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· 综述与讲座 ·

免疫低下宿主合并脓毒症的免疫监测与治疗

陈婉仪　裴飞　吴健锋

[摘要]　脓毒症是宿主对感染免疫反应失调引发的一系列危及生命的器官功能障碍综合征。其中，免疫低下宿主患者因持续免疫功能受损成为脓毒症发病及死亡的高危人群。免疫低下宿主合并脓毒症患者的临床表现不典型，易造成诊断延迟，错失最佳治疗窗口。因此，在免疫低下宿主合并脓毒症患者中进行免疫状态监测和精准免疫治疗是改善预后的关键。本文将聚焦该类人群免疫监测及免疫调节治疗的关键进展进行综述，旨在推动该领域从经验医学向循证医学快速转化。

[关键词]　免疫低下宿主；　脓毒症；　免疫抑制；　免疫监测；　免疫治疗
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作者单位：510080 广州，中山大学附属第一医院重症医学科 广东省急危重症医学临床研究中心
通讯作者：吴健锋，E-mail：wujianf@mail.sysu.edu.cn

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免疫低下宿主指因基础疾病、治疗干预或者先天性缺陷导致免疫应答能力受损的患者，其核心特征为免疫应答能力的结构性缺陷或者功能性抑制，典型群体包括 AIDS 患者、活动性结核患者、接受放疗/化疗/靶向治疗的恶性肿瘤患者、器官移植后长期使用免疫抑制剂或糖皮质激素治疗患者等[1]。近年来，随着器官移植手术普及和恶性肿瘤诊疗技术进步，免疫抑制治疗广泛应用，这使得 ICU 中免疫低下宿主的重症患者比例呈现逐渐上升的趋势[2]。此类患者因免疫防御屏障破损，不仅感染易感性显著增加，其病原体类型、临床表现及预后轨迹也均与免疫功能正常患者存在本质差异，从而需要得到高度关注[3-5]。

脓毒症是宿主对感染免疫反应失调引发的一系列危及生命的器官功能障碍综合征[6]。目前，脓毒症患者病死率为 20% ~50%，仍然是重症患者的首要死亡原因[7]。免疫低下宿主合并脓毒症后死亡率进一步增加[3]。免疫低下宿主合并脓毒症患者的特殊性体现在三个方面：(1)诊断困难：由于免疫系统应答能力受损，患者可能缺乏典型的全身炎症反应综合征，临床表现轻微或不典型，易导致诊断延迟，后续治疗难度极高[8]。(2)病理机制复杂：在基础免疫低下状态叠加脓毒症诱发的免疫抑制打击会进一步恶化免疫状态，形成双重免疫损伤，病理机制极其复杂。(3)循证医学证据匮乏：目前脓毒症免疫相关治疗的临床试验常常将免疫低下宿主排除在外，这导致现有的诊疗指南缺乏针对该人群的循证医学依据，而临床实践多依赖于经验性治疗，这极大地增加了医疗风险。

由于免疫低下宿主的定义缺乏统一标准，该类人群合并脓毒症时既无特异性诊断指标，也无明确治疗方案[9]。因此，本综述聚焦于免疫低下宿主和脓毒症，系统性梳理免疫低下宿主合并脓毒症患者的免疫功能监测与免疫调节治疗的最新进展，旨在推动该领域从经验医学向循证医学快速转化。

一、免疫功能监测

脓毒症免疫稳态失衡机制复杂，多种免疫标志物在脓毒症患者中均出现显著变化，如免疫细胞数量减少、功能受损等[10]。其中，单核细胞人类白细胞抗原-DR(mHLA-DR)、淋巴细胞数量常被认为是脓毒症免疫监测的较理想指标[11]。

1. mHLA-DR：其是目前脓毒症最常用的免疫监测指标之一，可通过标准化流式细胞仪进行快速检测。早期监测 mHLA-DR 有助于识别脓毒症免疫抑制及判断预后。脓毒症患者 mHLA-DR 表达往往明显降低[12]，其持续低表达与更高的死亡率和院内感染风险相关[13-16]。因此，mHLA-DR 表达降低可作为识别免疫抑制及感染风险的重要依据。此外，mHLA-DR 对脓毒症免疫抑制程度的分级作用已得到充分确定。以每个细胞上抗体(Ab/C)表达 5 000 和 15 000 作为阈值，根据 mHLA-DR 表达将免疫状态划分为正常(>15 000 Ab/C)、中度免疫抑制(5 000 ~ 15 000 Ab/C)和重度免疫抑制/免疫麻痹(<5 000 Ab/C)三个等级[17]。该分类方式简便有效，有助于快速识别不同程度的免疫抑制状态并给予相应干预。然而，该方法未能充分反映免疫状态的动态演变。在脓毒症病程中，免疫抑制程度受到患者基线状态、并发症及治疗干预的影响而不断变化，进一步影响后续治疗策略调整。近年来，基于无监督聚类、轨迹模型等方法研究逐渐增多，有研究将不同 mHLA-DR 变化轨迹与继发感染和死亡率相联系，发现 mHLA-DR 表达未恢复或下降时患者具有更高的继发感染和死亡风险[18-19]。这些发现丰富了 mHLA-DR 作为脓毒症免疫抑制监测指标的多重作用。近期的研究也证明了其在器官移植术后监测的临床价值，mHLA-DR 表达下降和恢复延迟与较高的感染发生率及感染严重程度相关。这些新的证据提示 mHLA-DR 可作为器官移植术后感染风险的早期潜在预警指标[20-21]。

2. 淋巴细胞数量及亚群：严重淋巴细胞减少是脓毒症适应性免疫损伤的重要特征之一[10,22]。早期监测淋巴细胞数量有助于识别脓毒症免疫抑制[23]。重症患者淋巴细胞数量减少与脓毒症发生率、病死率及慢性重症风险增加有关[24-25]。此外，淋巴细胞数量减少不同程度可反映患者预后变化趋势。以 0.7×10^9/L 和 1.1×10^9/L 为作为阈值，将淋巴细胞数量下降的程度划分为中度淋巴细胞减少(0.7×10^9/L ~ 1.1×10^9/L)和重度淋巴细胞减少(<0.7×10^9/L)两个等级，其下降程度越重，28 天病死率越高[26]。有研究进一步探索淋巴细胞数量变化轨迹与预后的关联性，发现淋巴细胞持续减少时患者持续炎症、免疫抑制、分解代谢综合征(PICS)发生风险和死亡风险更高[27]。这些发现明确了淋巴细胞数量动态演变对脓毒症患者免疫状态的区分价值和风险预警价值。此外，通过流式细胞术测定 $CD4^+$、$CD8^+$ T 细胞等亚群数目，可辅助免疫抑制识别及预后预测[22,28]。诸多研究也证实淋巴细胞在免疫低下宿主免疫监测的应用价值。在临床实践中，$CD4^+$ T 细胞绝对计数已经作为 AIDS 患者诊断分期、治疗启动及免疫重建效果评估的金标准，同时也是器官移植术后评估免疫抑制程度、免疫功能恢复趋势及继发感染风险分层的核心指标[29-32]。值得关注的是，免疫低下宿主合并脓毒症时，免疫系统可能呈现相似变化(如 $CD4^+$T 细胞计数下降)，但其变化幅度、动

态演变规律与脓毒症严重程度、器官功能损伤的关联性尚未明确。因此,如何建立适用这一特殊人群的免疫监测体系仍需进一步探索。

3. 其他监测指标:免疫细胞作为发挥免疫功能的主力,其数量减少直观反映免疫功能的下降[10]。在多种病理状态下,调节性 T 细胞(Treg)、髓源性抑制细胞(MDSCs)等抑制性免疫群体的扩增,为理解免疫低下宿主感染易感性增加提供重要依据[10]。

Treg、MDSCs 等抑制性免疫细胞可相互影响,通过抑制 T 淋巴细胞增殖、分泌抑制性细胞因子等方式介导免疫抑制[33-34]。Treg、MDSCs 比例升高与脓毒症患者更高的感染和死亡风险密切相关[34-35]。此外,其在肿瘤、器官移植领域的应用也备受关注。器官移植术后,Treg 有助于维持免疫系统过度激活和抑制之间的微妙平衡,其比例升高与移植物存活率提高相关[36-38]。在肿瘤免疫中,肿瘤微环境和外周血中的 Treg 被认为是潜在预后标志物[39]。肿瘤患者放疗后 MDSCs 产生增多与淋巴细胞减少及生存率下降相关[40]。关注抑制性免疫细胞有助于加强对患者免疫抑制网络的理解。然而,由于 Treg 存在异质性、动态性及其在肿瘤免疫中的双重作用尚不明确,Treg 在免疫低下宿主合并脓毒症患者中的应用仍面临诸多限制[41-43]。

二、免疫调节治疗

免疫低下宿主因原发病复杂的病理生理过程及长期治疗带来的免疫功能损伤,在发生脓毒症初期即面临较高的严重程度负荷。如何权衡原发疾病和脓毒症综合治疗之间的平衡,成为影响该类人群预后的关键。

1. 原发疾病与脓毒症治疗的平衡:当免疫低下宿主合并脓毒症时,应遵循脓毒症管理的一般原则(包括迅速开始适当抗感染、复苏)。然而,免疫低下宿主合并脓毒症的疾病状态不仅与脓毒症发生有关,更与其原发疾病、治疗措施密切相关。如孤立的恶性肿瘤和其治疗(包括放化疗、手术、骨髓移植)会增加脓毒症的发生风险,脓毒症等感染性疾病也会影响肿瘤的生长和预后。因此,对普通脓毒症患者有效的策略可能对合并恶性肿瘤的脓毒症患者无效,甚至有害[44]。

在临床实践中,部分原发疾病的治疗常常与脓毒症抗感染的核心治疗相互冲突。未经过精确免疫学评估而粗略调整免疫抑制药物,可能会加重感染或增加移植物排斥风险。因此,移植患者免疫抑制剂调整、自身免疫病患者糖皮质激素、生物制剂的使用等需要在维持基础疾病稳定与控制感染进展之间权衡[31,45-46]。对于 AIDS 患者,发生严重感染时具有病毒再激活的风险,及时开始或恢复高效抗反转录病毒疗法有助于改善预后[47]。在免疫低下宿主中,如何在降低脓毒症相关死亡风险的同时,兼顾原发病控制、优化免疫抑制剂使用,是目前尚未解决的难题,大多数治疗决策仍需依赖临床经验和个体化评估。《脓毒症免疫抑制监测与治疗临床专家共识》[48]建议,这类特殊人群可考虑进行免疫调节治疗。

2. 免疫稳态的调节治疗:对于免疫低下宿主,导致预后不良的核心矛盾在于基础免疫抑制叠加脓毒症诱导的免疫打击。目前,基于精准治疗理念,通过靶向药物逆转特定的免疫抑制表型是脓毒症免疫调节治疗的研究重点。

针对 mHLA-DR 表达下降或恢复不足的髓系细胞功能障碍,干扰素(IFN)-γ、粒细胞巨噬细胞集落刺激因子(GM-CSF)可以恢复单核/巨噬细胞的吞噬功能和抗原递呈能力[49-51]。1997 年,一项纳入 9 例脓毒症患者的研究发现 IFN-γ 具有逆转脓毒症免疫抑制的功能[49]。目前,关于 GM-CSF 与疾病预后相关的研究结论尚未统一。相关研究表明,GM-CSF 可以改善疾病严重程度,缩短机械通气及住院时间[51]。这项双盲、随机、安慰剂对照的多中心临床试验发现,对连续两天 mHLA-DR 表达低于 8 000 mAb/C 的患者进行 GM-CSF 治疗后,相比于对照组,脓毒症患者免疫细胞数量显著增加,同时 mHLA-DR 表达得到恢复。也有研究表明,GM-CSF 治疗并不能改善成人或小儿脓毒症患者的预后[52-53]。这可能与研究方法、纳入患者的异质性有关,以 mHLA-DR 为导向的 GM-CSF 免疫调节治疗的临床获益仍需新的证据证实。此外,GM-CSF 也具有直接抗肿瘤特性及抗癌相关免疫调节能力,可加速造血能力恢复并逆转移植后移植物失败的结局[54]。暂无相关临床试验证实 GM-CSF 在肿瘤合并脓毒症双重免疫打击的情况下是否同样有效。

针对淋巴细胞耗竭,IL-7 治疗可逆转淋巴细胞减少、促进淋巴细胞增殖活化,对继发院内感染风险控制有益[55-56]。研究证实,这种治疗在接受抗反转录病毒治疗后仍出现淋巴细胞减少的 AIDS 患者人群中应用也同样有效[57]。然而,目前的临床试验并未证实 IL-7 的应用对降低脓毒症患者死亡率有益[58-59]。此外,以胸腺肽 α1(Tα1)为代表的广泛免疫调节剂,以及抗程序性死亡受体-1(PD-1)/程序性死亡配体-1(PD-L1)抗体等免疫检查点抑制剂,已经应用于肿瘤、移植患者,它们在脓毒症患者中也展现出逆转免疫抑制的潜力[60-62]。目前,Tα1 能否改善脓毒症预后尚不能定论,脓毒症人群及治疗的异质性使研究结果不能统一[63-65]。一项关于 Tα1 治疗脓毒症疗效和安全性的多中心、随机、对照试验(TESTS)表明,Tα1 可能对老

年和慢性病患者有益[64]。该人群常常因慢性全身性炎症及免疫衰老而表现出潜在免疫功能低下的特点，我们推测 Tα1 可能是免疫低下宿主合并脓毒症患者潜在有效的药物[66-67]。未来还需要高质量的临床研究来证明它在免疫低下宿主合并脓毒症治疗中的安全性和有效性。

三、展望

1. 构建基于个体免疫特征的监测体系：目前，免疫低下宿主合并脓毒症患者的临床评估主要基于既往病史、临床表现及常规生物标志物的评估，缺乏充分的免疫学描述[67]。研究表明，自身免疫病患者免疫抑制剂的使用可以降低其发生脓毒症时的疾病严重程度并改善预后[68]。这进一步凸显了免疫低下宿主合并脓毒症人群的异质性，强调需要一种更精确的结构化监测体系来全面评估患者的免疫状态，旨在加强对免疫低下宿主合并脓毒症患者的管理。目前，mHLA-DR、淋巴细胞数量等生物标志物已成为临床实践中广泛用于指导患者分层及治疗的免疫监测指标[48]。在缺乏免疫低下宿主共识定义的情况下，基于单一生物标志物的分层难以界定出治疗有效的临床分型。在此基础上整合免疫细胞亚群、功能测定、分子亚型等多维信息可构建个体化免疫网络，精确识别该类人群高度异质的免疫状态，从而实现精准管理[47]。面对免疫低下宿主合并脓毒症患者复杂的病理机制，深入挖掘不同原发疾病背景下发生脓毒症时特有的或共同的免疫变化轨迹，有助于识别关键的干预靶点，为个体化精准治疗奠定生物学基础。近年来，随着多组学、机器学习、大语言模型等技术发展，新兴的免疫监测工具层出不穷，这可能是未来实现精准识别脓毒症各类风险人群并分层管理的研究方向之一。

2. 转向基于循证医学的综合管理策略：目前，诊疗指南缺乏对于免疫低下宿主合并脓毒症患者的循证医学依据，这限制了脓毒症相关临床试验结论在该类人群中的应用。实现该类人群标准化管理的关键挑战在于病理机制复杂且尚不明确，如何维持原发疾病和脓毒症之间的治疗平衡过度依赖医生的临床经验，施加干预的安全性和有效性缺乏可靠依据。在此基础上，Hjalmar 教授团队建议未来开展临床试验不应排除免疫功能低下患者，并提出具体可行的临床试验分层原则：结合客观的免疫标志物分析、基础疾病免疫状态评估、并发症等风险因素以及遗传内型进行综合评价，优化患者的免疫状态分层，为免疫功能低下特定人群的治疗提供循证医学证据[67]。此外，个性化免疫调节治疗在恢复免疫功能、减少感染风险及改善重症脓毒症患者预后等方面有极大的应用前景。重组 GM-CSF、重组 IL-7、Tα1、抗 PD-1/PD-L1 抗体等免疫调节药物靶向不同的免疫抑制机制，相关研究已经在临床转化实践中取得了一定成果。未来的临床试验考虑将免疫功能低下人群纳入研究，旨在为该类人群提供明确的治疗方案，为其综合管理提供可靠依据。

四、小结

免疫低下宿主是脓毒症发生的高危人群。当前免疫低下宿主合并脓毒症患者的治疗多依赖于临床经验，这极大地增加了管理难度和治疗风险。准确地监测免疫状态并给予靶向免疫调节治疗，是突破当前治疗瓶颈、改善预后的关键。因此，基于免疫功能低下合并脓毒症患者的临床试验将推动该领域从经验医学向循证医学转化，为这一特殊人群带来治疗的新希望。

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