>10\%$ 的患者院内病死率为 19% ,6h内乳酸清除率 $<10\%$ 的患者院内病死率为 60% ($P<0.001$)^[27]。Nguyen等^[24]通过对111例脓毒症患者进行前瞻性观察性研究发现,复苏6h内乳酸清除率 $\geq 10\%$ 者与 $<10\%$ 者相比,前者院内病死率、30d病死率、60d病死率均明显降低。Jones等^[28]通过对300例脓毒症患者液体复苏的研究发现,中心静脉血氧饱和度($ScvO_2$) >0.70 者的院内病死率为 23% ($95\%CI=0.17\sim 0.30$),6h内乳酸清除率 $>10\%$ 者的院内病死率为 17% ($95\%CI=0.11\sim 0.24$)。因此,复苏6h内乳酸清除率 $\geq 10\%$ 可能预示脓毒症患者的较低病死率^[24, 27-29]。但仍缺乏关于乳酸清除率的前瞻性多中心随机对照研究。

综上所述,血清乳酸水平是严重脓毒症和脓毒性休克患者预后的独立影响因素之一,复苏6h内乳酸清除率 $\geq 10\%$ 可能预示脓毒症患者的较低病死率。因此推荐,在严重脓毒症和脓毒性休克患者液体复苏过程中,乳酸和乳酸清除率可作为判断预后的指标。

液体与液体反应性

推荐意见3:推荐晶体液作为严重脓毒症和脓毒性休克的首选复苏液体。(1B)

严重脓毒症和脓毒性休克初始液体复苏时首选晶体液与胶体液,对患者的病死率无影响。Bansal等^[30]对7项多中心随机对照试验^[31-37]进行Meta分析显示,初始液体复苏选用晶体液(生理盐水、乳酸林格液)与胶体液(白蛋白、6%或10%羟乙基淀粉或其他胶体液)对脓毒症患者28~30d病死率无影响。CRISTAL研究的亚组分析显示,脓毒症患者进行液体复苏时应用晶体液(226/779例死亡)与胶体液(215/774例死亡),28d病死率无显著差异($HR=0.95, 95\%CI=0.78\sim 1.10$)。我们对4项RCT研究^[33, 36-39]进行的Meta分析显示,分别以晶体液(生理盐水、乳酸林格液)与胶体液(6%或10%羟乙基淀粉或其他胶体液)作为初始复苏液体,两组脓毒症患者的90d病死率无显著差异。由于胶体

液相对晶体液对病死率改善无明显受益,且价格较贵,因此推荐,对严重脓毒症和脓毒性休克的液体复苏首选晶体液。

推荐意见4:不建议使用羟乙基淀粉进行严重脓毒症和脓毒性休克的液体复苏。(2B)

Bansal等^[30]对Veneman、VISEP、CRYSTMAS、FINISS、6S、CHEST 6项RCT研究^[33-37, 39]进行的Meta分析显示,羟乙基淀粉与生理盐水、醋酸林格液比,对严重脓毒症或脓毒性休克28~30d病死率($OR=1.21, 95\%CI=0.98\sim 1.48$)、90d病死率($OR=1.29, 95\%CI=0.90\sim 1.82$)无改善。CRISTAL研究显示,羟乙基淀粉组与生理盐水组比,两组间28d病死率(28.00%比28.19%; $HR=0.97, 95\%CI=0.76\sim 1.25$)、90d病死率(32.00%比35.37%; $HR=0.89, 95\%CI=0.71\sim 1.11$)无显著差异^[38]。我们对以上RCT研究^[33-39]进行Meta分析显示,羟乙基淀粉较其他复苏液体对脓毒症和脓毒性休克的病死率无改善。Perner等^[40]进行了一项平行对照、双盲随机、多中心研究,纳入804例严重脓毒症患者,在液体复苏时分别选用6%羟乙基淀粉130/0.42和醋酸林格液,两组间6个月病死率(53.3%比47.5%; $RR=1.12, 95\%CI=0.98\sim 1.29, P=0.10$)、1年病死率(56.0%比51.5%; $RR=1.09, 95\%CI=0.96\sim 1.24, P=0.20$)无差异。因此,脓毒症患者液体复苏时选用羟乙基淀粉不能改善近期和远期生存率。

CHEST研究对近7000例ICU危重病患者进行研究,分别选用6%羟乙基淀粉130/0.42和生理盐水进行复苏,羟乙基淀粉组患者对肾脏替代治疗(RRT)的需求较高(7.0%比5.8%; $RR=1.21, 95\%CI=1.00\sim 1.45, P=0.04$),且肾损伤发生率更高(38.0%比34.6%, $P=0.005$)^[39]。Schortgen等^[41]的一项多中心随机研究发现,严重脓毒症或脓毒性休克患者应用6%的羟乙基淀粉200/0.60~0.66较3%明胶液有较高的急性肾损伤(AKI)发生率(42%比23%, $P=0.028$)。我们对6项RCT研究^[33-36, 39, 41]进行Meta分析显示,羟乙基淀粉与晶体液相比,前者可增加脓毒症患者的AKI发生率及RRT的需求。因此不建议使用羟乙基淀粉作为严重脓毒症或脓毒性休克的复苏液体。

推荐意见5:严重脓毒症和脓毒性休克患者液体复苏时可考虑应用白蛋白。(2B)

SAFE研究显示,严重脓毒症和脓毒性休克患者液体复苏时输注4%白蛋白很安全且效果与0.9%生理盐水无显著差异(合并脑外伤患者除外,脑外伤亚组病死率:白蛋白组比晶体组为24.5%比15.1%;

$RR=1.62, 95\%CI=1.12 \sim 2.34, P=0.009$)^[42]。Delaney等^[43]对17项相关研究进行Meta分析显示,白蛋白可能降低脓毒症患者28d病死率($OR=0.82, 95\%CI=0.67 \sim 1.00, P=0.047$)。一项纳入1 818例严重脓毒症患者的多中心随机对照的ALBIOS研究显示,应用20%白蛋白联合晶体液进行液体复苏,患者28d病死率与仅用晶体液组比无显著差异(31.8%比32.0%; $RR=1.00, 95\%CI=0.87 \sim 1.14, P=0.94$),90d病死率、新器官衰竭发生率也差异无统计学意义,然而白蛋白联合晶体液组7d内的液体正平衡量明显低于仅用晶体液组,平均心率低于仅用晶体液组,MAP高于仅用晶体液组^[44]。我们对CRISTAL研究(4%或20%白蛋白)、ALBIOS研究(20%白蛋白)、SAFE研究等5项RCT研究^[30,37-38,42,44]进行Meta分析显示,应用白蛋白进行液体复苏并不会增加严重脓毒症和脓毒性休克患者28d病死率。因此,严重脓毒症和脓毒性休克患者进行胶体复苏时可考虑应用白蛋白。然而目前的结论显示,液体复苏时使用白蛋白并不能降低患者病死率,且由于其价格较为昂贵,建议医师在治疗时认真考虑患者病情、药品价格及供应情况等社会因素。

推荐意见6:液体复苏时可考虑使用限氯晶体液复苏。(UG)

研究发现,大量使用生理盐水或以其为溶媒的液体进行液体复苏将导致稀释性高氯性酸中毒的发生^[45-46]。一项前瞻性、非盲、序贯试验对773例干预期(限氯液体治疗组,脓毒症患者55例)和760例对照期(不限氯液体治疗组,脓毒症患者75例; $P=0.08$)的危重患者的研究发现,限氯液体治疗组患者平均肌酐($14.8 \mu\text{mol/L}$)升高水平低于不限氯液体治疗组($22.6 \mu\text{mol/L}, P=0.03$),其肾脏损伤或衰竭的发生率明显低于不限氯液体治疗组(8.4%比14%, $P<0.001$),其需进行RRT的患者数量也明显少于不限氯液体治疗组(6.3%比10%, $P=0.005$),而两组间的院内病死率、住院时间、ICU住院时间及出院患者RRT治疗率无明显差异^[47]。Shaw等^[48]分析美国电子病历(US electronic health record, EHR)中近11万例全身炎症反应患者输入晶体液的相关资料发现,血清氯离子水平的增加与院内病死率增加相关。血清氯离子水平轻微增加(0~10 mmol/L)时的病死率及液体中总氯负荷低(100~200 mmol)时的病死率最低,校正液体容量和疾病严重性后这种相关性仍然成立;校正晶体液容量后,容量校正氯离子负荷为105~115 mmol/L

时病死率最低(2.6%);校正疾病严重性后,液体中氯离子负荷超过105 mmol/L与病死率增加有关($OR=1.094, 95\%CI=1.062 \sim 1.127$)。因此,可考虑根据实际情况选择限氯晶体液进行液体复苏。

推荐意见7:对无自主呼吸和心律失常、非小潮气量(V_T)通气的患者,可选用脉压变异度(PPV)、每搏变异度(SVV)作为脓毒症患者液体反应性的判断指标。(UG)

Marik等^[49]对29项研究进行Meta分析发现,PPV判断补液反应性的敏感度为89%,特异度为88%,诊断OR值为59.86,其最佳敏感度及特异度阈值为 $(12.5 \pm 1.6)\%$ [补液反应阳性组的PPV基线水平为 $(16.6 \pm 2.9)\%$;无反应组的PPV基线水平为 $(7.1 \pm 1.5)\%$, $P<0.001$];SVV判断液体反应性的敏感度为82%、特异度为86%,诊断OR值为27.34,其最佳敏感度及特异度阈值为 $(11.6 \pm 1.9)\%$ [补液反应阳性组的SVV基线水平为 $(15.3 \pm 3.4)\%$;无反应组的SVV基线水平为 $(8.4 \pm 1.9)\%$, $P<0.001$]。Yang等^[50]对纳入807例 $V_T \geq 8 \text{ mL/kg}$ 、无自主呼吸和心律失常的机械通气患者的22项研究进行Meta分析发现,以每搏量(SV)或心排血量(CO) $\geq 15\%$ 作为液体反应阳性标准,PPV判断液体反应性的敏感度为88%($95\%CI=81\% \sim 92\%$),特异度为89%($95\%CI=84\% \sim 92\%$)。Drvar等^[51]对46例窦性心律、接受机械通气[间歇正压通气(IPPV),吸入氧浓度(FiO_2)0.4, $V_T 7 \text{ mL/kg}$,呼气末正压(PEEP)5 cmH₂O(1 cmH₂O=0.098 kPa)]、左室射血分数(LVEF) ≥ 0.45 的脓毒症患者的单中心、前瞻性、观察性研究发现,以 $SV \geq 15\%$ 作为液体反应阳性标准,SVV用于区分容量反应组与容量无反应组的阈值为10%[敏感度为96.15%,特异度为100%,受试者工作特征曲线(ROC)下面积(AUC)=0.960, $95\%CI=0.859 \sim 0.996$],PPV用于区分容量反应组与容量无反应组的阈值为12%(敏感度为100%,特异度为100%,AUC=1.00, $95\%CI=0.93 \sim 1.00$)。

因此对无自主呼吸和心律失常、 $V_T \geq 8 \text{ mL/kg}$ 的机械通气患者,可选用PPV和SVV作为脓毒症患者补液反应性的判断指标。然而由于临床个体差异及单一指标的局限性,可应用一种以上血流动力学指标指导液体复苏治疗^[18]。

推荐意见8:机械通气、自主呼吸或心律失常时,可选用被动抬腿试验(PLR)预测脓毒症患者的液体反应性。(UG)

PLR是一种功能性血流动力学监测方法,指通

过监测 PLR 前后心排血量的变化来预测机体的容量反应性^[52]。通过抬高患者的双下肢,可使回心血量增加 300~400 mL,增加心脏前负荷,如 CO 增加 10% 以上,定义为容量反应性阳性。Cavallaro 等^[52]对 9 项^[53-58]PLR 预测成人 ICU 患者容量反应性和准确性的临床研究进行了系统回顾,结果显示,353 例 ICU 患者中有容量反应性者占 52.9%, PLR 预测容量反应性的敏感度为 89.4% (95%CI=84.1%~93.4%),特异度为 91.4% (95%CI=85.9%~95.2%);亚组分析显示, PLR 预测容量反应性的价值在窦性心律与心律失常、机械通气与自主呼吸者间差异无统计学意义。但在腹内压增高的患者, PLR 预测容量反应性的价值低^[59]。

综上所述, PLR 后 SV 或 CO 增加 10% 以上可作为脓毒性休克患者预测液体反应性阳性的指标。

碳酸氢钠

推荐意见 9:对低灌注导致的高乳酸血症患者,当 pH 值 ≥ 7.15 时,不建议使用碳酸氢盐来改善血流动力学状态或减少血管活性药物的使用。(2B)

两项双盲交叉 RCT 对用等当量生理盐水和碳酸氢盐治疗乳酸血症的效果进行比较,结果显示两种方法在血流动力学状态或血管活性药物需求方面无任何差异,但这些研究中 pH 值 < 7.15 的患者数量较少^[60-61]。

血制品

推荐意见 10:建议对无组织灌注不足,且无心肌缺血、重度低氧血症或急性出血的患者,可在血红蛋白(Hb) < 70 g/L 时输注红细胞,使 Hb 维持在目标值 70~90 g/L。(2B)

目前认为脓毒症患者输注红细胞会增加氧输送,而通常不会增加氧耗。虽然缺乏关于严重脓毒症患者最佳 Hb 的研究,但通过对重症患者的研究显示, Hb 70~90 g/L 与 100~120 g/L 相比,患者病死率无显著性差异^[62]。

推荐意见 11:对无出血或无计划进行有创操作的脓毒症患者,不建议预防性输注新鲜冰冻血浆。(2D)

尽管无临床研究评估输注新鲜冰冻血浆对脓毒症患者预后的影响,但当证实有凝血因子缺乏〔凝血酶原时间(PT)、国际标准化比值(INR)或活化部分凝血活酶时间(APTT)延长〕、活动性出血或在外科手术或侵入性操作之前,加拿大医学会、意大利输血协会已推荐使用新鲜冰冻血浆^[63-64]。但无研究

证实其他情况下预防性输注新鲜冰冻血浆对无出血患者有益。而近年两项共包括 80 项 RCT 的系统性综述均未发现,预防性或治疗性应用新鲜冰冻血浆有显著益处^[65-66]。

推荐意见 12:当严重脓毒症患者血小板计数(PLT) $\leq 10 \times 10^9/L$ 且不存在明显出血,以及当 PLT $\leq 20 \times 10^9/L$ 并有明显出血风险时,建议预防性输注血小板。当存在活动性出血或需进行手术、有创操作的患者需要达到 PLT $\geq 50 \times 10^9/L$ 。(2D)

输注血小板的指南来源于专家共识意见和化疗引起患者血小板减少症的经验^[67-68]。严重脓毒症患者与化疗患者一样很可能一定程度地限制了血小板的生成,此外,外周血小板的消耗可能也明显增加^[69]。推荐意见考虑了血小板减少症的病因、血小板功能异常、出血危险以及伴随的出凝血功能紊乱。严重脓毒症患者的出血风险增高,可能需要更高的 PLT,但目前暂无相关 RCT 研究支持。

缩血管药物

推荐意见 13:推荐缩血管药物治疗的初始目标是 MAP 达到 65 mmHg。(1C)

由于休克的根本病理生理改变在于组织、细胞甚至线粒体水平的氧供/需平衡失调,休克治疗的终点为改善全身和器官组织的灌注状态。经过充分的液体复苏后仍然存在着组织低灌注或面对致命性低血压时,应使用血管活性药物维持血压达到一定水平,建议血压治疗的初始目标是 MAP 达到 65 mmHg^[70-71]。近期 SEPSISPAM 研究^[72]发现,脓毒性休克患者维持较高 MAP 组(80~85 mmHg)与低 MAP 组(65~70 mmHg)相比,提高 MAP 水平未能显著改善 28 d 或 90 d 病死率,而心房颤动(房颤)的发生率有所升高。

最佳 MAP 应根据患者个体化情况而定,有高血压基础的脓毒性休克患者可能需要维持较高的 MAP。SEPSISPAM 研究还发现,有高血压基础的脓毒性休克患者维持较高的 MAP 水平(80~85 mmHg)需要 RRT 较少。

推荐意见 14:推荐去甲肾上腺素作为首选缩血管药物。(1B)

脓毒性休克患者去甲肾上腺素和多巴胺均能通过收缩血管而升高 MAP,与多巴胺相比,去甲肾上腺素对心率和 SV 的影响较小,却能更有效地改善脓毒性休克患者的低血压状态^[73]。近期有 8 项 RCT^[74-81]的 Meta 分析显示,脓毒性休克患者使用去甲肾上腺素和多巴胺在 28~30 d 病死率无

明显差别 ($RR=0.92$, $95\%CI=0.84\sim 1.00$)。但去甲肾上腺素组室性或室上性心律失常发生率明显低于多巴胺组 ($RR=0.46$, $95\%CI=0.38\sim 0.56$, $P=0.15$)^[74-75,79,81],因此推荐去甲肾上腺素作为脓毒性休克患者的首选血管升压药物。

推荐意见 15: 建议对快速性心律失常风险低或心动过缓的患者,可用多巴胺作为去甲肾上腺素的替代缩血管药物。(2C)

多巴胺通过提高脓毒性休克患者的 SV 和心率提高 MAP 和 CO,可能对心功能低下的患者更有效^[82],但与去甲肾上腺素相比,多巴胺具有更高的心律失常(如心动过速、室性或室上性心律失常)发生率^[74-75,79,81]。De Backer 等^[83]对脓毒性休克患者的一项 Meta 分析显示,多巴胺会增加患者心律失常的不良风险,因此建议,对无快速心律失常风险或存在绝对或相对缓脉的脓毒性休克患者使用多巴胺作为去甲肾上腺素的替代血管升压药物。

推荐意见 16: 当需要使用更多的缩血管药物来维持足够的血压时,建议选用肾上腺素(加用或替代去甲肾上腺素)。(2B)

尽管一些研究显示,肾上腺素对内脏循环有不良作用并会导致高乳酸血症,但这些作用是短暂可逆的,尚无临床证据表明肾上腺素会导致更差的预后^[84]。脓毒性休克中使用肾上腺素和去甲肾上腺素使 MAP 以及其他血流动力学指标达标的时间无差异^[85]。有 4 项 RCT^[84-87]将去甲肾上腺素和肾上腺素进行对比研究显示,两者间的病死率无差别 ($RR=1.04$, $95\%CI=0.83\sim 1.30$)。因此,当需要使用更多的血管升压药来维持足够的血压时,建议肾上腺素作为去甲肾上腺素的首选替代药物。

推荐意见 17: 可考虑在去甲肾上腺素基础上加用小剂量血管加压素以升高 MAP 或减少去甲肾上腺素用量(2B);较大剂量的血管加压素应用于挽救治疗(使用其他缩血管药物却未达到足够的 MAP)。(UG)

研究显示,脓毒性休克早期,血管加压素水平升高,随着休克的进展,血管加压素在 24~48 h 内会降至正常水平,称之为血管加压素相对缺乏,因为血压降低时,体内血管加压素水平应升高^[88]。小剂量血管加压素 (0.03 U/min) 可用于其他升压药治疗无效的脓毒性休克患者,以提高 MAP 或减少去甲肾上腺素的用量^[89-92]。VASST^[93]是一项多中心随机对照试验,比较了单用去甲肾上腺素与去甲肾上腺素联合血管升压素 (0.03 U/min) 的病死率及不良事件,结果显示,两组 28 d (35.4% 比 39.3%) 和 90 d

(43.9% 比 49.6%) 病死率无明显差异 ($P=0.26$, $P=0.11$),严重不良事件发生率无显著差异 (10.3% 比 10.5%, $P=1.00$);但在病情较轻的脓毒性休克患者中,去甲肾上腺素联合血管加压素的 28 d 病死率较低 (26.5% 比 35.7%, $P=0.05$);在病情较重的脓毒性休克患者中,28 d 病死率无差别 (44.0% 和 42.5%, $P=0.76$)。VASST 后续研究也表明,对伴有急性肾衰竭的脓毒性休克患者,应用小剂量血管加压素联用去甲肾上腺素较单用去甲肾上腺素更受益^[94]。我们对 7 项^[93-100]RCT 进行 Meta 分析显示 (1 717 例),脓毒症应用小剂量血管升压素或其类似药特利加压素与去甲肾上腺素相比,两者 28~30 d 病死率无显著差异 ($RR=0.96$, $95\%CI=0.85\sim 1.08$; $RR=0.95$, $95\%CI=0.85\sim 1.07$),不良事件发生率亦无差异 ($RR=0.95$, $95\%CI=0.66\sim 1.36$)。因此建议,在去甲肾上腺素基础上加用小剂量血管加压素,以升高 MAP 或减少去甲肾上腺素用量。

研究发现,大剂量血管加压素 (0.06 U/min) 可明显提高 MAP 并减少去甲肾上腺素的用量^[100-103]。但较大剂量的血管加压素不良反应较多^[104],如心肌缺血、内脏灌注减少、胆红素升高、血清转氨酶增高、PLT 降低等。因此,较大剂量的血管加压素仅作为其他血管升压药无效时的替代治疗。

特利加压素是血管加压素的类似物,具有类似的升压作用,但药效慢^[105]。一些研究^[106-111]显示,特利加压素因其具有高选择性的 V1 受体和较长的半衰期,升压作用更加有效,维持时间更久。一项针对脓毒性休克患者的随机对照试验 (TERLIVAP) 显示^[96],持续低剂量的特利加压素 ($1.3\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) 较血管加压素 (0.03 U/min) 能更有效地减少儿茶酚胺的用量,以及更低的心律失常发生率,但两者的预后无差别。

推荐意见 18: 不建议应用苯肾上腺素治疗脓毒性休克,除外下述情况: (1) 应用去甲肾上腺素引起严重心律失常; (2) 持续的高 CO 和低血压; (3) 当正性肌力药 / 缩血管药物与小剂量血管加压素联合应用未能达到目标 MAP 时,应用苯肾上腺素进行挽救治疗。(2C)

苯肾上腺素与去甲肾上腺素一样能改善 MAP,苯肾上腺素仅作用于 α -肾上腺素受体,较少导致心动过速,但由于其可减少 SV,应用范围有限,不常规应用于脓毒性休克治疗,下述情况除外: (1) 去甲肾上腺素引起严重心律失常; (2) 已知存在高 CO,但血压仍较低; (3) 当其他血管升压药未能达到目标 MAP 时,应用苯肾上腺素进行挽救治疗^[112-113]。

推荐意见 19 :不推荐将低剂量多巴胺作为肾脏保护药物。(1A)

一项大型随机临床试验和 Meta 分析^[114-115]在比较低剂量多巴胺和安慰剂的作用时发现,不论是主要疗效指标(如血清肌酐峰值、RRT 需求、尿量等),还是次要疗效指标(如患者生存率、ICU 治疗时间、住院时间、心律失常等)均无差异。因此,不推荐使用小剂量多巴胺保护肾功能。

推荐意见 20 :对所有需要应用缩血管药物的患者,建议在条件允许的情况下尽快置入动脉导管测量血压。(UG)

在休克状态,使用有创动脉导管监测血压比无创袖带血压计测量更准确、及时,且可进行连续的数据监测,有助于医务人员迅速评估患者的休克状态,指导治疗。

正性肌力药物

推荐意见 21 :存在下述情况时,建议以 $2 \sim 20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ 的速度输注多巴酚丁胺:(1) 心脏充盈压升高、CO 降低提示心肌功能障碍;(2) 尽管已取得了充足的血容量和足够的 MAP 仍出现灌注不足征象。(2C)

以往的研究表明^[116-120],多巴酚丁胺可提高脓毒症或脓毒性休克患者的 SV、CO、心排血指数(CI)。液体复苏后仍存在低血压的脓毒症患者,其 CO 可能降低、正常或升高。如果有 CO 降低,多巴酚丁胺是首选强心类药物。多巴酚丁胺可通过增加心肌收缩力提高氧输送,改善混合静脉血氧饱和度、血清乳酸水平等全身灌注指标,如果患者的血容量和 MAP 达到足够水平,而组织灌注不足却持续存在,建议增加心肌收缩力药物作为备选方案。但近年有研究表明^[121],多巴酚丁胺虽改善了全身血流动力学指标,却并未改善组织微循环(舌下微循环)情况,脓毒症患者多巴酚丁胺的应用需更多循证医学支持。

推荐意见 22 :如果充足的液体复苏和足够的 MAP, CO 仍低,可考虑使用左西孟旦。(2C)

脓毒性心肌抑制是严重脓毒症和脓毒性休克的严重并发症,约 50% 的严重脓毒症和脓毒性休克患者存在心功能抑制^[122]。多种机制参与导致心肌功能的抑制和损伤^[123-125],如交感神经系统的激活和过度兴奋,儿茶酚胺大量释放致心肌毒性,毒素和炎症因子的直接损伤,细胞内钙转运失调和钙敏感性的降低等,使心肌细胞肿胀、凋亡、坏死,导致心脏扩大、收缩或舒张功能障碍、心律失常等。

左西孟旦作为一种钙增敏剂,可使 SV、CO、CI 增加,而心率和心肌耗氧无明显变化^[126-129]。LIDO^[130]、CASINO^[131]、REVIVE II^[132]、SURVIVE^[133]、RUSSLAN^[134]等多项大型研究显示,对合并急、慢性心力衰竭的重症患者及心脏手术患者,左西孟旦在疗效和改善预后方面较安慰剂或对照组有优势。一项左西孟旦与安慰剂的随机对照研究证实^[135],左西孟旦除改善血流动力学状态外,还能改善脓毒症患者的组织微循环状态。我们对 5 项比较左西孟旦和多巴酚丁胺治疗脓毒症患者的小规模 RCT 进行 Meta 分析发现^[136-141],左西孟旦较多巴酚丁胺在提高 CI ($RR=0.58, 95\%CI=0.37 \sim 0.80, P=0.0007$)、改善氧供指数 ($RR=30.13, 95\%CI=5.83 \sim 54.44, P=0.02$) 方面具有更好的效果,但并未改善生存预后,两者 28 d 病死率无明显差异 ($RR=0.82, 95\%CI=0.63 \sim 1.07, P=0.14$)。基于脓毒性休克患者中的低血压风险,建议在充分液体复苏和 MAP 已达标的患者中使用左西孟旦。

推荐意见 23 :不推荐使用增加 CI 达到超常水平的疗法。(1B)

两项大型前瞻性临床试验将 ICU 重症患者的 CI 和氧输送量通过多巴酚丁胺达到超常水平并未获得更好的生存预后,高 CI 组与正常 CI 组的病死率无显著差异 ($RR=0.84, 95\%CI=0.53 \sim 1.31, P=0.07$)^[142-143],因此不推荐将 CI 提高到超常水平。

β 受体阻滞剂

推荐意见 24 :如果充足的液体复苏后 CO 不低、心率较快,可考虑使用短效 β 受体阻滞剂。(UG)

脓毒性休克时往往伴交感神经系统的过度激活,儿茶酚胺大量释放、心肌抑制及血管低反应性等^[144-145]。快速性心律失常的发生增加了心肌负荷和氧耗,限制心室舒张时间,减少冠状动脉的灌注, β 受体阻滞剂能抑制交感神经的过度兴奋,降低心率^[146]。Morelli 等^[147]进行了一项随机对照研究,纳入了 177 例充分液体复苏、心率 >95 次/min 的脓毒性休克患者,采用去甲肾上腺素维持 $MAP \geq 65$ mmHg,其中 77 例受试者接受持续短效 β 受体阻滞剂(艾司洛尔),将患者在 ICU 期间的心率维持在 $80 \sim 94$ 次/min;另 77 例受试者接受标准治疗;结果显示,艾司洛尔组所有患者均达到目标心率,治疗期间心率显著低于标准治疗组 ($P < 0.05$);艾司洛尔组 28 d 病死率为 49.4%,而标准治疗组为 80.5%;两组间不良事件无明显差异。鉴于 β 受体阻滞剂的负性肌力等作用,如果充足的液体复苏后

CO 不低、心率较快的脓毒性休克患者,可考虑使用短效 β 受体阻滞剂。

感 染

推荐意见 25 : 建议对有潜在感染的重症患者进行常规脓毒症的筛查,确定是否发生了严重脓毒症/脓毒性休克。(2C)

有研究表明,严重脓毒症/脓毒性休克的早期识别及早期治疗能改善预后,降低脓毒症相关病死率^[17,148-149]。同时也有证据表明,缩短严重脓毒症/脓毒性休克的诊断时间是降低脓毒症所致多器官功能障碍病死率的重要手段^[26,28],但目前尚无相关的 RCT 研究。

具体的脓毒症筛查工具的研究也只是观察性研究,结果提示,应用脓毒症的识别体系及评分系统(如:Robson 识别工具、脓毒症筛查表格、脓毒症早期识别卡片等,其主要包括:临床表现、感染相关的实验室检查和影像学检查等)在一定程度上降低了脓毒症的病死率^[150-158],但目前无 RCT 研究证明某项具体筛查工具的有效性。

推荐意见 26 : 推荐在抗菌药物应用前,均需留取恰当的标本进行需氧瓶、厌氧瓶的培养或其他特殊的培养。(1C)

留取恰当的标本进行细菌学培养有助于脓毒症的病原学鉴别及抗菌药物方案的确定。因为在首次给予抗菌药物治疗后的几小时内细菌可能被杀死,所以血培养标本必须在抗菌药物应用前抽取。建议同时留取 2 个或 2 个以上不同部位的血培养,以提高培养的敏感性。建议留取 2 套血培养标本,至少 1 份外周血标本,每个血管通路装置内留取 1 份血标本(48 h 内置入的血管通路除外),不同部位的血培养应同时抽取。其他部位培养(最好定量培养),如尿、脑脊液、伤口分泌物、呼吸道分泌物或其他可能的感染源标本,也应在抗菌药物应用前留取^[159]。建议对留置超过 48 h 的血管通路至少留 1 份血标本。建议抽血量应 ≥ 10 mL^[160]。注意不能因留取标本时间过长而延误抗菌药物治疗的时机。

推荐意见 27 : 当感染病原菌的鉴别诊断涉及侵袭性真菌病时,建议采用 1,3- β -D 葡聚糖检测(G 试验)(2B)和/或甘露聚糖(GM 试验)和抗甘露聚糖抗体检测。(2C)

重症患者是否合并系统性真菌(通常是念珠菌)感染的鉴别诊断具有挑战性,快速的诊断方法如采用 G 试验或 GM 试验和抗甘露聚糖抗体检测有助于重症患者检测念珠菌病^[161-170]。

我们对 10 个临床试验^[161-170]进行 Meta 分析显示,应用 G 试验诊断侵袭性念珠菌感染的 AUC 为 0.89,敏感度为 78% (95%CI=76%~81%),特异度为 81% (95%CI=80%~82%)。对两个临床试验进行 Meta 分析显示,应用 GM 试验诊断侵袭性念珠菌感染的 AUC 为 0.69,敏感度为 59% (95%CI=44%~66%),特异度为 71% (95%CI=62%~78%)。

这些测试通常早于标准培养方法,但单纯定植可导致检验结果的假阳性^[168]。但需要指出的是,目前国内外开展的 G 试验和 GM 试验的检测试剂及判定折点各不相同,导致其敏感性和特异性不统一。

推荐意见 28 : 建议应用降钙素原对可疑感染的重症患者进行脓毒症的早期诊断。(2B)

脓毒症的早期诊断非常重要。一项包含 30 个临床试验的 Meta 分析显示,应用降钙素原诊断脓毒症的敏感度为 77% (95%CI=72%~81%),特异度为 79% (95%CI=74%~84%),AUC 为 0.85 (95%CI=0.81~0.88),提示降钙素原是重症患者脓毒症早期诊断的有效指标^[171]。

近期有研究发现,肝素结合蛋白是可疑感染的重症患者早期诊断严重脓毒症/脓毒性休克的有效指标。前瞻性研究发现,发热患者中,高水平的血浆肝素结合蛋白有助于识别具有快速进展为脓毒症循环衰竭危险的患者^[172-175]。我们对上述 4 个 RCT^[172-175]进行 Meta 分析发现,肝素结合蛋白作为诊断脓毒症的敏感度为 80% (95%CI=76%~84%),特异度为 81% (95%CI=77%~84%),AUC 为 0.87 (95%CI=0.86~0.88),提示肝素结合蛋白也是重症患者严重脓毒症/脓毒性休克早期诊断的有效指标。

推荐意见 29 : 推荐一旦明确诊断严重脓毒症/脓毒性休克,应在 1 h 内开始有效的静脉抗菌药物治疗。(1C)

一旦确诊严重脓毒症/脓毒性休克,尽早静脉应用抗菌药物至关重要^[176-177]。对脓毒性休克患者而言,每延迟 1 h 应用抗菌药物将增加病死率^[148,176,178-180],无论是否伴有休克,严重脓症患者均应尽早应用抗菌药物^[148,176,178-184]。

推荐意见 30 : 推荐初始经验性抗感染治疗方案采用覆盖所有可能致病菌(细菌和/或真菌)且在疑似感染源组织内能达到有效浓度的单药或多药联合治疗。(1B)

目前有多项初始经验性抗感染治疗方案的相关研究,我们对 9 项临床试验^[176,179,185-191]进行 Meta 分析显示,如果初始经验性抗感染治疗方案未采

取恰当的抗菌药物治疗,将增加严重脓毒症/脓毒性休克的发病率和病死率($OR=0.38,95\%CI=0.23\sim 0.62$)。因此,严重脓毒症/脓毒性休克患者的初始经验性抗感染治疗方案应采用覆盖所有可能致病菌(细菌和/或真菌)且能进入疑似感染源组织内并达到有效浓度的单药或多药联合治疗。脓毒症患者常伴有肝肾功异常及体内液体异常分布,必要时需检测血药浓度来确保达到有效药物浓度及减少药物毒性^[192-193]。

推荐意见 31:推荐一旦有明确病原学依据,应考虑降阶梯治疗策略。(1D)

目前有几项观察性研究结果显示,抗菌药物的降阶梯治疗能降低病死率^[194-195]。而且有一项针对严重脓毒症的对比抗菌药物的降阶梯治疗与延续经验性治疗的多中心非盲随机非劣性试验显示,经验性抗菌治疗基础上的降阶梯抗菌药物战略导致了脓毒症患者 ICU 停留时间延长,降阶梯治疗组的住院天数为 9 d^[5-22],抗菌药物应用天数为 9 d (7~15 d);延续经验性治疗组的住院天数为 8 d (4~15 d),抗菌药物应用天数为 7.5 d (6~13 d),降阶梯治疗未导致脓毒症患者病死率升高及 ICU 住院时间延长^[196]。因此推荐,一旦有明确病原学依据,应考虑降阶梯治疗策略。

推荐意见 32:建议应用低水平的降钙素原作为脓毒症停用抗菌药物的辅助手段。(2C)

近期多项 RCT 研究显示,应用降钙素原作为脓毒症停用抗菌药物的辅助手段可减少抗菌药物应用时间且不增加病死率^[197-205]。多项观察性研究也证实了相同的结论^[206-207]。

我们对 9 项^[197-205]脓毒症及严重脓毒症/脓毒性休克的 RCT 进行 Meta 分析发现,采用降钙素原指导抗菌药物应用可减少患者的抗菌药物应用天数($RR=-2.00,95\%CI=-2.37\sim -1.64$),且不增加 ICU 住院时间($RR=-0.83,95\%CI=-2.35\sim 0.70$)及住院病死率($RR=0.92,95\%CI=0.62\sim 1.39$)。

推荐意见 33:建议脓毒症患者的抗菌药物的疗程一般为 7~10 d。(2C)

对脓毒症患者抗菌药物的应用、更换和停用均应依据临床医师的判断及患者的临床情况而定,一般情况下建议抗菌药物的疗程 7~10 d^[208],但对临床反应缓慢、感染灶难以充分引流和/或合并免疫缺陷者可适当延长疗程^[209-210]。如粒细胞缺乏患者并发脓毒症时,用药时间可适当延长;如存在深部组织感染及血流感染 > 72 h 的粒细胞缺乏患者,抗菌药物的疗程需延长至 > 4 周或至病灶愈合、症状消失^[209]。

推荐意见 34:对流感病毒引起的严重脓毒症/脓毒性休克尽早开始抗病毒治疗。(UG)

一些观察性研究发现,对疑似或确诊流感、严重流感引起的脓毒症,早期应用抗病毒治疗有可能降低病死率^[211-215]。常用抗病毒药物为神经氨酸酶抑制剂(奥司他韦或扎那米韦)。研究发现,双倍剂量的奥司他韦抗病毒治疗流感病毒引起的脓毒症未显示出优越性,建议应用常规剂量治疗^[216]。但尚无相关的 RCT 研究。

推荐意见 35:建议对可能有特定感染源(如坏死性软组织感染、腹腔感染、导管相关性血流感染)的脓毒症患者,应尽快明确其感染源,并尽快采取恰当的控制措施。(2C)

研究结果提示,脓毒症感染源控制原则包括感染源的早期诊断和及时处理(特别是脓肿引流、感染坏死组织清创、处理可能感染的装置等)^[217]。对可以通过手术或引流等方法清除的感染灶,包括:腹腔内脓肿、胃肠道穿孔、胆管炎、肾盂肾炎、肠缺血、坏死性软组织感染和其他深部间隙感染(如脓胸或严重的关节内感染),均应在复苏成功后尽快清除^[218]。如考虑感染源为血管通路,应及时清除^[219-220]。以上研究均为观察性研究,无相关的 RCT 研究。

机械通气

推荐意见 36:推荐对脓毒症诱发急性呼吸窘迫综合征(ARDS)患者进行机械通气时设定小 V_T (6 mL/kg)。(1B)

对 ARDS 患者应进行肺保护通气策略,设置较小的 V_T 。4 项 RCT 的 Meta 分析显示,ARDS 患者机械通气时设定较小的 V_T (6 mL/kg 比 12 mL/kg 左右),可改善 ICU 病死率^[221-224]。6 项 RCT 的 Meta 分析显示,ARDS 患者机械通气时设定较小的 V_T (6 mL/kg 比 12 mL/kg),可改善住院病死率^[221-225]。更小的 V_T (如 3 mL/kg) 可能减少呼吸机相关肺损伤,但对生存率的影响还有待进一步证实^[226]。

推荐意见 37:建议测量 ARDS 患者的机械通气平台压,平台压的初始上限设定为 30 cmH₂O 以达到肺保护的目。(2B)

一项 Meta 分析提示,对确诊 ARDS 患者采取限制气道压和 V_T 的方法可以降低病死率^[227]。一项回顾性研究显示,即使平台压 ≤ 30 cmH₂O 也应降低 V_T ^[228],因为小 V_T 会降低住院病死率^[229]。

推荐意见 38:对脓毒症诱发 ARDS 的患者应使用 PEEP 防止肺泡塌陷。(1C)

对 ARDS 患者提高 PEEP 可以保持肺单位处于开放状态,防止肺泡塌陷,有利于血气交换。6 项 RCT 的 Meta 分析显示,ARDS 患者使用较高 PEEP 与较低 PEEP 比,不改善住院病死率,但可以改善 ICU 病死率^[223,230-234]。对其中 3 项研究进行亚组 Meta 分析显示,中度或重度 ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$) 患者使用较高 PEEP 后,住院病死率也有所下降^[223,233-234]。避免呼气末肺泡塌陷有助于在使用相对较高平台压时最大程度地降低呼吸机引起的肺损伤。

推荐意见 39: 建议对脓毒症诱发的中重度 ARDS 患者使用俯卧位通气,尤其适用于 $\text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg}$ 患者 (2B)。

俯卧位通气可降低胸膜腔压力梯度,提高胸壁顺应性,促进分泌物的清除,从而改善 ARDS 患者的通气。9 项 RCT 的 Meta 分析显示,针对 ARDS 患者采用俯卧位通气时可改善 28 ~ 30 d 病死率^[235-243]。亚组的 Meta 分析显示,俯卧位通气对轻度 ARDS ($200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$) 患者 28 ~ 30 d 病死率改善不明显^[235-241],但可以改善中度 ARDS ($100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$) 患者 28 ~ 30 d 病死率,对重度 ARDS ($\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$) 患者 28 ~ 30 d 病死率改善最明显^[236,239-241]。在实施俯卧位通气时应结合肺保护性通气并较长时间(如 > 17 h)的实施才可能获益。同时,需注意避免致命的并发症,如气管插管和胸管意外脱出的发生。

推荐意见 40: 建议对脓毒症诱发的轻度 ARDS 试用无创通气 (non-invasive ventilation, NIV)。(2C)

NIV 避免了气管插管,可降低感染发生率,减少镇静用药。4 项 RCT 的 Meta 分析显示,与氧疗相比,NIV 可降低 ARDS 患者 30 d 住院病死率^[244-247]。亚组的 Meta 分析显示,NIV 可以改善轻度 ARDS ($200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$) 患者 ICU 再插管率和病死率^[246-247]; NIV 可以降低中度 ARDS ($100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$) 患者的 ICU 再插管率^[244-245,248-249],但不能改善 ICU 病死率^[244,248-249]。不同的 NIV 方式中,双水平气道内正压通气可降低 ICU 再插管率^[246,247-249]和 ICU 病死率^[247-249];持续气道内正压通气可降低 ICU 再插管率,但不能降低 ICU 病死率^[244,246]。

推荐意见 41: 高频振荡通气不能改善脓毒症 ARDS 患者病死率。(2A)

虽有研究显示,高频振荡通气可改善 ARDS 患者的氧合^[250-251],但包括 2013 年两项大型多中心 RCT 研究在内的 6 项研究的 Meta 分析显示,高频振荡通气不能降低 ARDS 患者的病死率^[250-255]。对高

频振荡通气在 ARDS 中的应用时机、适应证及方式还有待进一步的 RCT 研究来增加证据。

推荐意见 42: 建议无组织低灌注证据的情况下,对脓毒症所致的 ARDS 使用限制性液体策略。(2C)

肺水肿的机制包括毛细血管渗透性增加、静水压增加和胶体渗透压降低。血管外肺水增多与肺损伤评分及脓症患者发生 ARDS 的风险相关,监测血管外肺水并采取限制性液体策略对降低脓症患者 ARDS 的发生率有益处,在发生脓毒性休克的 12 h 以内,血管外肺水指数的下降意味着生存率的提高^[256]。小样本的研究显示,对重症患者采用限制性液体策略与采用液体正平衡策略相比,病死率更低,机械通气时间更短,住院时间更短^[257]。对 1 000 例急性肺损伤的患者进行研究^[258]发现,与开放液体治疗组相比较,限制性液体治疗组患者 60 d 病死率未见明显改善,相对于开放液体治疗组而言,限制性液体治疗组的患者氧合改善,肺损伤评分降低,机械通气时间缩短。另外既往认为,肺动脉导管 (PAC) 可以提供患者容量状态的相关信息,然而其应用结果并非十分理想。Heresi 等^[259]对 1 000 例 ARDS 患者的随机对照研究发现,与深静脉导管相比,使用 PAC 指导治疗并不能改善患者的生存率和器官功能,且会带来更多的并发症。此外,在其他不同类型的重症患者^[259-262],常规使用 PAC 并无明确益处。因此建议,对脓毒症所致的 ARDS,采用限制性的液体策略,但不建议常规使用 PAC。

镇静与肌松

推荐意见 43: 建议在脓症患者使用机械通气时,使用程序化镇静。(2A)

程序化镇静是指以镇痛为基础,有镇静计划和目标,并根据镇静深度评分调节镇静剂用量的系统镇静。使用程序化镇静可以既达到镇静目标,又减少镇静剂的用量。对 3 项 RCT 研究的 Meta 分析显示,使用程序化镇静,虽不能缩短 ICU 患者机械通气时间,但可以缩短 ICU 住院时间及总住院时间,并可以降低病死率^[263-265]。有理由认为,脓症患者会从中受益。

推荐意见 44: 建议脓毒症所致严重 ARDS 可早期短疗程 ($\leq 48 \text{ h}$) 应用神经肌肉阻滞剂。(2C)

2013 年一项纳入 3 个早期、 $\text{PaO}_2/\text{FiO}_2 < 150 \text{ mmHg}$ 或 200 mmHg 的 ARDS 患者的随机临床试验的 Meta 分析显示,与安慰剂相比,短疗程 ($\leq 48 \text{ h}$) 连续输注顺阿曲库铵可以降低 28 d 和 90 d 病死率,降低机械通气所致气压伤风险,但并不延长机械通气时间及不会增加 ICU 获得性肌无力的风险^[266]。

免疫调理

推荐意见 45 : 不建议严重脓毒症或脓毒性休克成人患者常规静脉注射免疫球蛋白。(2B)

脓毒症患者的病理生理机制复杂,其中炎症失衡及免疫功能异常是导致患者死亡的重要原因,包括一系列细胞因子、补体等的激活与释放,期中涉及到免疫系统的激活、免疫应答等多个过程^[267]。2013年Cochrane开展的一项系统回顾分析,纳入了脓毒症患者使用免疫球蛋白的RCT研究,确定了10个多克隆静脉注射免疫球蛋白(IVIG)试验(1430例)和7个富含IgM的多克隆IVIG研究(528例)^[268]。与安慰剂相比,IVIG显著降低了住院病死率($RR=0.81, 95\%CI=0.70\sim 0.93$)。同样,与安慰剂相比,7个富含IgM的IVIG试验也显示出了病死率显著下降($RR=0.66, 95\%CI=0.51\sim 0.85$)。但剔除其中的低偏倚风险的试验分析表明,使用多克隆IVIG不会降低病死率($RR=0.97, 95\%CI=0.81\sim 1.15$; 5个试验, 945例)。这些研究中3个试验使用了标准的多克隆IVIG^[269-271],两项使用了富含IgM的IVIG^[272-273]。此外,Karnad等^[274]的研究发现,以28d病死率作为主要观察终点,与安慰剂相比,使用乌司他丁的脓毒症患者其28d病死率明显降低。国内管向东教授的团队^[275]开展的多中心随机对照研究发现,对严重脓毒症患者使用胸腺肽 α_1 治疗也能降低28d病死率,因此认为,对脓毒症患者进行免疫调理以改善其免疫麻痹的状态有一定意义。

深静脉血栓预防

推荐意见 46 : 建议在无禁忌证的情况下,推荐对严重脓毒症患者应用肝素进行深静脉血栓的预防。(2B)

脓毒症导致凝血功能紊乱的机制包括内毒素及致炎因子将组织因子和血小板激活,导致血小板、内皮细胞之间的黏附、聚集,从而使血液凝固,血栓形成;抗凝血酶系统、蛋白C系统等生理性抗凝系统的减弱;纤溶系统作用减弱等,使血液处于高凝状态,因此,相对于普通ICU患者,严重脓毒症患者发生静脉血栓的风险更高,如果发生肺动脉栓塞等情况可能会致命。3项RCT研究^[276-278]及2项Meta分析^[279-280]显示,对无禁忌证的脓毒症患者,低分子肝素可以有效降低静脉血栓的发生率($RR=0.61, 95\%CI=0.46\sim 0.79$)及肺动脉栓塞的风险。因此深静脉血栓的预防非常必要。

营养支持治疗

推荐意见 47 : 严重脓毒症 / 脓毒性休克复苏后血流动力学稳定者尽早开始营养支持(48 h内),首选肠内营养(enteral nutrition, EN)。小剂量血管活性药物不是使用早期EN的禁忌证。(2C)

早期EN可维持肠道黏膜完整性,并防止细菌移位和器官功能障碍,虽然并未观察到早期EN对病死率的影响^[281-283],但有证据表明血流动力学稳定(能维持全身氧代谢和器官功能正常的循环状态,包括应用小剂量血管活性药物的情况)者早期EN可降低感染发生率^[281, 283-288],缩短机械通气时间、ICU住院时间及总住院时间^[285-286]。针对脓毒症患者是否可以开始早期EN(定义为 $<48\text{ h}$),检索近年来相关文献,研究结果并不一致,主要由于研究对象的异质性,以及干预手段的多样性。多项RCT研究均发现,24~48 h对包括创伤在内的ICU患者给予EN可以显著降低病死率,且可以显著减少ICU患者的住院费用^[289-291]。

推荐意见 48 : 存在营养风险的严重脓毒症患者,早期营养支持应避免过度喂养,以83.68~104.60 kJ/kg (20~25 kcal/kg)为目标。(2C)

将重症患者接受早期全热量和较低热量的EN进行比较,结果发现病死率未受到任何影响^[292-295],6个月或12个月的生存率及器官衰竭均无显著差异^[296]。虽然有研究发现,全热量喂养感染性并发症降低^[292],但腹泻和胃潴留症状有所增加^[294-295]。另一项研究发现,在给予EN的情况下,喂养量越多病死率越高^[297]。因此认为,患有严重脓毒症/脓毒性休克的最初1周,不建议过度喂养,采用允许性低热量/渐进性喂养的非全量喂养(以83.68~104.60 kJ/kg (20~25 kcal/kg))为目标,蛋白摄入量建议为 $1.2\sim 1.5\text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, 3~5 d不低于50%目标量,5~7 d不低于80%目标量可能是比较合适的营养支持策略^[294, 297-298]。

推荐意见 49 : 对有营养风险的脓毒症患者,接受EN 3~5 d仍不能达到50%目标量,建议添加补充性肠外营养(parenteral nutrition, PN)。(2C)

对于何时开始PN,在存在早期EN相对禁忌证的脓毒症患者中,相关研究均提示早期EN并未改善ICU病死率和住院病死率。一项纳入1372例重症患者的前瞻性多中心RCT研究(EPaNIC, 2011)发现,早期提供(24 h内)PN未缩短ICU住院时间及总住院时间,但也未增加60 d病死率^[299-301]。近期在英国进行的多中心研究(CALORIES Trial)也

提示,在重症患者早期营养的给予途径上,无论是肠外还是肠内途径,30 d病死率(33.1%比34.2%, $P=0.57$)、感染并发症、90 d病死率以及其他14项次级指标均无显著差异,但肠外途径营养组低血糖和呕吐显著减少^[302]。

补充性PN是在接受EN后3~5 d仍不能达到目标喂养量时开始,可以减少院内感染,且可以改善肠内营养不足的ICU患者的临床预后。Heidegger等^[303]发现,入住ICU 4 d后开始补充性PN,可以减少院内感染发生率,且可以改善EN供给能量不足ICU患者的临床预后。

推荐意见 50:对脓毒性休克患者不推荐使用谷氨酰胺;(UG) 应用含鱼油的脂肪乳剂能缩短脓毒症合并ARDS患者机械通气时间和ICU住院时间,但对降低病死率并无影响。(2C)

研究发现,低谷氨酰胺水平与重症预后较差相关,外源性补充谷氨酰胺可以改善肠道黏膜萎缩和渗透率,减少细菌移位;并且有增强免疫细胞功能,减少促炎性细胞因子的产生及提高谷胱甘肽水平和抗氧化能力的作用^[304-305]。早期多项随机对照研究及Meta分析显示,补充谷氨酰胺可能降低感染风险,缩短住院时间,并降低死亡风险^[306-310]。近年来多项大型临床研究结果对在重症患者中使用谷氨酰胺提出了质疑,SIGNET研究显示,静脉给予低剂量谷氨酰胺对接受PN的患者无益处^[311]。REDOXS研究显示,早期接受PN联合肠内谷氨酰胺治疗重症患者的病死率增加^[312]。

由于存在研究偏倚和终点事件影响因素不一,仍有待更多大规模前瞻性随机对照研究明确了PN添加谷氨酰胺的作用。虽然目前对谷氨酰胺的剂量、使用时间等仍有争论^[313],根据现有循证医学证据支持对脓毒性休克患者不添加谷氨酰胺^[314]。

ω -3脂肪酸十二碳五烯酸(EPA)和次亚麻油酸(GLA)均为类花生酸的前体。研究发现,EPA/GLA可使脓症患者病死率显著下降,非机械通气天数增加,并且降低新发生器官功能障碍的风险^[315]。随后多项研究虽未再观察到脓症患者病死率下降^[316-317],但证实其可缩短脓症患者ICU住院时间。对需要机械通气的急性肺损伤或ARDS患者,近期进行的多项研究结果显示,添加EPA和GLA的饮食能改善重症患者氧合和临床预后,降低病死率^[318-320]。因此应用含鱼油的脂肪乳剂有助于改善疾病严重程度,但对严重脓毒症/脓毒性休克患者的预后影响尚需更大规模的研究进一步明确。

血 糖

推荐意见 51:伴有高血糖[连续两次血糖>10 mmol/L (>180 mg/dL)]的严重脓症患者,应控制血糖 ≤ 10 mmol/L (≤ 180 mg/dL),并建议采用规范化(程序化)血糖管理方案。(1A)

严重脓症患者连续两次血糖>10 mmol/L (180 mg/dL),应考虑高血糖。既往多项研究提出,强化胰岛素治疗能减少感染发生率,降低病死率,尤其是外科ICU患者获益较多^[321-322]。多项随机对照试验^[323-327]及几项关于血糖控制范围的Meta分析^[328-332]显示,强化胰岛素治疗[3.89~6.11 mmol/L (70~110 mg/dL)]与传统血糖控制[10~11.1 mmol/L (180~200 mg/dL)]相比,并未降低外科、内科或综合ICU患者的病死率,反而增加了严重低血糖事件[≤ 2.2 mmol/L (40 mg/dL)]的发生。几项针对脓毒症和脓毒性休克的研究也同样得出上述结论^[325-326,333-334]。近期对不同类型ICU患者的血糖控制目标进行Meta分析^[310,321-323,325-327,335-341]显示,重症患者住院病死率及ICU病死率差异不大,而强化胰岛素组低血糖的发生率却明显增高,因此不推荐对重症患者采用强化胰岛素治疗。鉴于目前尚无证据显示,将血糖控制在6.11~7.78 mmol/L (110~140 mg/dL)比7.78~10 mmol/L (140~180 mg/dL)对预后有明显改善作用^[342-344],建议血糖上限目标应 ≤ 10 mmol/L (≤ 180 mg/dL),各医疗单位应采用合适的规范化(程序化)血糖管理方案进行血糖管理。

推荐意见 52:建议脓毒症/脓毒性休克患者每1~2 h监测一次血糖,直至血糖和胰岛素用量稳定后可每4 h监测一次。(UG)

2010年Holzinger等^[344]对持续动态血糖监测(CGMS)的回顾性研究发现,CGMS的低血糖发生率仅是对照组(2 h监测血糖)的1/7,但两组血糖低于6.11 mmol/L (110 mg/dL)、8.33 mmol/L (150 mg/dL)的发生率、平均血糖值、ICU住院时间及病死率等并无差异。CGMS有助于降低低血糖事件发生,但不同皮下组织间液血糖浓度的差异、不同血糖测定仪、病理性肥胖等因素,均可能使测定的准确性下降,此外CGMS设备常使医疗花费增加。多项关于强化胰岛素治疗的研究^[322,324-326,335]阐述了初期血糖监测间隔多为每30 min~1 h或每1~2 h,血糖相对平稳后每2~4 h、每4~6 h监测,但对此尚无较强的证据支持,尽管均是脓症患者,但其糖代谢状态并非相

同,具体监测间隔也应以具体病情为基础,在血流动力学不稳定和应用儿茶酚胺等情况下需注意低血糖的发生,多数患者1~2h的监测间隔应能满足血糖调整,又能避免低血糖的发生;血糖较稳定可延长监测时间,持续血糖监测应更有助于血糖的安全有效管理^[344-349]。需注意可能影响床边末梢血糖快速检测准确性和可重复性的因素,包括仪器类型和型号、操作者间差异,以及患者的因素,如红细胞比容(贫血时假性升高)、动脉血氧分压(PaO₂)和药物,尤其是高血压和使用儿茶酚胺的患者^[350-351],必要时测血浆血糖水平。

连续性肾脏替代治疗(CRRT)

推荐意见 53:建议脓毒症合并肾衰竭的患者,如需RRT,应采用CRRT。(2D)

CRRT治疗适应证主要是两大类:一是重症患者并发肾损害,二是非肾脏疾病或肾损害的重症状态。包括:急性肾衰竭、全身感染、SIRS(重症急性胰腺炎、创伤)、心脏手术后、重度血钠异常、顽固性心力衰竭、横纹肌溶解、中毒等。

CRRT与间歇性肾脏替代治疗(IRRT):近年有9项研究未发现何种RRT模式更为有利。一项回顾性队列研究认为,CRRT相对间歇性血液透析而言,前者进展为慢性透析的可能性较小^[352]。一项前瞻性随机对照试验纳入了104例ICU患者,比较了间歇性血液透析(3~4h一次,每日1次)与CRRT(18~35 mL·kg⁻¹·h⁻¹)对远期预后的影响,结果显示,两者28d生存率及总生存率未见明显差异。该研究认为,两种方法互补:间歇性血液透析适合于快速电解质和废物清除,CRRT适合于高热量需求和血流动力学不稳定者^[353]。美国一项多中心前瞻性RCT研究认为,CRRT与IRRT对ICU内AKI患者的结局无明显影响^[354]。法国21个医疗中心、跨学科的ICU内多器官功能障碍综合征(MODS)患者(包含63%脓毒症患者)的前瞻性随机试验发现,间歇性血液透析组与连续性静脉-静脉血液透析滤过组28、60、90d生存率及RRT时间、ICU住院时间、总住院时间均无明显差异^[355]。两项关于CRRT与延长的IRRT的研究认为,延长的IRRT与CRRT同样安全、有效,并未增加病死率^[356-357]。一项研究比较了CRRT和IRRT结果显示,两种方法的住院病死率及总住院病死率、肾功能恢复、住院时间均无明显差异,但CRRT对血流动力学稳定有较好的耐受性^[358-359]。另外两项包括部分脓毒症患者的研究未

发现何种RRT模式更有利^[360-361]。

CRRT的时机:法国12个ICU的80例患者的前瞻性随机、多中心研究认为,严重脓毒症/脓毒性休克患者早期使用CRRT是有害的^[362]。美国一项多中心观察性研究(PICARD)认为,尿素氮(>4.22 mmol/L (>76 mg/dL))较高时再行RRT生存率将降低^[363]。来自23个ICU的观察性队列研究(RENAL)发现,早期[达到RIFLE-I(急性肾损伤的诊断和分级标准1期)到CRRT的时间间隔]应用CRRT并未提高28d及90d生存率^[364]。有研究认为,早期使用2L/h的持续性静脉-静脉血液滤过(CVVH)并不能减少脓毒症相关的炎性介质,如白细胞介素(IL-6、IL-8、IL-10)、肿瘤坏死因子-α(TNF-α),也不能改善脓毒症引起的器官功能障碍。对无严重急性肾衰竭的MODS患者不建议行CVVH治疗^[365]。

推荐意见 54:不建议使用高容量血液滤过治疗脓毒症合并AKI。(2B)

有关RRT的剂量,我们对5项针对脓毒症或脓毒症为亚组的RCT进行Meta分析显示,标准容量血液滤过组(≤35 mL·kg⁻¹·h⁻¹)与高容量血液滤过组(>35 mL·kg⁻¹·h⁻¹)相比,两组病死率无明显差异,死亡相对风险为0.73(95%CI=0.46~1.16)^[366-370]。2013年发表的研究显示^[371],无充分证据推荐对脓毒症/脓毒性休克患者进行高容量血液滤过治疗,需要进行更大的多中心及相关结局资料的研究。2014年发表的高容量血液滤过对脓毒症引起AKI治疗效果的Meta分析显示^[372],无充分证据支持对脓毒症引起的AKI患者进行常规高容量血液滤过治疗有益处。

关于标准容量血液滤过(≤35 mL·kg⁻¹·h⁻¹),有2项RCT研究比较了相对高剂量血液滤过组(35 mL·kg⁻¹·h⁻¹)和相对低剂量血液滤过组(20 mL·kg⁻¹·h⁻¹),结果显示,两组重症患者病死率无差异。其中一项大规模多中心随机对照试验(含63%脓毒症患者)比较了强化RRT组(35 mL·kg⁻¹·h⁻¹,每周6次)和低强化RRT组(20 mL·kg⁻¹·h⁻¹,每周2次),结果显示,两组重症患者60d病死率无差异(RR=1.19,95%CI=0.88~1.62)^[373]。另一项包含了54%脓毒症患者的随机对照研究结果显示,标准容量血液滤过组(20 mL·kg⁻¹·h⁻¹)与高容量血液滤过组(35 mL·kg⁻¹·h⁻¹)的连续性静脉-静脉血液透析滤过治疗对ICU住院时间和30d生存率无明显差异^[374]。

对高容量血液滤过 ($>35 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$), 有 3 项研究认为更高剂量的血液滤过对脓毒症预后无益处。一项前瞻性随机多中心 IVOIRE 研究, 包含 18 个 ICU 的 140 例严重脓毒症合并 AKI 的患者, 比较了 $35 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 血液滤过与 $70 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ 血液滤过的结果显示, 两者 28、60、90 d 病死率均无明显差异^[375]。一项针对 280 例脓毒症合并 AKI 患者的单中心随机临床试验, 比较了特大容量血液滤过 ($85 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) 与大容量血液滤过 ($50 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) 的结果显示, 两者对 28 d、90 d 病死率无明显差异^[376]。一项小规模 (33 例) 随机对照试验显示, 高容量血液滤过 ($100 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) 与相对低容量血液滤过 ($35 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) 治疗脓毒症患者 6 h, 两者 60 d 生存率无差异, 但发现早期高容量血液滤过有利于清除血浆中某些炎性介质, 如 IL-6 等, 20 d 时炎性介质则无明显差异^[377]。

有 2 项研究显示, 高容量血液滤过可减少血管活性药物的使用; 其中一项单中心随机对照研究 (43 例) 比较了高容量血液滤过 ($65 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) 与高容量血液滤过 ($35 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) 的结果显示, 前者可增加尿量, 减少血管活性药物, 但两者病死率无差异, 由于该方案不是盲法, 尚需大规模试验证实^[366]。另一项单中心随机交叉试验 (11 例), 比较了高容量血液滤过 (6 L/h) 与标准容量血液滤过 (1 L/h) 治疗脓毒性休克患者 8 h 的结果显示, 高容量血液滤过能明显减少去甲肾上腺素用量 ($10.5 \mu\text{g}/\text{min}$ 降至 $1.0 \mu\text{g}/\text{min}$), 但该研究未比较病死率的情况^[378]。

糖皮质激素

推荐意见 55 : 不推荐常规使用糖皮质激素治疗脓毒性休克。(1B)

糖皮质激素应用于治疗肾上腺皮质功能不全, 但低剂量糖皮质激素是否预防重症患者严重感染和脓毒性休克的发生目前尚无定论。对低剂量糖皮质激素治疗脓毒性休克, 我们对 15 项 RCT 进行 Meta 分析发现, 糖皮质激素组 (1 058 例, 死亡 353 例) 和安慰剂组 (1 032 例, 死亡 359 例) 病死率无显著差异, 糖皮质激素不能降低病死率 ($RR=0.96$, $95\%CI=0.86 \sim 1.07$, $P=0.44$)^[379-393]。其中一项 RCT 为欧洲一项大规模多中心试验 (CORTICUS), 选取了无持续休克、死亡风险较低的严重脓症患者, 且不考虑血压对血管活性药物是否敏感, 结果显示, 糖皮质激素未降低病死率^[389]。有研究认为, 糖皮质激素会引起休克复发、消化道出血的可能性^[379]。

两项回顾性研究^[394-395]及两项小规模 RCT^[388, 396]证实了使用低剂量糖皮质激素可缩短使用血管活性药物的时间。英国一项大规模随机双盲对照试验提示, 糖皮质激素可缩短住院时间, 但不会影响病死率^[393]。德国的双盲随机对照交叉试验选择了有血管活性药物依赖的脓毒性休克患者, 结果显示, 氢化可的松可使血流动力学恢复稳定, 并减少肾上腺素用量^[397]。德国的前瞻性随机双盲对照试验显示, 应激剂量的氢化可的松可降低脓毒性休克患者创伤后应激障碍的发生率, 但未减少去甲肾上腺素的用量, 格拉斯哥昏迷评分 (GCS) 无改善^[398]。

应激性溃疡

推荐意见 56 : 建议使用 H_2 受体拮抗剂 (H_2RA) 或质子泵抑制剂 (PPI) 预防有出血危险因素的严重脓症患者发生应激性溃疡。(2B)

在包括 20% ~ 25% 的脓毒症的 ICU 住院患者中开展的多项研究证实了, 应激性溃疡的预防可减少上消化道出血的发生率^[399-402]。这种获益同样适用于严重脓毒症和脓毒性休克患者。3 项 Meta 分析显示, 应激性溃疡的预防虽然未被证实可降低病死率, 但可减少上消化道出血的风险^[403-405], 我们对 21 项 RCT 进行 Meta 分析显示, 预防性应用 PPI/ H_2RA 能减少上消化道出血^[406-426]。一项包含 13 项比较预防性使用 PPI/ H_2RA 的医院获得性肺炎风险 RCT 的 Meta 分析显示, 预防性使用 PPI/ H_2RA 可增加院内获得性肺炎的发生^[407-428], 对病死率却未见明显改善^[407-415, 419-422]。

推荐意见 57 : 应激性溃疡的预防, 建议优先使用 PPI。(2C)

Meta 分析证据表明, PPI 较 H_2RA 能更有效地预防上消化道出血^[405, 428-430], 而对住院时间及院内获得性肺炎的发生率、病死率无明显差异。预防上消化道出血的同时, 需警惕因胃内 pH 值升高而致感染风险增加的可能。加拿大的一项系统性评价表明, 抑酸剂与肠源性感染的增加有关, 尚需进一步研究其是否有因果关系^[427]。美国一项系统性回顾研究亦表明, 应用 PPI 可增加肠源性细菌感染的易感性^[431]。美国一项 Meta 分析和德国一项回顾性观察研究发现, ICU 患者 PPI 与难辨梭菌感染 (CDI) 的发生可能有关联, PPI 是难辨梭菌相关性疾病的独立危险因素, 这一危险因素在抗菌药物与 PPI 联合用药时危险性增加^[432-433]。

中医中药治疗

脓毒症属于祖国医学“外感热病”“脱证”“血证”“暴喘”“神昏”“脏竭症”等范畴。其发生主要由于素体正气不足,外邪入侵,入里化热,耗气伤阴;正气虚弱,毒邪内陷,络脉气血运行不畅,导致毒热、瘀血、痰浊内阻,瘀阻脉络,进而令各脏器受邪而损伤,引发本病。

脓毒症治疗的要旨是在脓毒症初期阶段即截断其病势,防止向严重脓毒症方向发展,这与《黄帝内经》提出的“治未病”理论不谋而合。目前临床多分为“四证四法”:毒热证与清热解毒法、腑气不通证与通里攻下法、血瘀证与活血化瘀法、急性虚证与扶正固本法。其中热证又分热邪之轻重、病位之浅深、病势之缓急,并结合具体脏腑进行分型治疗;瘀证分病情轻重、虚证分阴虚阳虚分别予以不同治疗。

1 辨证施治

1.1 清热解毒法:症见高热持续不退,烦躁,神昏,恶心呕吐,舌质红绛,脉数等。临床常用清热解毒中药及热毒清、热毒平、清瘟败毒饮、清气凉营汤、黄连解毒汤、凉膈散等清热解毒的方药治疗。中成药有清开灵、醒脑静注射液等^[434]。

1.2 通腑泻下法:症见腹胀,呕吐,无排便排气,肠鸣音减弱或消失,舌苔黄腻,脉弦等。代表方大承气汤能显著降低 MODS 患者病死率,用于脓毒症的治疗可减少炎性介质的产生、抑制炎症反应、调节免疫功能,同时还具有抗菌作用^[435]。

1.3 活血化瘀法:症见高热,或神昏,或疼痛状如针刺刀割,痛处固定不移,常于夜间加重,肿块,出血,舌质紫暗或有瘀斑,脉沉迟或沉弦等。常予以红花、赤芍、川芎、当归、丹参等活血化瘀中药及血府逐瘀汤等方药治疗。中成药以复方丹参注射液和血必净注射液为代表,而血必净治疗脓毒症显示出一定的疗效特点,但缺乏严格的循证医学证据证实其疗效、安全性和作用机制,应开展进一步深入研究^[436-437]。

1.4 扶正固脱法:阴脱症见意识恍惚或烦躁不安,面色潮红,两眶内陷,皮肤皱褶,身热心烦,口渴欲饮,少尿或无尿,舌红干燥,脉细数等,临床常用生脉注射液^[438]或参麦注射液以益气养阴固脱;阳脱症见冷汗淋漓,四肢逆冷,忽尔昏愤,面赤唇紫,口开目闭,手撒遗尿,舌淡或紫,脉微欲绝或散大无根等,临床常用参附注射液以益气温阳固脱。阴阳俱脱而症见急病重病,突然大汗不止或汗出如油,精神疲惫不支,声短息微,遗尿失禁,舌卷少津,脉微细欲绝或脉大无力等,可联用生脉注射液、参麦注射液及参附注射液。

2 单味药

2.1 大黄:单味生大黄可治疗严重脓毒症,具有促进胃肠蠕动、保护肠道黏膜、促进内毒素排出、减少细菌及毒素移位及抗炎抑菌作用^[439-440],对 MODS 有显著的预防治疗作用,能提高累及 4 个以上脏器 MODS 的存活率^[441]。

2.2 丹参:丹参的水溶性成分具有良好的抗血栓形成和改善循环作用,从而减轻脏器功能的损害。体外实验发现丹参有肯定拮抗脂多糖(LPS)作用,其对肺的保护作用可能是通过抑制或减少 TNF- α 等细胞因子在血及肺组织中的表达,减轻了由此介导的肺部急性炎症反应。

2.3 人参:诸多实验研究证实^[442],人参多种有效成分对内毒素结构的直接破坏作用不明显,但对其引起的发热、白细胞骤降及休克、死亡均有较强的拮抗和防护效果。

近年来动物实验显示,一些单味中药及提取物如黄芪、丹参、银杏叶制剂、雷公藤提取物、三七总皂苷、黄芩提取物等,可减轻组织或器官的炎性损伤。

3 针灸

电针足三里穴具有抗炎和减轻脏器损伤的作用,可降低脓毒症胃肠功能障碍患者的腹腔压力,改善胃液滞留,促进胃肠蠕动。

中医药治疗脓毒症尚存在一些问题与不足,主要是现有文献报道多限于简单的疗效观察,缺乏前瞻性、大样本、多中心 RCT 资料的支持。研究结果虽然有疗效,但对其产生疗效的机制认识的并不太清楚,结果可信度不高,尚需进一步研究。

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