Advances in Clinical Medicine 临床医学进展, 2026, 16(4), 4856-4865
Published Online April 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1641759

Hans汉斯

雌二醇在脓毒症及相关器官功能障碍的最新研究进展

谷立宏[1,2]，李钰琦[2]，田　章[2]，张　云[1,2]，舒林飞[2]，谌　磊[2*]

[1]吉首大学医学院，湖南　吉首
[2]株洲市中心医院泌尿外一科，湖南　株洲

收稿日期：2026年3月24日；录用日期：2026年4月18日；发布日期：2026年4月27日

摘　要

脓毒症是宿主对感染的反应失调所致的危及生命的器官功能障碍，全球发病率和死亡率居高不下。流行病学数据显示脓毒症预后存在显著性别差异，绝经前女性发病率和死亡率低于同龄男性，提示雌激素可能发挥保护作用。雌二醇(E2)作为生物活性最强的雌激素，具有抗炎、抗氧化、保护内皮等多重效应。本文系统综述雌二醇在脓毒症及其相关器官功能障碍(急性肾损伤、心肌病、肝损伤、肺损伤等)中的研究进展，梳理其与疾病预后的临床相关性，阐明其调控炎症、氧化应激和细胞凋亡的分子机制，并分析当前研究的矛盾与争议，探讨其作为脓毒症辅助治疗的临床转化前景与挑战。

关键词

雌二醇，脓毒症，器官功能障碍，炎症反应，氧化应激，免疫调节

Latest Research Advances on Estradiol in Sepsis and Sepsis-Related Organ Dysfunction

Lihong Gu[1,2], Yuqi Li[2], Zhang Tian[2], Yun Zhang[1,2], Linfei Shu[2], Lei Chen[2*]

[1]School of Medicine, Jishou University, Jishou Hunan
[2]First Department of Urology, Zhuzhou Central Hospital, Zhuzhou Hunan

Received: March 24, 2026; accepted: April 18, 2026; published: April 27, 2026

Abstract

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection,

*通讯作者。

文章引用: 谷立宏, 李钰琦, 田章, 张云, 舒林飞, 谌磊. 雌二醇在脓毒症及相关器官功能障碍的最新研究进展[J]. 临床医学进展, 2026, 16(4): 4856-4865. DOI: 10.12677/acm.2026.1641759

with persistently high global incidence and mortality. Epidemiological data show significant sex-based differences in sepsis outcomes: premenopausal women have lower incidence and mortality than age-matched men, suggesting a potential protective role of estrogen. Estradiol (E2), the most biologically active estrogen, exerts multiple effects including anti-inflammatory, antioxidant, and endothelial-protective actions. This article systematically reviews research progress on estradiol in sepsis and related organ dysfunction (acute kidney injury, septic cardiomyopathy, liver injury, lung injury, etc.), summarizes its clinical associations with prognosis, elucidates molecular mechanisms by which it regulates inflammation, oxidative stress, and apoptosis, and analyzes current inconsistencies and controversies. Finally, it discusses the translational prospects and challenges of estradiol as an adjunctive therapy for sepsis.

Keywords

Estradiol, Sepsis, Organ Dysfunction, Inflammatory Response, Oxidative Stress, Immunomodulation

1. 引言

脓毒症是宿主对感染的反应失调所致的危及生命的器官功能障碍。根据全球疾病负担研究(GBD)数据，全球每年约有 4890 万脓毒症病例，1100 万相关死亡，占全球死亡总数的 19.7% [1] [2]。脓毒症相关多器官功能障碍综合征(MODS)是导致患者死亡的关键因素，其中脓毒症相关急性肾损伤(SA-AKI)发生率高达 60%~70%，急性心肌病、急性肺损伤/急性呼吸窘迫综合征(ALI/ARDS)和肝功能障碍同样严重威胁患者生命[3]。

多项研究表明，绝经前女性脓毒症的发生率和死亡率低于同龄男性，而该保护效应在绝经后逐渐消失，提示性激素在脓毒症病理生理过程中发挥重要作用[4]。雌二醇(17β-estradiol, E2)是生物活性最强的天然雌激素，主要由卵巢合成，在免疫调节、血管保护和细胞存活等方面功能显著[5]。早期动物实验已证实雌二醇在创伤出血、缺血再灌注等模型中具有器官保护作用[6]。然而，临床研究显示脓毒症患者血清雌二醇水平显著升高，且高水平雌二醇与不良预后相关[7] [8]；而动物实验则普遍显示外源性雌二醇具有保护作用。这种矛盾使雌二醇与脓毒症的关系成为当前研究的重点。

本文旨在系统梳理雌二醇在脓毒症及相关器官功能障碍中的最新研究进展，包括其与预后的临床相关性、器官保护作用及分子机制、当前研究的矛盾与争议，以及临床转化的前景与挑战。

2. 雌二醇的生物学特性

2.1. 生理功能与受体信号通路

雌二醇主要由卵巢颗粒细胞在芳香化酶催化下由雄烯二酮转化而来。绝经前女性血清雌二醇浓度随月经周期波动，卵泡期约 30~100 pg/mL，排卵期可达 200~400 pg/mL；绝经后女性及男性水平显著降低，通常低于 30 pg/mL [9]。

雌二醇的生物学效应主要通过三类受体介导：核受体雌激素受体 α (ERα)和雌激素受体 β (ERβ)，以及膜受体 G 蛋白偶联雌激素受体(GPER/GPR30) [10]。ERα 和 ERβ 激活后转位至细胞核，与靶基因启动子区雌激素反应元件(ERE)结合，调控基因转录(基因组效应)，通常需数小时至数天起效。同时，雌二醇

也可通过膜定位受体激活 PI3K/Akt、MAPK、PKA 等快速信号通路，在数秒至数分钟内产生非基因组效应[11]。在不同器官中，ERα 和 ERβ 的表达具有组织特异性：ERβ 在心血管保护和抗炎作用中更为重要，而 ERα 主要参与代谢调节和肾脏功能[12]。

2.2. 免疫调节作用

雌二醇对免疫系统具有复杂的双重调节作用，取决于浓度、免疫细胞类型和微环境[13]。在先天免疫方面，生理浓度的雌二醇可促进巨噬细胞向 M2 型(抗炎表型)极化，增强 LC3 相关吞噬作用(LAP)，提高病原体清除能力[14]；同时抑制 TNF-α、IL-1β、IL-6 等促炎细胞因子产生，促进 IL-10 释放[15]。在适应性免疫方面，低浓度雌二醇倾向于促进 Th1 型反应，高浓度则促进 Th2 型反应，该浓度依赖性效应可能解释了雌二醇在不同疾病状态下的差异化作用[16]。

3. 脓毒症及相关器官功能障碍

3.1. 定义、诊断与流行病学

根据 Sepsis-3 定义，脓毒症是宿主对感染反应失调引起的危及生命的器官功能障碍[17]。临床上以 SOFA 评分增加≥2 分表示器官功能障碍，涵盖呼吸、凝血、肝脏、心血管、神经和肾脏六个系统[18]。脓毒症休克定义为充分液体复苏后仍需血管活性药物维持平均动脉压 ≥65 mmHg 且血清乳酸 >2 mmol/L，院内死亡率超过 40% [17]。2021 GBD 数据显示，尽管年龄标准化发病率和死亡率自 1990 年以来分别下降 37.0%和 52.8%，但绝对负担仍巨大，撒哈拉以下非洲和南东亚地区负担最重[2]。脓毒症发病率和死亡率随年龄增长显著升高，存在明显性别差异[19]。

3.2. 多器官功能障碍的病理生理

脓毒症相关 MODS 的病理生理涉及多个相互关联的环节。PAMPs 和 DAMPs 激活 TLRs 等模式识别受体，引发 NFκB 活化，导致“细胞因子风暴”[20] [21]。内皮细胞激活与通透性增加引起组织水肿和微血栓形成，微循环障碍成为器官损伤的关键环节[22]。线粒体功能障碍和代谢重编程进一步加重细胞能量供应不足[23]。此外，器官间相互作用(organcrosstalk)在 MODS 发展中发挥重要作用，如 AKI 通过炎症介质释放影响远隔器官，心功能障碍可导致肾脏灌注不足[24]。

4. 雌二醇与脓毒症的临床相关性研究

4.1. 血清雌二醇水平与预后

一项纳入 131 名脓毒症患者的前瞻性队列研究发现，患者生物可利用雌二醇浓度显著升高，且高水平与死亡率增加相关[7]。Tsai 等[25]对 107 名肺炎相关脓毒症休克患者的研究显示，死亡患者血清雌二醇和孕酮水平显著高于存活者($p<0.001$)，多因素 Cox 回归表明雌二醇 >40 pg/mL ($p=0.047$)和 APACHE II 评分 ≥25 ($p<0.001$)是 28 天死亡的独立预测因素。另一项外科和创伤 ICU 研究证实，48 小时血清雌二醇浓度是 28 天全因死亡的有效预测指标(AUC = 0.64)，预测能力与 IL8 相当[8]。这些观察提示内源性雌二醇升高可能是脓毒症严重程度的标志物，而非保护因素。

4.2. 脓毒症相关急性肾损伤

SAAKI 是脓毒症最常见的器官并发症，其病理生理涉及微循环障碍、炎症和线粒体功能障碍等[3] [23] [26]。Tsai 等[25]发现雌二醇 > 40 pg/mL 是发生 AKI 的独立预测因素($p = 0.002$)，且与 RIFLE 分级呈正相关，可预测 28 天内新发 AKI 的风险($p=0.013$)。然而动物实验呈现不同图景。最新研究发现雌二醇可

通过诱导肾小管细胞的抗铁死亡状态提供肾脏保护[27]；Feng 等[28]证明雌二醇通过 ERα 介导的 TGF-βRI-SMAD 通路抑制，减轻缺血再灌注损伤中的纤维化、氧化应激和炎症反应。

4.3. 脓毒症相关心肌病

脓毒症诱导的心肌病以心肌收缩舒张功能障碍、心室扩张和射血分数下降为特征，机制涉及线粒体功能障碍、钙稳态失衡和氧化应激[29]。动物研究表明，与卵巢切除雌鼠相比，正常雌鼠在脓毒症中心脏指数、每搏输出量和舒张末期容积显著保留；卵巢切除后心脏指数下降 52%，补充雌二醇可防止心功能恶化[30]。

机制研究揭示雌二醇通过多种途径发挥心肌保护：通过 ERβ 激活 PGC-1α 改善线粒体功能[31]；激活 PI3K/Akt 通路抑制心肌细胞凋亡[32]；减少 ROS 生成，增强抗氧化酶活性[33]；抑制 NF-κB 活化减少促炎细胞因子[34]。

4.4. 脓毒症相关急性肝损伤

脓毒症相关肝功能障碍发生率约 30%~50%，肝脏在脓毒症中既承担急性期蛋白合成和病原体清除，又承受炎症介质的损伤[35]。Sener 等[36]在 CLP 模型中证明雌二醇可显著降低肝脏 MDA 水平和 MPO 活性，增加 GSH 水平，改善 AST、ALT 和 LDH 等功能指标，组织病理学证实损伤程度明显减轻。其保护机制包括增强 SOD 和 CAT 活性以减少脂质过氧化，以及调节 TLR-4/NF-κB 信号通路抑制 TNF-α 等促炎因子释放[36] [37]。

4.5. 脓毒症相关急性肺损伤

ALI/ARDS 是脓毒症严重并发症，死亡率高达 40%，病理特征为弥漫性肺泡损伤和肺水肿[38]。动物研究表明雌二醇预处理可减少肺组织中性粒细胞浸润、降低肺泡灌洗液蛋白含量和炎症细胞因子水平[39]。雌二醇的内源性代谢产物 2-甲氧基雌二醇(2-ME)亦显示肺保护作用：通过上调 Annexin A1 表达抑制 NF-κB 活化和 MAPK 信号传导[40]；通过抑制 HIF-1α 和 iNOS 表达减少炎症因子和 NO 产生，改善脓毒症小鼠肺损伤和生存率[41]。

4.6. 其他器官损伤

雌二醇对脓毒症相关脑病(SAE)具有潜在保护效应，通过抗氧化、抗炎和促进神经营养因子表达等机制发挥神经保护作用[42]。在胃肠道方面，雌二醇可改善脓毒症大鼠肠道微循环，减少白细胞－内皮细胞相互作用，增加功能性毛细血管密度[43]。此外，雌二醇可通过调节凝血因子合成和纤溶系统活性影响脓毒症的凝血状态，但具体机制仍需深入研究[44]。

5. 雌二醇在脓毒症中的作用机制

5.1. 调节炎症反应

雌二醇调控炎症反应的核心机制涉及 NF-κB 信号通路[45]。雌二醇可通过多种方式抑制 NF-κB 活化：通过 ERβ 增强 IκBα 合成，增加对 NF-κB 的抑制性结合[46]；减少 LPS 诱导的 p65 核转位，降低其与靶基因启动子的结合[47]；ER 与 NF-κB 在某些启动子区域存在相互拮抗作用。此外，雌二醇可通过上调 miR-29a-5p 表达下调 NLRP3 炎症小体活性，减轻 LPS 诱导的巨噬细胞炎症反应和脓毒症血管炎症[48]。Sun 等[14]进一步发现雌二醇可促进 RelB 核转位，增强巨噬细胞的训练免疫，提高对脓毒症的抵抗力。值得注意的是，RelB 核转位的背后涉及深层次的表观遗传学机制：雌二醇可通过诱导组蛋白 H3K4me3 和 H3K27ac 等活性修饰标记，促进训练免疫相关基因(如 IL-6、TNF-α 等)的染色质开放状

态，使巨噬细胞在再次受到病原体刺激时能够产生更强烈的炎症应答[49]。然而，这一表观遗传重编程机制在脓毒症病程中具有潜在的双重作用：在脓毒症早期高炎症阶段，训练免疫的激活有助于增强病原体清除能力，发挥保护性作用；但在脓毒症后期免疫麻痹阶段，若持续的表观遗传活化过度放大炎症信号，则可能进一步损害已处于抑制状态的免疫细胞功能恢复，甚至加重组织损伤。因此，雌二醇通过 RelB－表观遗传轴调控训练免疫的确切效应，需结合脓毒症不同疾病分期进行评估，其在免疫麻痹期的潜在双重效应尚待深入研究。

5.2. 调节氧化应激

雌二醇具有直接和间接的抗氧化作用。其酚羟基结构可直接清除自由基，抑制脂质过氧化[36]。通过 ER 介导的基因组效应，雌二醇可上调 SOD、GPx 和 CAT 等抗氧化酶的表达[33]；通过激活 Nrf2 通路诱导 HO-1 等抗氧化基因表达[50]。在线粒体保护方面，雌二醇可维持线粒体膜电位稳定性，抑制细胞色素 c 释放，通过蛋白激酶 G 依赖性机制减少线粒体来源的 ROS 产生，改善脓毒症心脏线粒体呼吸功能[51]。

5.3. 保护内皮功能

内皮功能障碍是脓毒症微循环障碍的核心环节。雌二醇通过 ERα 和 ERβ 介导的信号通路快速激活 eNOS，增加 NO 产生，发挥血管舒张和抗血小板聚集作用[52] [53]；减少 VCAM-1、ICAM-1 等黏附分子表达，降低白细胞－内皮细胞相互作用[54]；保护紧密连接蛋白以维持内皮屏障[30]；通过 PI3K/Akt 生存信号通路抑制内皮细胞凋亡[55]。动物研究证实，雌二醇及其受体激动剂可减少脓毒症大鼠肠系膜血管中白细胞滚动和黏附，增加功能性毛细血管密度[43]。

5.4. 调节细胞凋亡与自噬

雌二醇主要通过以下途径发挥抗凋亡作用：通过 ERα 和 GPER 激活 Akt 磷酸化，抑制 Bad 和 Bax 活性，上调 Bcl-2 表达[56]；维持线粒体膜完整性，减少细胞色素 c 释放和 caspase-3 活化[51]；在心肌细胞中抑制 p53 磷酸化和线粒体转位，减少 ROS 产生[57]。在自噬调节方面，雌二醇通过调节 mTOR 和 AMPK 信号通路维持自噬活性在适当水平，促进受损细胞器清除和细胞存活[58]。

6. 研究矛盾与争议

6.1. 临床观察与实验研究的差异

当前存在明显的“转化鸿沟”(translational gap)：临床研究普遍显示脓毒症患者血清雌二醇升高与不良预后相关[7] [8] [25]；而动物实验则显示外源性雌二醇具有保护作用[30] [36] [39]。可能原因包括：内源性雌二醇升高可能是机体多重应激机制共同作用的结果，而非直接致病因素，其上游驱动机制涉及以下几个层面：① 外周组织芳香化酶活性增强——脓毒症时，应激激素(皮质醇、ACTH)大量释放及炎症介质(尤其是 IL-6)可显著上调脂肪组织、肾上腺和肌肉中芳香化酶(CYP19A1)的表达与活性，促进雄激素向雌二醇的转化，在腹型肥胖患者中尤为突出[59]；② 肝脏清除能力下降——肝脏是雌二醇代谢灭活的主要场所(通过 CYP3A4 等细胞色素 P450 酶进行 2-羟基化)，脓毒症相关肝功能损伤(ALT/AST 升高、凝血功能障碍)可直接减弱肝脏对雌二醇的氧化代谢和结合清除，导致血清雌二醇被动积累；③ 肠肝循环紊乱——脓毒症引起的肠道屏障破坏和胆汁分泌障碍可影响雌二醇结合物的肠肝循环，进一步阻碍其排泄。综合上述机制，临床检测到的内源性 E2 升高更可能是反映器官损伤程度(尤其是肝功能受损)和全身炎症强度的综合标志物，而非保护因素；临床观察浓度可能超出生理保护范围；临床多在脓毒症发生后检测而实验在早期干预；人与啮齿动物在雌激素合成、受体表达和免疫反应上存在物种差异[60]。

6.2. 剂量－效应关系

雌二醇生物学效应具有明显的剂量依赖性。生理浓度倾向于产生保护作用，高剂量则可能增加死亡风险、恶化心功能并导致肾损伤[61]。这种双相效应可能与不同浓度下优先激活的受体亚型和信号通路不同有关。确定最佳剂量范围和治疗窗口是临床转化的重要挑战。

6.3. 干预时机与疾病分期

动物实验显示早期干预效果优于延迟干预[41]。脓毒症动态演变，早期高炎症阶段雌二醇的抗炎作用可能有益，而后期免疫抑制阶段过度抑制炎症可能不利于病原体清除[62]。根据疾病分期个体化调整治疗策略是未来的重要方向。

6.4. 受体亚型与组织特异性

ERα 和 ERβ 在不同组织中表达和功能存在差异：ERβ 在心血管保护和抗炎中作用更重要，ERβ 激动剂在创伤出血模型中可产生与雌二醇相似的心肌保护效果；ERα 在肝脏代谢和肾脏中发挥主要作用[28] [63]。这种受体亚型特异性提示选择性雌激素受体调节剂(SERMs)可能克服传统雌激素治疗的局限性[64]。

6.5. 方法学局限性

常用的 CLP 和 LPS 模型难以完全反映人类脓毒症的复杂性；临床研究设计异质性大，结果难以比较；观察性研究难以建立因果关系；不同检测方法测定的雌二醇水平存在差异，影响可比性[25] [65]。

7. 临床转化前景与挑战

7.1. 应用潜力

雌二醇的多重保护作用使其在脓毒症多器官损伤中具有广泛应用潜力[66]。除传统雌二醇制剂外，SERMs 如雷洛昔芬和他莫昔芬可在不同组织发挥选择性激动或拮抗作用，减少不良反应[64]；植物雌激素(如大豆异黄酮)因温和的雌激素样活性和良好的安全性，也是潜在替代选择[67]。

7.2. 面临的挑战

安全性是首要考虑：雌激素可能增加静脉血栓栓塞和激素相关肿瘤风险，在凝血功能已紊乱的脓毒症患者中尤需谨慎[68]。性别差异与个体化治疗亦是挑战，男女对雌激素反应不同，绝经前后基线激素状态存在差异，需根据患者特征制定个体化方案[69]。给药途径、剂量和疾病阶段的优化均有待进一步研究。

7.3. 未来研究方向

需开展大规模随机对照临床试验提供高质量证据；利用组学技术开发生物标志物实现患者分层和精准治疗[70]；探索雌二醇与现有治疗手段的联合应用；研发具有改良特性的雌激素类似物。

8. 结论

雌二醇在脓毒症中的作用是一个复杂而多面的课题。基础研究表明其通过抗炎、抗氧化、保护内皮和促进细胞存活等机制对器官损伤具有保护作用；而临床观察显示内源性雌二醇升高与不良预后相关，提示其作用具有剂量依赖性、时相特异性和组织特异性。当前主要挑战包括转化鸿沟、最佳剂量和治疗窗口的确定以及受体亚型与组织特异性等问题的解决。展望未来，阐明内源性雌二醇升高的生理病理意义、确定外源性补充的最优方案、开发选择性受体调节剂并通过大规模临床试验验证其有效性和安全性，将是推动该领域发展的关键。

参考文献

[1] Rudd, K.E., Johnson, S.C., Agesa, K.M., Shackelford, K.A., Tsoi, D., Kievlan, D.R., *et al*. (2020) Global, Regional, and National Sepsis Incidence and Mortality, 1990-2017: Analysis for the Global Burden of Disease Study. *The Lancet*, **395**, 200-211. https://doi.org/10.1016/s0140-6736(19)32989-7

[2] GBD 2021 Sepsis Collaborators (2025) Global, Regional, and National Sepsis Incidence and Mortality, 1990-2021: A Systematic Analysis. *Lancet Glob Health*, **13**, e1431-e1440.

[3] Poston, J.T. and Koyner, J.L. (2019) Sepsis Associated Acute Kidney Injury. *BMJ*, **364**, k4891. https://doi.org/10.1136/bmj.k4891

[4] Angele, M.K., Pratschke, S., Hubbard, W.J. and Chaudry, I.H. (2013) Gender Differences in Sepsis: Cardiovascular and Immunological Aspects. *Virulence*, **5**, 12-19. https://doi.org/10.4161/viru.26982

[5] Fuentes, N. and Silveyra, P. (2019) Estrogen Receptor Signaling Mechanisms. *Advances in Protein Chemistry and Structural Biology*, **116**, 135-170.

[6] Chaudry, I.H., Samy, T.S.A., Schwacha, M.G., Wang, P., Rue, L.W. and Bland, K.I. (2003) Endocrine Targets in Experimental Shock. *Journal of Trauma*: *Injury*, *Infection & Critical Care*, **54**, S118-S125. https://doi.org/10.1097/01.ta.0000064511.14322.f1

[7] Lichtenstern, C., Brenner, T., Bardenheuer, H.J. and Weigand, M.A. (2012) Predictors of Survival in Sepsis: What Is the Best Inflammatory Marker to Measure? *Current Opinion in Infectious Diseases*, **25**, 328-336. https://doi.org/10.1097/qco.0b013e3283522038

[8] Tsang, G., Insel, M.B., Weis, J.M., Morgan, M.A.M., Gough, M.S., Frasier, L.M., *et al*. (2016) Bioavailable Estradiol Concentrations Are Elevated and Predict Mortality in Septic Patients: A Prospective Cohort Study. *Critical Care*, **20**, Article No. 335. https://doi.org/10.1186/s13054-016-1525-9

[9] Gruber, C.J., Tschugguel, W., Schneeberger, C. and Huber, J.C. (2002) Production and Actions of Estrogens. *New England Journal of Medicine*, **346**, 340-352. https://doi.org/10.1056/nejmra000471

[10] Prossnitz, E.R. and Barton, M. (2011) The G-Protein-Coupled Estrogen Receptor GPER in Health and Disease. *Nature Reviews Endocrinology*, **7**, 715-726. https://doi.org/10.1038/nrendo.2011.122

[11] Levin, E.R. (2005) Integration of the Extranuclear and Nuclear Actions of Estrogen. *Molecular Endocrinology*, **19**, 1951-1959. https://doi.org/10.1210/me.2004-0390

[12] Heldring, N., Pike, A., Andersson, S., Matthews, J., Cheng, G., Hartman, J., *et al*. (2007) Estrogen Receptors: How Do They Signal and What Are Their Targets. *Physiological Reviews*, **87**, 905-931. https://doi.org/10.1152/physrev.00026.2006

[13] Chakraborty, B., Byemerwa, J., Krebs, T., Lim, F., Chang, C. and McDonnell, D.P. (2022) Estrogen Receptor Signaling in the Immune System. *Endocrine Reviews*, **44**, 117-141. https://doi.org/10.1210/endrev/bnac017

[14] Sun, Z., Pan, Y., Qu, J., Xu, Y., Dou, H. and Hou, Y. (2020) 17β-Estradiol Promotes Trained Immunity in Females against Sepsis via Regulating Nucleus Translocation of Relb. *Frontiers in Immunology*, **11**, Article ID: 1591. https://doi.org/10.3389/fimmu.2020.01591

[15] Straub, R.H. (2007) The Complex Role of Estrogens in Inflammation. *Endocrine Reviews*, **28**, 521-574. https://doi.org/10.1210/er.2007-0001

[16] Kovats, S. (2015) Estrogen Receptors Regulate Innate Immune Cells and Signaling Pathways. *Cellular Immunology*, **294**, 63-69. https://doi.org/10.1016/j.cellimm.2015.01.018

[17] Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., *et al*. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, **315**, 801-810. https://doi.org/10.1001/jama.2016.0287

[18] Seymour, C.W., Liu, V.X., Iwashyna, T.J., Brunkhorst, F.M., Rea, T.D., Scherag, A., *et al*. (2016) Assessment of Clinical Criteria for Sepsis: For the Third International Con-Sensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, **315**, 762-774. https://doi.org/10.1001/jama.2016.0288

[19] La Via, L., Sangiorgio, G., Stefani, S., Marino, A., Nunnari, G., Cocuzza, S., *et al*. (2024) The Global Burden of Sepsis and Septic Shock. *Epidemiologia*, **5**, 456-478. https://doi.org/10.3390/epidemiologia5030032

[20] Liu, S.F. and Malik, A.B. (2006) Nf-κB Activation as a Pathological Mechanism of Septic Shock and Inflammation. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, **290**, L622-L645. https://doi.org/10.1152/ajplung.00477.2005

[21] Lawrence, T. (2009) The Nuclear Factor NF-B Pathway in Inflammation. *Cold Spring Harbor Perspectives in Biology*, **1**, a001651. https://doi.org/10.1101/cshperspect.a001651

[22] Raia, L. and Zafrani, L. (2022) Endothelial Activation and Microcirculatory Disorders in Sepsis. *Frontiers in Medicine*,

9, Article ID: 907992. https://doi.org/10.3389/fmed.2022.907992

[23] Kellum, J.A., Wen, X., de Caestecker, M.P. and Hukriede, N.A. (2019) Sepsis-Associated Acute Kidney Injury: A Problem Deserving of New Solutions. *Nephron*, **143**, 174-178. https://doi.org/10.1159/000500167

[24] Zarbock, A., Gomez, H. and Kellum, J.A. (2014) Sepsis-Induced Acute Kidney Injury Revisited: Pathophysiology, Prevention and Future Therapies. *Current Opinion in Critical Care*, **20**, 588-595. https://doi.org/10.1097/mcc.0000000000000153

[25] Feng, J., Liu, K., Abraham, E., Chen, C., Tsai, P., Chen, Y., *et al*. (2014) Serum Estradiol Levels Predict Survival and Acute Kidney Injury in Patients with Septic Shock—A Prospective Study. *PLOS ONE*, **9**, e97967. https://doi.org/10.1371/journal.pone.0097967

[26] Peerapornratana, S., Manrique-Caballero, C.L., Gómez, H. and Kellum, J.A. (2019) Acute Kidney Injury from Sepsis: Current Concepts, Epidemiology, Pathophysiology, Prevention and Treatment. *Kidney International*, **96**, 1083-1099. https://doi.org/10.1016/j.kint.2019.05.026

[27] Tonnus, W., Meyer, C., Steinhoff, A., *et al*. (2025) Hydroxyestradiol Suppresses Ferroptosis to Protect the Kidney from Ischemic Injury. *Nature*, **634**, 623-630.

[28] Ren, L., Li, F., Di, Z., Xiong, Y., Zhang, S., Ma, Q., *et al*. (2022) Estradiol Ameliorates Acute Kidney Ischemia-Reperfusion Injury by Inhibiting the TGF-βRI-SMAD Pathway. *Frontiers in Immunology*, **13**, Article ID: 822604. https://doi.org/10.3389/fimmu.2022.822604

[29] Hollenberg, S.M. and Singer, M. (2021) Pathophysiology of Sepsis-Induced Cardiomyopathy. *Nature Reviews Cardiology*, **18**, 424-434. https://doi.org/10.1038/s41569-020-00492-2

[30] Xerri, A., Gallardo, F., Kober, F., Mathieu, C., Fourny, N., Tran, T.T., *et al*. (2022) Female Hormones Prevent Sepsis-Induced Cardiac Dysfunction: An Experimental Randomized Study. *Scientific Reports*, **12**, Article No. 4939. https://doi.org/10.1038/s41598-022-08889-4

[31] Hsieh, Y., Choudhry, M.A., Huang-Ping, Y., Shimizu, T., Yang, S., Suzuki, T., *et al*. (2006) Inhibition of Cardiac Pgc-1α Expression Abolishes Erβ Agonist-Mediated Cardioprotection Following Trauma-Hemorrhage. *The FASEB Journal*, **20**, 1109-1117. https://doi.org/10.1096/fj.05-5549com

[32] Lagranha, C.J., Deschamps, A., Bhatt, N.Y., *et al*. (2010) Estrogen Modulates Mitochondrial Cardioprotection via PI3K-Dependent Mechanisms. *Journal of Molecular and Cellular Cardiology*, **49**, 1021-1028.

[33] Xiang, D., Liu, Y., Zhou, S., Zhou, E. and Wang, Y. (2021) Protective Effects of Estrogen on Cardiovascular Disease Mediated by Oxidative Stress. *Oxidative Medicine and Cellular Longevity*, **2021**, Article ID: 5523516. https://doi.org/10.1155/2021/5523516

[34] Hamilton, K.L., Mbai, F.N., Gupta, S. and Knowlton, A.A. (2004) Estrogen, Heat Shock Proteins, and NFκB in Human Vascular Endothelium. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **24**, 1628-1633. https://doi.org/10.1161/01.atv.0000137188.76195.fb

[35] Nesseler, N., Launey, Y., Aninat, C., Morel, F., Mallédant, Y. and Seguin, P. (2012) Clinical Review: The Liver in Sepsis. *Critical Care*, **16**, Article 235. https://doi.org/10.1186/cc11381

[36] Şener, G., Arbak, S., Kurtaran, P., Gedik, N. and Yeğen, B.Ç. (2005) Estrogen Protects the Liver and Intestines against Sepsis-Induced Injury in Rats. *Journal of Surgical Research*, **128**, 70-78. https://doi.org/10.1016/j.jss.2005.02.019

[37] Eisa, M.A., Mansour, A.M., Salama, S.A., *et al*. (2021) Estrogen/Estrogen Receptor Activation Protects against DEN-Induced Liver Fibrosis in Female Rats via Modulating TLR-4/NF-κB Signaling. *Toxicology and Applied Pharmacology*, **431**, Article 115740.

[38] Thompson, B.T., Chambers, R.C. and Liu, K.D. (2017) Acute Respiratory Distress Syndrome. *New England Journal of Medicine*, **377**, 562-572. https://doi.org/10.1056/nejmra1608077

[39] Speyer, C.L., Rancilio, N.J., McClintock, S.D., Crawford, J.D., Gao, H., Sarma, J.V., *et al*. (2005) Regulatory Effects of Estrogen on Acute Lung Inflammation in Mice. *American Journal of Physiology-Cell Physiology*, **288**, C881-C890. https://doi.org/10.1152/ajpcell.00467.2004

[40] Liao, W., Wu, S., Tsai, S., Pao, H., Huang, K. and Chu, S. (2021) 2-Methoxyestradiol Protects against Lung Ischemia/Reperfusion Injury by Upregulating Annexin A1 Protein Expression. *Frontiers in Immunology*, **12**, Article ID: 596376. https://doi.org/10.3389/fimmu.2021.596376

[41] Yeh, C., Chou, W., Chu, C., So, E.C., Chang, H., Wang, J., *et al*. (2011) Anticancer Agent 2-Methoxyestradiol Improves Survival in Septic Mice by Reducing the Production of Cytokines and Nitric Oxide. *Shock*, **36**, 510-516. https://doi.org/10.1097/shk.0b013e318231866f

[42] Li, Z., Chen, H., Lv, J., *et al*. (2020) Estradiol and Brain Protection: Mechanisms and Clinical Implications. *Brain Research Bulletin*, **158**, 156-168.

[43] Sharawy, N., Pavlovic, D., Wendt, M., Cerny, V. and Lehmann, C. (2011) Evaluation of the Effects of Gender and

Estradiol Treatment on the Intestinal Microcirculation during Experimental Sepsis. *Microvascular Research*, **82**, 397-403. https://doi.org/10.1016/j.mvr.2011.06.010

[44] Darabi, M., Ani, M., Movahedian, A., *et al*. (2008) Effect of Estrogen on Platelet Aggregation and Activation in Whole Blood. *Journal of Thrombosis and Thrombolysis*, **26**, 213-218.

[45] Kalaitzidis, D. and Gilmore, T.D. (2005) Transcription Factor Cross-Talk: The Estrogen Receptor and NF-κB. *Trends in Endocrinology & Metabolism*, **16**, 46-52. https://doi.org/10.1016/j.tem.2005.01.004

[46] Ghisletti, S., Meda, C., Maggi, A. and Vegeto, E. (2005) 17β-Estradiol Inhibits Inflammatory Gene Expression by Controlling NF-κB Intracellular Localization. *Molecular and Cellular Biology*, **25**, 2957-2968. https://doi.org/10.1128/mcb.25.8.2957-2968.2005

[47] Xing, D., Oparil, S., Yu, H., Gong, K., Feng, W., Black, J., *et al*. (2012) Estrogen Modulates NF-κB Signaling by Enhancing IKBα Levels and Blocking P65 Binding at the Promoters of Inflammatory Genes via Estrogen Receptor-β. *PLOS ONE*, **7**, e36890. https://doi.org/10.1371/journal.pone.0036890

[48] Zhang, M., Chen, H., Yang, Z., Zhang, M., Wang, X., Zhao, K., *et al*. (2021) 17*β*-Estradiol Attenuates LPS-Induced Macrophage Inflammation in Vitro and Sepsis-Induced Vascular Inflammation *in Vivo* by Upregulating Mir-29a-5p Expression. *Mediators of Inflammation*, **2021**, Article ID: 9921897. https://doi.org/10.1155/2021/9921897

[49] Saeed, S., Quintin, J., Kerstens, H.H.D., Rao, N.A., Aghajanirefah, A., Matarese, F., *et al*. (2014) Epigenetic Programming of Monocyte-to-Macrophage Differentiation and Trained Innate Immunity. *Science*, **345**, Article 1251086. https://doi.org/10.1126/science.1251086

[50] Dong, W., Chen, T., Miao, M., *et al*. (2017) Protective Effect of 17β-Estradiol on Acute Lung Injury Induced by Lipopolysaccharide in Rats. *International Immunopharmacology*, **52**, 55-63.

[51] Morkuniene, R., Arandarcikaite, O. and Borutaite, V. (2006) Estradiol Prevents Release of Cytochrome C from Mitochondria and Inhibits Ischemia-Induced Apoptosis in Perfused Heart. *Experimental Gerontology*, **41**, 704-708. https://doi.org/10.1016/j.exger.2006.02.010

[52] Mendelsohn, M.E. and Karas, R.H. (1999) The Protective Effects of Estrogen on the Cardiovascular System. *New England Journal of Medicine*, **340**, 1801-1811. https://doi.org/10.1056/nejm199906103402306

[53] Chambliss, K.L. and Shaul, P.W. (2002) Estrogen Modulation of Endothelial Nitric Oxide Synthase. *Endocrine Reviews*, **23**, 665-686. https://doi.org/10.1210/er.2001-0045

[54] Simoncini, T. and Genazzani, A. (2003) Non-Genomic Actions of Sex Steroid Hormones. *European Journal of Endocrinology*, **148**, 281-292. https://doi.org/10.1530/eje.0.1480281

[55] Razandi, M., Pedram, A., Park, S.T. and Levin, E.R. (2003) Proximal Events in Signaling by Plasma Membrane Estrogen Receptors. *Journal of Biological Chemistry*, **278**, 2701-2712. https://doi.org/10.1074/jbc.m205692200

[56] Hsu, J.T., Kan, W.H., Hsieh, C.H., *et al*. (2008) Role of Estrogen Receptor in Trauma-Hemorrhage-Induced Activation of PI3K/Akt Pathway. *Molecular Medicine Reports*, **1**, 347-351.

[57] Liu, H., Liu, K., Zhou, G.J., *et al*. (2011) 17beta-Estradiol Reduces Apoptosis and Attenuates ROS Production by Inhibiting p53 Phosphorylation and Translocation to Mitochondria in Cardiomyocytes after Hypoxia and Reoxygenation. *American Journal of Physiology-Cell Physiology*, **300**, C23-C32.

[58] Yang, L., Bhattacharya, D. and Bhattacharya, S. (2020) Role of Autophagy in ER Stress and Mitophagy-Mediated Cardiovascular Protection. *Autophagy*, **16**, 1333-1335.

[59] Spratt, D.I., Morton, J.R., Kramer, R.S., Mayo, S.W., Longcope, C. and Vary, C.P.H. (2006) Increases in Serum Estrogen Levels during Major Illness Are Caused by Increased Peripheral Aromatization. *American Journal of Physiology-Endocrinology and Metabolism*, **291**, E631-E638. https://doi.org/10.1152/ajpendo.00467.2005

[60] May, A.K., Dossett, L.A., Norris, P.R., Hansen, E.N., Dorsett, R.C., Popovsky, K.A., *et al*. (2008) Estradiol Is Associated with Mortality in Critically Ill Trauma and Surgical Patients. *Critical Care Medicine*, **36**, 62-68. https://doi.org/10.1097/01.ccm.0000292015.16171.6d

[61] Kang, S., Matsutani, T., Choudhry, M.A., *et al*. (2004) Are the Immune Responses Different in Middle-Aged and Young Mice Following Bone Fracture, Tissue Trauma and Hemorrhage? *Cytokine*, **26**, 223-230. https://doi.org/10.1016/j.cyto.2004.03.005

[62] Hotchkiss, R.S., Monneret, G. and Payen, D. (2013) Sepsis-Induced Immunosuppression: From Cellular Dysfunctions to Immunotherapy. *Nature Reviews Immunology*, **13**, 862-874. https://doi.org/10.1038/nri3552

[63] Hsu, J.T., Kan, W.H., Hsieh, C.H., *et al*. (2009) Role of ERbeta in Salutary Effects of 17beta-Estradiol on Cardiac Function Following Trauma-Hemorrhage. *American Journal of Physiology-Heart and Circulatory Physiology*, **297**, H1003-H1009.

[64] Iorga, A., Cunningham, C.M., Moazeni, S., Ruffenach, G., Umar, S. and Eghbali, M. (2017) The Protective Role of Estrogen and Estrogen Receptors in Cardiovascular Disease and the Controversial Use of Estrogen Therapy. *Biology of*

Sex Differences, **8**, Article No. 33. https://doi.org/10.1186/s13293-017-0152-8

[65] Dejager, L., Pinheiro, I., Dejonckheere, E. and Libert, C. (2011) Cecal Ligation and Puncture: The Gold Standard Model for Polymicrobial Sepsis? *Trends in Microbiology*, **19**, 198-208. https://doi.org/10.1016/j.tim.2011.01.001

[66] Br. Haloho, A. (2025) Unveiling New Horizons: Estrogen as a Breakthrough Therapy for Sepsis. *Journal of Cellular and Molecular Anesthesia*, **10**, e159284. https://doi.org/10.5812/jcma-159284

[67] Paterni, I., Granchi, C., Katzenellenbogen, J.A. and Minutolo, F. (2014) Estrogen Receptors Alpha (Erα) and Beta (Erβ): Subtype-Selective Ligands and Clinical Potential. *Steroids*, **90**, 13-29. https://doi.org/10.1016/j.steroids.2014.06.012

[68] Rietjens, I.M.C.M., Louisse, J. and Beekmann, K. (2016) The Potential Health Effects of Dietary Phytoestrogens. *British Journal of Pharmacology*, **174**, 1263-1280. https://doi.org/10.1111/bph.13622

[69] Rossouw, J.E., Anderson, G.L., Prentice, R.L., *et al*. (2002) Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial. *JAMA*: *The Journal of the American Medical Association*, **288**, 321-333. https://doi.org/10.1001/jama.288.3.321

[70] Weniger, M., D'Haese, J.G., Angele, M.K. and Chaudry, I.H. (2015) Potential Therapeutic Targets for Sepsis in Women. *Expert Opinion on Therapeutic Targets*, **19**, 1531-1543. https://doi.org/10.1517/14728222.2015.1057570