Journal of Clinical Personalized Medicine 临床个性化医学, 2025, 4(3), 259-265
Published Online June 2025 in Hans. https://www.hanspub.org/journal/jcpm
https://doi.org/10.12677/jcpm.2025.43341

Hans汉斯

# 脓毒症异质性与精准医学：从临床综合征到分子机制的分型挑战

盛　硕[1]，谢学猛[2]，李嘉铮[1]，孙　强[2*]

[1]济宁医学院　临床医学院，山东　济宁
[2]济宁医学院附属医院重症医学科，山东　济宁

收稿日期：2025年5月5日；录用日期：2025年5月27日；发布日期：2025年6月6日

## 摘　要

**脓毒症作为一种宿主免疫反应失调引发的致死性器官功能障碍，其高死亡率与多维异质性密切相关，涉及病原体多样性、宿主免疫动态差异及分子机制复杂性。传统“一刀切”治疗模式因无法应对异质性而面临临床试验失败与疗效瓶颈。精准医学通过整合多组学技术(如转录组学、单细胞测序)与人工智能，致力于解析脓毒症的分子内型与动态表型，推动个体化治疗。然而，精准医学转化仍面临挑战，包括内型动态演变、临床试验设计适配性不足、资源匮乏地区的技术可及性及数据伦理问题。未来需通过跨学科协作、自适应临床试验及低成本技术研发，推动脓毒症精准分型从理论迈向临床实践，最终突破传统治疗困境，改善患者预后。**

## 关键词

**脓毒症，精准医学，分子机制，分型**

# Sepsis Heterogeneity and Precision Medicine: Typing Challenges from Clinical Syndromes to Molecular Mechanisms

**Shuo Sheng[1], Xuemeng Xie[2], Jiazheng Li[1], Qiang Sun[2*]**

[1]Department of Clinical Medicine, Jining Medical University, Jining Shandong
[2]Department of Intensive Care Unit, Affiliated Hospital of Jining Medical University, Jining Shandong

Received: May 5th, 2025; accepted: May 27th, 2025; published: Jun. 6th, 2025

*通讯作者。

文章引用: 盛硕, 谢学猛, 李嘉铮, 孙强. 脓毒症异质性与精准医学: 从临床综合征到分子机制的分型挑战[J]. 临床个性化医学, 2025, 4(3): 259-265. DOI: 10.12677/jcpm.2025.43341

## Abstract

**Sepsis, a life-threatening organ dysfunction caused by a dysregulated host immune response, exhibits high mortality rates closely associated with its multidimensional heterogeneity, encompassing pathogen diversity, dynamic variations in host immunity, and complexity in molecular mechanisms. Traditional "one-size-fits-all" treatment paradigms have encountered clinical trial failures and therapeutic efficacy bottlenecks due to their inability to address this heterogeneity. Precision medicine aims to resolve sepsis molecular endotypes and dynamic phenotypes through integration of multi-omics technologies (such as transcriptomics and single-cell sequencing) with artificial intelligence, thereby advancing personalized treatment strategies. However, the translation of precision medicine faces challenges including the dynamic evolution of endotypes, inadequate adaptability in clinical trial design, limited technological accessibility in resource-constrained regions, and data ethics concerns. Future advancements require interdisciplinary collaboration, adaptive clinical trials, and development of low-cost technologies to propel sepsis molecular subtyping from theoretical frameworks to clinical implementation, ultimately overcoming traditional therapeutic limitations and improving patient outcomes.**

## Keywords

**Sepsis, Precision Medicine, Molecular Mechanisms, Classification**



## 1. 引言

脓毒症是宿主对感染的反应失调引发的危及生命的器官功能障碍，死亡率极高[1]。据数据统计，在2017年全球脓毒症年发病率估计为508例/10万人[2]，其导致的死亡率为10%~25%，若进展为感染性休克，死亡率可升至30%~50% [3]。脓毒症作为全球重症医学领域的重要挑战，其治疗困难在于异质性根源的多维性，体现在病因多样性(细菌、真菌等)、宿主免疫反应差异、临床表现及预后差异等[4] [5]。目前传统治疗处在困境中，因脓毒症异质性导致临床试验失败或缺乏精准治疗靶点[6]。精准医学是一种以个体化医疗为核心的新型医学模式，其核心目标是通过整合多维度生物数据(如遗传信息、表型特征、环境因素及生活方式等)，为患者制定高度定制化的诊断、治疗及预防策略，从而突破传统"一刀切"医疗模式的局限性[7] [8]。因此，我们亟需应用精准医学推动脓毒症研究从"群体治疗"转向"个体化医疗"，以突破当前"泛化治疗"的瓶颈。

## 2. 脓毒症异质性的多维度

脓毒症的异质性体现在宿主因素、病原体特征、免疫反应动态、临床表型及分子机制等多个维度，这些因素共同构成其复杂的病理生理特征[9]。其中宿主个体差异是脓毒症异质性的核心驱动因素之一，包括人口学特征(年龄、性别、遗传背景等)、基础疾病(糖尿病、HIV感染等)和免疫状态[10] [11]。感染病原体的种类与毒力差异直接导致宿主反应的多样性[12]。宿主免疫应答的时空变化是脓毒症异质性的核心特征，比如早期过度炎症反应可能迅速转为免疫麻痹，但这一转换的时机和强度存在个体差异；中性粒细胞、巨噬细胞等具有高度可塑性，例如中性粒细胞在脓毒症肝损伤中兼具促炎与抗炎功能，而特

定巨噬细胞亚群可能驱动组织修复或持续损伤[13]。另外，脓毒症患者可呈现截然不同的临床特征与预后，基因组学与单细胞技术也揭示了脓毒症分子通路的多样性。

## 3. 分型策略与技术进展

脓毒症的异质性表现为多维度的临床特征和分子机制差异，传统基于疾病严重程度和预后的分型(如SOFA 评分)已无法满足精准治疗需求[14]。近年来，以转录组学为核心的多组学技术成为解析脓毒症分子异质性的关键工具，例如通过 RNA 测序识别出具有不同基因表达特征的脓毒症亚型(如 SRS1/SRS2)，这些亚型在炎症反应强度、内皮功能障碍和代谢紊乱等方面呈现显著差异，并与 28 天死亡率密切相关[6] [15]。动态表型分型策略结合时序性生物标志物(如细胞因子谱)和机器学习算法(如无监督聚类)，可实时追踪宿主免疫状态从过度炎症到免疫麻痹的演变轨迹[16] [17]。空间转录组学和微流控技术的突破进一步解析了脓毒症中组织特异性细胞通讯网络，例如肺部感染微环境中髓系细胞与内皮细胞的异常相互作用[18]。此外，功能基因组学与人工智能的结合推动了“数字表型”的发展，通过整合电子病历、微生物组数据和蛋白质组数据构建预测模型，实现治疗反应的个性化预测[19] [20]。

## 4. 精准医学的优势与挑战

脓毒症的异质性导致传统“一刀切”治疗模式效果有限，研究显示，脓毒症患者的免疫反应呈现高度动态变化，既有过度炎症反应(如细胞因子风暴)，又存在免疫抑制状态(如淋巴细胞耗竭)，甚至同时出现双重特征，并且不同年龄、性别、基因背景及合并症患者的免疫调节能力差异显著，使得统一的抗炎或免疫增强治疗可能对部分患者产生反效果[21]-[23]，传统固定剂量的糖皮质激素或抗炎药物可能加重部分患者的免疫抑制[24]；另外，传统诊断脓毒症依赖 PCT、CRP 等非特异性指标，无法反映脓毒症复杂的免疫内型，即使 SOFA 评分相同的患者，其单核细胞 HLA-DR 表达水平可相差 10 倍以上，这种免疫异质性导致传统抗生素/液体复苏方案对部分患者治疗无效[25]。在这种局限性的存在下，精准医学逐渐开始成为一种新的治疗理念和方法，为脓毒症的治疗带来了新的希望和方向，其优势在于：

1) 免疫内型识别与靶向治疗

精准医学可以通过分子机制和生物标志物定义特定免疫内型(如炎症亢进型或免疫抑制型)，为免疫疗法的个体化应用提供依据。例如，通过转录组学分析可识别患者免疫状态，针对性地使用免疫调节药物(如拮抗炎性细胞因子或增强免疫应答的药物) [25]，此外，新型纳米级免疫调节剂通过精准靶向递送药物，可能减少全身副作用并提高疗效[26]。

2) 多组学与人工智能驱动的患者分层

整合基因组、转录组、代谢组等多组学数据，结合临床参数和机器学习技术，可识别可重复的脓毒症亚型(如儿童脓毒症癌症患者的独特内型) [27] [28]。这种分层有助于预测患者对治疗的反应(如液体复苏或抗生素选择)及预后，为动态调整治疗方案提供支持[29] [30]，例如，基于 RNA 测序的亚型分类已被用于指导临床试验设计[31]。

3) 新型生物标志物与治疗靶点

精准医学推动了对脓毒症病理机制中关键分子(如线粒体 ROS、LPS 家族分子)的深入研究，为开发靶向药物提供方向。例如，BAM15 通过调节线粒体功能减轻脓毒症相关急性肾损伤(SA-AKI) [32]。而新型血液吸附剂可特异性清除脓毒症中的 LPS 毒素，展现出精准治疗的潜力[33]。

4) 动态监测与个性化调整

通过实时监测患者免疫状态和代谢变化，结合人工智能算法，可实现治疗方案的动态优化。例如，脓毒症表型从静态分型转向动态分型后，治疗策略可随病情演变调整(如从抗炎转向免疫增强疗法) [34]。

5) 性别与人群特异性治疗

性别分层分析显示，脓毒症相关急性肾损伤(SA-AKI)的发病率和危险因素存在性别差异，提示需针对不同人群优化治疗方案[35]。类似地，儿童癌症患者脓毒症的内型与非癌症患者显著不同，需针对性干预[36] [37]。

尽管精准医学在理论上为脓毒症等复杂疾病的治疗提供了极具潜力的新方向，但其临床转化仍面临多重挑战。这些挑战涉及技术、临床实践、经济等多个层面，限制了精准医学从实验室研究到临床应用的进程。其挑战在于：

1) 时序多模态数据整合平台的构建：脓毒症的病理过程涉及基因组、转录组、蛋白质组、代谢组及临床参数的多维度动态交互，但现有数据多为静态、单模态，且缺乏标准化存储格式[38]。因此，可以通过动态建模技术，采用时间依赖的多组学整合方法，结合纵向样本采集与机器学习，捕捉宿主反应的关键转折点(如免疫衰竭期向修复期过渡) [39]，或开发整合临床、影像、组学和实时监测数据(如连续生命体征)的深度学习框架，通过注意力机制识别关键驱动特征[40]，来促进平台的构建。

2) 基于分子分型的适应性试验设计：现有临床试验设计未充分考虑亚型特异性疗效，传统随机对照试验无法适应脓毒症亚组的异质性，导致疗效被群体平均效应掩盖[41]。下一步需建立基于分子分型的适应性试验框架，采用“主协议–模块化”设计，根据实时分子分型(如 SRS 或免疫内型)动态调整治疗分配。例如，在富集特定内型的亚组中优先测试靶向免疫调节剂[42] [43]。

3) 精准医学的实施需要先进的检测设备和专业的医疗团队，但这些资源在不同地区分布不均。例如，在资源有限环境下(如非洲)，需发展低成本快速分型技术以应对病原体多样性[44] [45]。

4) 此外，精准医学涉及大量的基因数据，这些数据具有高度的敏感性，需要严格保护患者的隐私，伦理问题如数据隐私保护和算法可解释性方面同样存在挑战[46]，需解决数据隐私(如欧盟通用数据保护条例)、算法偏见(如对特定种族或年龄组的泛化性不足)及医疗资源可及性问题，确保精准医学的公平实施[45] [47] [48]。

## 5. 结论与展望

精准医学使脓毒症治疗从“危机处理”转变为“精准调控”，为脓毒症治疗提供了从分子机制到临床实践的革新方向，但其成功依赖于跨学科协作、技术创新和伦理框架的完善。未来需通过大规模生物样本库建设、自适应临床试验设计以及低成本技术开发，推动精准医学从理论走向实践。

## 基金项目

济宁市重点研发计划(编号：2023YXNS114)。

## 参考文献

[1] Chiu, C. and Legrand, M. (2021) Epidemiology of Sepsis and Septic Shock. *Current Opinion in Anaesthesiology*, **34**, 71-76. https://doi.org/10.1097/aco.0000000000000958

[2] Wilcox, M.E., Daou, M., Dionne, J.C., Dodek, P., Englesakis, M., Garland, A., *et al.* (2022) Protocol for a Scoping Review of Sepsis Epidemiology. *Systematic Reviews*, **11**, Article No. 125. https://doi.org/10.1186/s13643-022-02002-6

[3] Xu, J., Zhang, W., Fu, J., Fang, X., Gao, C., Li, C., *et al.* (2024) Viral Sepsis: Diagnosis, Clinical Features, Pathogenesis, and Clinical Considerations. *Military Medical Research*, **11**, Article No. 78. https://doi.org/10.1186/s40779-024-00581-0

[4] Bruserud, Ø., Mosevoll, K.A., Bruserud, Ø., Reikvam, H. and Wendelbo, Ø. (2023) The Regulation of Neutrophil Migration in Patients with Sepsis: The Complexity of the Molecular Mechanisms and Their Modulation in Sepsis and the Heterogeneity of Sepsis Patients. *Cells*, **12**, Article 1003. https://doi.org/10.3390/cells12071003

[5] Kolodyazhna, A., Wiersinga, W.J. and van der Poll, T. (2025) Aiming for Precision: Personalized Medicine through

Sepsis Subtyping. *Burns & Trauma*, **13**, tkae073. https://doi.org/10.1093/burnst/tkae073

[6] Chenoweth, J.G., Brandsma, J., Striegel, D.A., Genzor, P., Chiyka, E., Blair, P.W., *et al.* (2024) Sepsis Endotypes Identified by Host Gene Expression across Global Cohorts. *Communications Medicine*, **4**, Article No. 120. https://doi.org/10.1038/s43856-024-00542-7

[7] Vadapalli, S., Abdelhalim, H., Zeeshan, S. and Ahmed, Z. (2022) Artificial Intelligence and Machine Learning Approaches Using Gene Expression and Variant Data for Personalized Medicine. *Briefings in Bioinformatics*, **23**, bbac191. https://doi.org/10.1093/bib/bbac191

[8] McCoy, M., Yeang, C., Bahnassy, S., Tam, S., Riggins, R.B., Parashar, D., *et al.* (2025) Generalized Evolutionary Classifier for Evolutionary Guided Precision Medicine. *JCO Precision Oncology*, **9**, e2300714. https://doi.org/10.1200/po.23.00714

[9] Wang, W. and Liu, C. (2023) Sepsis Heterogeneity. *World Journal of Pediatrics*, **19**, 919-927. https://doi.org/10.1007/s12519-023-00689-8

[10] Cummings, M.J., Lutwama, J.J., Owor, N., Tomoiaga, A.S., Ross, J.E., Muwanga, M., *et al.* (2025) Unsupervised Classification of the Host Response Identifies Dominant Pathobiological Signatures of Sepsis in Sub-Saharan Africa. *American Journal of Respiratory and Critical Care Medicine*, **211**, 357-369. https://doi.org/10.1164/rccm.202407-1394oc

[11] Brandes-Leibovitz, R., Riza, A., Yankovitz, G., Pirvu, A., Dorobantu, S., Dragos, A., *et al.* (2024) Sepsis Pathogenesis and Outcome Are Shaped by the Balance between the Transcriptional States of Systemic Inflammation and Antimicrobial Response. *Cell Reports Medicine*, **5**, Article ID: 101829. https://doi.org/10.1016/j.xcrm.2024.101829

[12] Sun, P., Cui, M., Jing, J., Kong, F., Wang, S., Tang, L., *et al.* (2023) Deciphering the Molecular and Cellular Atlas of Immune Cells in Septic Patients with Different Bacterial Infections. *Journal of Translational Medicine*, **21**, Article No. 777. https://doi.org/10.1186/s12967-023-04631-4

[13] Tao, X., Wang, J., Liu, B., Cheng, P., Mu, D., Du, H., *et al.* (2024) Plasticity and Crosstalk of Mesenchymal Stem Cells and Macrophages in Immunomodulation in Sepsis. *Frontiers in Immunology*, **15**, Article 1338744. https://doi.org/10.3389/fimmu.2024.1338744

[14] Zhang, X., Zhang, W., Zhang, H. and Liao, X. (2025) Sepsis Subphenotypes: Bridging the Gaps in Sepsis Treatment Strategies. *Frontiers in Immunology*, **16**, Article 1546474. https://doi.org/10.3389/fimmu.2025.1546474

[15] Burnham, K.L., Milind, N., Lee, W., Kwok, A.J., Cano-Gamez, K., Mi, Y., *et al.* (2024) eQTLs Identify Regulatory Networks and Drivers of Variation in the Individual Response to Sepsis. *Cell Genomics*, **4**, Article ID: 100587. https://doi.org/10.1016/j.xgen.2024.100587

[16] Santacroce, E., D'Angerio, M., Ciobanu, A.L., Masini, L., Lo Tartaro, D., Coloretti, I., *et al.* (2024) Advances and Challenges in Sepsis Management: Modern Tools and Future Directions. *Cells*, **13**, Article 439. https://doi.org/10.3390/cells13050439

[17] Wang, L., Tian, W., Zhang, W., Wen, D., Yang, S., Wang, J., *et al.* (2024) A Machine Learning Model for Predicting Sepsis Based on an Optimized Assay for Microbial Cell-Free DNA Sequencing. *Clinica Chimica Acta*, **559**, Article ID: 119716. https://doi.org/10.1016/j.cca.2024.119716

[18] Shen, X., Zhao, Y., Wang, Z. and Shi, Q. (2022) Recent Advances in High-Throughput Single-Cell Transcriptomics and Spatial Transcriptomics. *Lab on a Chip*, **22**, 4774-4791. https://doi.org/10.1039/d2lc00633b

[19] Cajander, S., Kox, M., Scicluna, B.P., Weigand, M.A., Mora, R.A., Flohé, S.B., *et al.* (2024) Profiling the Dysregulated Immune Response in Sepsis: Overcoming Challenges to Achieve the Goal of Precision Medicine. *The Lancet Respiratory Medicine*, **12**, 305-322. https://doi.org/10.1016/s2213-2600(23)00330-2

[20] Eloranta, S. and Boman, M. (2022) Predictive Models for Clinical Decision Making: Deep Dives in Practical Machine Learning. *Journal of Internal Medicine*, **292**, 278-295. https://doi.org/10.1111/joim.13483

[21] Feng, J., Liu, L., Liu, J. and Wang, J. (2024) Immunological Alterations in the Endothelial Barrier: A New Predictive and Therapeutic Paradigm for Sepsis. *Expert Review of Clinical Immunology*, **20**, 1205-1217. https://doi.org/10.1080/1744666x.2024.2366301

[22] von Groote, T. and Meersch-Dini, M. (2022) Biomarkers for the Prediction and Judgement of Sepsis and Sepsis Complications: A Step Towards Precision Medicine? *Journal of Clinical Medicine*, **11**, Article 5782. https://doi.org/10.3390/jcm11195782

[23] Monneret, G., Haem Rahimi, M., Lukaszewicz, A., Venet, F. and Gossez, M. (2024) Shadows and Lights in Sepsis Immunotherapy. *Expert Opinion on Pharmacotherapy*, **25**, 2125-2133. https://doi.org/10.1080/14656566.2024.2418987

[24] Liang, C., Pan, S., Wu, W., Chen, F., Zhang, C., Zhou, C., *et al.* (2024) Glucocorticoid Therapy for Sepsis in the AI Era: A Survey on Current and Future Approaches. *Computational and Structural Biotechnology Journal*, **24**, 292-305. https://doi.org/10.1016/j.csbj.2024.04.020

[25] Giamarellos-Bourboulis, E.J., Aschenbrenner, A.C., Bauer, M., Bock, C., Calandra, T., Gat-Viks, I., *et al.* (2024) The

Pathophysiology of Sepsis and Precision-Medicine-Based Immunotherapy. *Nature Immunology*, **25**, 19-28. https://doi.org/10.1038/s41590-023-01660-5

[26] Lin, L., Liu, H., Zhang, D., Du, L. and Zhang, H. (2024) Nanolevel Immunomodulators in Sepsis: Novel Roles, Current Perspectives, and Future Directions. *International Journal of Nanomedicine*, **19**, 12529-12556. https://doi.org/10.2147/ijn.s496456

[27] Wösten-van Asperen, R.M., la Roi-Teeuw, H.M., van Amstel, R.B., Bos, L.D., Tissing, W.J., Jordan, I., *et al.* (2023) Distinct Clinical Phenotypes in Paediatric Cancer Patients with Sepsis Are Associated with Different Outcomes—An International Multicentre Retrospective Study. *eClinicalMedicine*, **65**, Article ID: 102252. https://doi.org/10.1016/j.eclinm.2023.102252

[28] Langston, J.C., Yang, Q., Kiani, M.F. and Kilpatrick, L.E. (2022) Leukocyte Phenotyping in Sepsis Using Omics, Functional Analysis, and *in Silico* Modeling. *Shock*, **59**, 224-231. https://doi.org/10.1097/shk.0000000000002047

[29] Komorowski, M., Green, A., Tatham, K.C., Seymour, C. and Antcliffe, D. (2022) Sepsis Biomarkers and Diagnostic Tools with a Focus on Machine Learning. *eBioMedicine*, **86**, Article ID: 104394. https://doi.org/10.1016/j.ebiom.2022.104394

[30] Bomrah, S., Uddin, M., Upadhyay, U., Komorowski, M., Priya, J., Dhar, E., *et al.* (2024) A Scoping Review of Machine Learning for Sepsis Prediction- Feature Engineering Strategies and Model Performance: A Step Towards Explainability. *Critical Care*, **28**, Article No. 180. https://doi.org/10.1186/s13054-024-04948-6

[31] Murao, A., Jha, A., Aziz, M. and Wang, P. (2024) Transcriptomic Profiling of Immune Cells in Murine Polymicrobial Sepsis. *Frontiers in Immunology*, **15**, Article 1347453. https://doi.org/10.3389/fimmu.2024.1347453

[32] Tsuji, N., Tsuji, T., Yamashita, T., Hayase, N., Hu, X., Yuen, P.S.T., *et al.* (2023) BAM15 Treats Mouse Sepsis and Kidney Injury, Linking Mortality, Mitochondrial DNA, Tubule Damage, and Neutrophils. *Journal of Clinical Investigation*, **133**, e152401. https://doi.org/10.1172/jci152401

[33] Shi, Z., Zhang, X., Yang, X., Zhang, X., Ma, F., Gan, H., *et al.* (2023) Specific Clearance of Lipopolysaccharide from Blood Based on Peptide Bottlebrush Polymer for Sepsis Therapy. *Advanced Materials*, **35**, e2302560. https://doi.org/10.1002/adma.202302560

[34] Suh, G.J., shin, T.G., Kwon, W.Y., Kim, K., Jo, Y.H., Choi, S., *et al.* (2023) Hemodynamic Management of Septic Shock: Beyond the Surviving Sepsis Campaign Guidelines. *Clinical and Experimental Emergency Medicine*, **10**, 255-264. https://doi.org/10.15441/ceem.23.065

[35] Peng, J., Tang, R., Yu, Q., Wang, D. and Qi, D. (2022) No Sex Differences in the Incidence, Risk Factors and Clinical Impact of Acute Kidney Injury in Critically Ill Patients with Sepsis. *Frontiers in Immunology*, **13**, Article 895018. https://doi.org/10.3389/fimmu.2022.895018

[36] Zhou, T.L., Zhou, Y.P., Zhang, Y.C., *et al.* (2020) [Clinical Features and Outcomes of Cancer-Related versus Non-Cancer-Related Sepsis in Pediatric Intensive Care Unit]. *Chinese Journal of Pediatrics*, **58**, 482-487.

[37] Williams, J.C., Ford, M.L. and Coopersmith, C.M. (2023) Cancer and Sepsis. *Clinical Science*, **137**, 881-893. https://doi.org/10.1042/cs20220713

[38] Sinha, P., Meyer, N.J. and Calfee, C.S. (2023) Biological Phenotyping in Sepsis and Acute Respiratory Distress Syndrome. *Annual Review of Medicine*, **74**, 457-471. https://doi.org/10.1146/annurev-med-043021-014005

[39] Na, A., Lee, H., Min, E.K., Paudel, S., Choi, S.Y., Sim, H., *et al.* (2023) Novel Time-Dependent Multi-Omics Integration in Sepsis-Associated Liver Dysfunction. *Genomics, Proteomics & Bioinformatics*, **21**, 1101-1116. https://doi.org/10.1016/j.gpb.2023.04.002

[40] Santacroce, G., Zammarchi, I., Nardone, O.M., Capobianco, I., Puga-Tejada, M., Majumder, S., *et al.* (2025) Rediscovering Histology—The Application of Artificial Intelligence in Inflammatory Bowel Disease Histologic Assessment. *Therapeutic Advances in Gastroenterology*, **18**, 1-17. https://doi.org/10.1177/17562848251325525

[41] Scherger, S.J. and Kalil, A.C. (2024) Sepsis Phenotypes, Subphenotypes, and Endotypes: Are They Ready for Bedside Care? *Current Opinion in Critical Care*, **30**, 406-413. https://doi.org/10.1097/mcc.0000000000001178

[42] Stevens, J., Tezel, O., Bonnefil, V., Hapstack, M. and Atreya, M.R. (2024) Biological Basis of Critical Illness Subclasses: From the Bedside to the Bench and Back Again. *Critical Care*, **28**, Article No. 186. https://doi.org/10.1186/s13054-024-04959-3

[43] van Amstel, R.B.E., Kennedy, J.N., Scicluna, B.P., Bos, L.D.J., Peters-Sengers, H., Butler, J.M., *et al.* (2023) Uncovering Heterogeneity in Sepsis: A Comparative Analysis of Subphenotypes. *Intensive Care Medicine*, **49**, 1360-1369. https://doi.org/10.1007/s00134-023-07239-w

[44] Cummings, M.J., Lutwama, J.J., Tomoiaga, A.S., Owor, N., Lu, X., Ross, J.E., *et al.* (2024) Molecular Phenotypes of Critical Illness Confer Prognostic and Biological Enrichment in Sub-Saharan Africa: A Prospective Cohort Study from Uganda. *Thorax*, **80**, 175-179. https://doi.org/10.1136/thorax-2024-222412

[45] Li, N., Riazi, K., Pan, J., Thavorn, K., Ziegler, J., Rochwerg, B., *et al.* (2025) Unsupervised Clustering for Sepsis

Identification in Large-Scale Patient Data: A Model Development and Validation Study. *Intensive Care Medicine Experimental*, **13**, Article No. 37. https://doi.org/10.1186/s40635-025-00744-w

[46] Düsing, C., Cimiano, P., Rehberg, S., Scherer, C., Kaup, O., Köster, C., *et al.* (2024) Integrating Federated Learning for Improved Counterfactual Explanations in Clinical Decision Support Systems for Sepsis Therapy. *Artificial Intelligence in Medicine*, **157**, Article ID: 102982. https://doi.org/10.1016/j.artmed.2024.102982

[47] Ukanwa, K. (2024) Algorithmic Bias: Social Science Research Integration through the 3-D Dependable AI Framework. *Current Opinion in Psychology*, **58**, Article ID: 101836. https://doi.org/10.1016/j.copsyc.2024.101836

[48] Wang, H.E., Weiner, J.P., Saria, S., Lehmann, H. and Kharrazi, H. (2024) Assessing Racial Bias in Healthcare Predictive Models: Practical Lessons from an Empirical Evaluation of 30-Day Hospital Readmission Models. *Journal of Biomedical Informatics*, **156**, Article ID: 104683. https://doi.org/10.1016/j.jbi.2024.104683