

慢加急性肝衰竭治疗进展： 从靶向新策略到人工肝技术

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摘要: 慢加急性肝衰竭 (acute-on-chronic liver failure, ACLF) 是在慢性肝病基础上出现的急性肝功能失代偿, 以全身炎症反应和多器官功能衰竭为特征, 短期死亡率极高。目前除肝移植外尚无特异性治疗方法, 关于 ACLF 的治疗手段仍存在明显空白。本文系统梳理了 ACLF 治疗领域的三大前沿方向: ①靶向治疗方面, 重点介绍丙酮酸脱氢酶激酶 4、let-7a-5p、信号素 6B、N-乙酰半乳糖胺 (N-acetylgalactosamine, GalNAc)-脂质纳米颗粒 (lipid nanoparticle, LNP)-丝裂原活化蛋白激酶激酶 4-siRNA (mitogen-activated protein kinase kinase 4-siRNA, siMKK4) 等新兴靶点的作用机制与研究进展; ②人工肝支持系统方面, 系统阐述从非生物型人工肝 (血浆置换、血液灌注、双重血浆分子吸附系统、多功能等离子净化系统) 到生物型人工肝的技术演进; ③肝移植新技术的探讨 (无缺血性肝移植、ABO 血型不合型活体供肝移植), 旨在为 ACLF 的临床治疗决策和未来研究方向提供参考。

关键词: 肝衰竭, 慢加急性; 靶向治疗; 人工肝支持系统; 血浆置换; 肝移植

Advances in the treatment of acute-on-chronic liver failure: from novel targeted strategies to artificial liver support technologies

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Abstract: Acute-on-chronic liver failure (ACLF) was an acute decompensation of liver function occurring on a background of chronic liver disease, which was characterized by systemic inflammatory response and multiple organ failure and with an extremely high short-term mortality rate. Currently, apart from liver transplantation, there were no specific treatments and there was still a significant gap in therapeutic approaches for ACLF. This article systematically reviewed three major frontier directions in the treatment of ACLF: ①In terms of targeted therapy, it focused on the mechanisms and research progress of emerging targets such as pyruvate dehydrogenase kinase 4, let-7a-5p, semaphorin 6B and N-acetylgalactosamine (GalNAc)-lipid nanoparticle (LNP)-mitogen-activated protein kinase kinase 4-siRNA (siMKK4); ②Regarding artificial liver support systems, it systematically elaborated the technological evolution from non-bioartificial liver support system (plasma exchange, hemoperfusion, double plasma molecular adsorb system, versatile plasma purification system) to bioartificial liver support system; ③Exploration of new liver transplantation techniques (ischemia-free liver transplantation, ABO-incompatible living-donor liver transplantation), aiming to provide references for clinical treatment decisions and

future research directions in ACLF.

Keywords: Liver failure, acute-on-chronic; Targeted therapy; Artificial liver support system; Plasma exchange; Liver transplantation

慢加急性肝衰竭(acute-on-chronic liver failure, ACLF)是在慢性肝病基础上因急性损伤因素短期内出现肝功能恶化的一种严重临床综合征,以全身炎症反应和一种或多种器官功能衰竭为特征^[1]。目前ACLF的定义尚无统一标准,但其强烈的全身炎症反应、快速进展的器官功能障碍以及极高的短期死亡率已得到学术界的公认^[2]。一项纳入202 022例肝硬化患者的回顾性队列研究显示,ACLF患者90 d死亡率高达50%,显著高于失代偿期肝硬化患者^[3]。目前,除肝移植外尚缺乏特异性治疗手段,临床上以病因治疗与并发症防治为主,总体预后不理想。因此,ACLF的临床干预存在大量亟待填补的治疗空白。本文对ACLF靶向治疗、人工肝支持治疗及肝移植的研究进展进行系统综述,旨在深化对该病治疗策略的认识,为临床实践和后续研究提供参考。

1 药物治疗

药物治疗主要从抑制肝脏炎症、保护肝细胞、调节免疫等方面改善ACLF患者的临床症状,难以逆转已坏死的肝细胞,且无法代偿肝脏的核心生理功能,故在阻止疾病进展方面疗效有限。

1.1 间充质干细胞制剂 间充质干细胞(mesenchymal stromal cell, MSC)作为一种多功能的非造血干细胞,已显示出减轻肝损伤和调节免疫应答的潜力^[4],具有强效且持续的抗炎和抗纤维化特性,这表明其可作为治疗肝纤维化或晚期肝硬化等炎症性疾病的治疗药物^[5]。Schacher等^[6]指出,MSC治疗过程中最重要的不良反应是高钠血症和胃肠道出血,但其推测这与MSC的作用无关,针对病情较轻的ACLF患者应进一步探索MSC治疗的应用。在使用MSC治疗ACLF患者时,应仔细评估不同来源的MSC的特性,这对促进细胞植入并防止非预期分化具有重要意义。总之,MSC在治疗ACLF方面安全且有效,未来亟需制定标准治疗方案来提升MSC的疗效,包括充足的细胞数量、最佳给药方式、最佳时间和细胞来源^[7]。

1.2 粒细胞集落刺激因子 近年来,粒细胞集落刺激因子(granulocyte colony-stimulating factor, G-CSF)已成为治疗ACLF患者的潜在选择^[8],G-CSF可促进骨髓来源的干细胞进入外周循环,从而改善患者的肝细胞状况。但对于其治疗效果一直存在争议,

欧洲的一项多中心研究发现G-CSF对ACLF患者并无显著疗效^[9],但随后不断有研究证明了G-CSF对ACLF有效。Qiu等^[10]研究表明G-CSF对于ACLF患者,特别是高感染风险患者具有潜在的治疗益处。2025年一项关于不同治疗方法对ACLF患者90 d预后的荟萃分析认为G-CSF是改善ACLF患者90 d预后最有效的单药^[11]。G-CSF治疗ACLF患者临床结局间存在的异质性表明,患者的反应可能存在高度个体差异。此外,G-CSF治疗预后不佳的患者,其对G-CSF的细胞反应也较弱。鉴于应对ACLF的复杂性需个性化及联合治疗,根据患者对G-CSF的预期反应对其进行分组,将有助于更好地调整治疗方案^[12]。

1.3 白细胞介素-22 白介素-22(interleukin-22, IL-22)属于细胞因子家族,其不仅能刺激成熟肝细胞的增殖,还能通过靶向肝前体细胞促进严重或慢性肝损伤患者肝脏的修复与再生。其是治疗人类肝脏疾病的一种极具前景的新型候选药物^[13]。IL-22受体仅在上皮细胞表达,提示其治疗的不良反应可能较其他细胞因子少。Tang等^[14]开发的F-652是一种由人源IL-22与IgG2恒定区(IgG2-Fc)连接而成的重组融合蛋白,2018年对健康受试者接受F-652治疗的首项I期临床研究显示其不良反应极少且效果良好。2019年,Xiang等^[15]通过构建ACLF小鼠模型证明F-652通过重编程再生通路并减轻细菌感染改善ACLF。2020年,一项评估F-652在中度和重度酒精性肝炎患者中安全性和疗效的研究表明,治疗后患者血清和血浆中炎症标志物水平下降,再生标志物水平上升^[16]。结合IL-22在ACLF的临床前模型中展现出的保肝和免疫调节能力,以及其他肝脏疾病的临床试验中获得的正向结果,有助于确定IL-22作为ACLF治疗的可行选择^[17]。

1.4 VS-01 VS-01是一种脂质体制剂,含有包裹柠檬酸的跨膜pH梯度脂质体及游离柠檬酸,通过腹腔内输注进行ACLF的治疗。德国一项关于VS-01的Ib期、首次人体试验(开放标签、非随机、单次递增剂量及多次给药)研究表明,VS-01可改变与ACLF相关感染和器官衰竭相关的血液代谢物,总体耐受性及安全性良好,在肝硬化、腹水和隐匿性肝脑病患者中显示出了初步疗效^[18]。

2 靶向治疗

靶向治疗通过干预 ACLF 发病机制中的关键分子,有望从源头抑制炎症级联反应、减轻肝细胞损伤。近年来,多个新型靶点展现出潜在应用价值。

2.1 丙酮酸脱氢酶激酶 4 丙酮酸脱氢酶激酶 4 (pyruvate dehydrogenase kinase 4, PDK4) 属于丙酮酸脱氢酶激酶家族成员,在心脏、骨骼肌、肝脏等多种组织中广泛表达,在机体代谢调控中发挥关键作用^[19,20]。PDK4 缺乏可显著减少促炎细胞因子的分泌^[21]。Dong 等^[22]发现,ACLF 患者肝巨噬细胞和外周血单核细胞中 PDK4 显著上调,通过激活信号转导及转录激活因子 1 (signal transducer and activator of transcription 1, STAT1) 促进 ACLF 中的 M1 型巨噬细胞极化,从而加剧肝细胞损伤和全身性炎症;进一步动物实验证实,抑制 PDK4 可有效缓解 ACLF 模型小鼠肝脏炎症和肝组织损伤。但是 PDK4 对非巨噬细胞产生的影响尚未明确,其与 STAT1 间的信号转导也尚未得到验证。然而,亦有研究指出, PDK4 可能有助于保护小鼠肝脏免受凋亡损伤, PDK4 缺失可能增强肝脏对二乙基亚硝胺和砷的毒性敏感性,从而导致自发性肝细胞凋亡。PDK4 在代谢以外的作用尚未明确,在肝脏再生中的作用仍值得探讨^[23]。

2.2 let-7a-5p Lin 等^[24]研究表明, let-7a-5p 天然存在于间充质干细胞分泌体中,可通过促进自噬发挥肝脏保护作用,为 ACLF 的治疗提供了新思路。转录因子 ARID3A 是富含 AT 相互作用结构域 (AT-rich interaction domain, ARID) 蛋白家族成员,在发育调控、组织特异性基因表达和细胞增殖调控中发挥重要作用^[25]。髓样上皮生殖酪氨酸激酶 (Mer receptor tyrosine kinase, MerTK) 是一种受体酪氨酸激酶,在多种组织中表达,负责识别和清除凋亡细胞^[26]。Wang 等^[27]研究表明 let-7a-5p 通过 ARID3A/MerTK 轴增强巨噬细胞的吞噬作用,显著抑制 ARID3A 的表达并上调 MerTK 的表达,从而减轻炎症反应。上述研究为 let-7a-5p 作为 ACLF 的治疗靶点提供了有力证据。

2.3 信号素 6B 信号素 (semaphorins, SEMAs) 家族在炎症、血管生成、细胞凋亡、纤维化及细胞侵袭等过程中发挥重要作用^[28],信号素 6B (semaphorin 6B, SEMA6B) 是 SEMAs 家族的成员之一,是巨噬细胞特异性基因^[29]。Yang 等^[30]研究发现,SEMA6B 可作为 ACLF 的潜在诊断生物标志物,靶向 SEMA6B 有望减轻由病原体相关分子模式 (pathogen-associated molecular pattern, PAMP)

和损伤相关分子模式 (damage-associated molecular patterns, DAMP) 诱导的巨噬细胞介导的全身炎症反应及肝细胞凋亡。以上研究提示 SEMA6B 是极具潜力的 ACLF 的早期治疗靶点。

2.4 GalNAc-LNP-siMKK4 丝裂原活化蛋白激酶激酶 4 (mitogen-activated protein kinase kinase 4, MKK4) 是一种丝裂原活化蛋白 2 (mitogen-activated protein 2, MAP2) 激酶,负责调控细胞的增殖与分化^[31],抑制 MKK4 可促进肝细胞增殖^[32]。合适的基因递送载体可有效将小干扰 RNA (small interfering RNA, siRNA) 送达目标细胞^[33],脂质纳米颗粒 (lipid nanoparticle, LNP) 作为非病毒载体凭借其良好的肝靶向特性,已被用于治疗肝脏疾病^[34]。而 N-乙酰半乳糖胺 (N-acetylgalactosamine, GalNAc) 作为在肝细胞上高表达的特异性去唾液酸糖蛋白受体 (asialoglycoprotein receptor, ASGPR) 的分子组分,与 ASGPR 具有高亲和力,许多药物都通过 GalNAc 实现 siRNA 对肝细胞的靶向递送^[35]。Zhai 等^[36]基于 MKK4 在促进肝细胞增殖中的作用以及 siRNA 基因治疗的优势,首次将 MKK4-siRNA (siMKK4) 用于促进肝脏再生,开发出双重靶向基因治疗系统“GalNAc-LNP-siMKK4”。该系统具有靶向递送治疗性基因至肝细胞的能力,可实现高效基因治疗以促进肝脏再生,为临床治疗 ACLF 提供了新的策略,但未来还需进行系统的安全性评估,包括全转录组脱靶分析、全面免疫毒性分析以及长期毒理学研究。

3 人工肝支持系统

人工肝支持系统 (artificial liver support system, ALSS) 通过体外机械或生物装置替代肝脏部分功能,清除炎症介质及代谢毒素,为肝衰竭患者提供过渡性支持或促进肝再生。根据其构成及作用机制,可分为非生物型人工肝和生物型人工肝两大类。

3.1 非生物型人工肝

3.1.1 血浆置换 血浆置换通过去除 ACLF 患者富含有毒代谢物和促炎细胞因子的血浆,以同等量新鲜冷冻血浆补充凝血因子、白蛋白、免疫球蛋白及其他重要成分,可达到改善肝脏微环境的作用^[37]。血浆置换具有良好的解毒和免疫调节作用,可提高肝衰竭患者的生存率^[38],能够选择性清除致病性炎症介质并补充必需蛋白质,对于抗感染、激素治疗、补充白蛋白、肾脏替代治疗等标准药物治疗后效果不佳的患者,其可作为一种新的治疗选择^[39]。然而,目前血浆置换的启动时机、置换剂量以及持续

时间等尚无统一标准,仍需要临床进一步探索以达到更优的效果。Kumar等^[40]研究表明,与标准药物治疗相比,低剂量血浆置换(每次治疗置换50%的血浆量)联合低剂量糖皮质激素可提高ACLF患者1年生存率,且低剂量血浆置换更安全,资源消耗更少。Jog等^[41]报道了1例酒精性ACLF病例,在标准药物治疗无效后接受5个疗程高容量血浆置换后,临床症状和生物化学指标均显著改善,肝功能得以恢复。近期有研究指出,标准量血浆交换与高容量血浆交换ACLF患者30 d死亡率、90 d死亡率及细胞因子水平变化方面无显著差异^[42]。提示尚需进一步研究以全面确定血浆置换在优化治疗效果中的作用。病因治疗及血浆置换均可提高ACLF患者的生存率,改善患者1个月、3个月甚至长达1年的预后^[43]。Fernández等^[44]指出,使用5%白蛋白作为置换液的血浆置换治疗可显著改善ACLF患者的肝脏、肾脏及脑功能,且具有良好的可行性和耐受性。血浆置换置换液的改变可能影响治疗效果为后续研究提供了新思路。

3.1.2 血液灌注 血液灌注是通过吸附剂直接清除血液中的毒性物质,细胞因子吸附器CytoSorb是目前临床应用最广泛的血液灌注装置^[45]。CytoSorb具有清除胆红素的作用,且与高级器官支持(advanced organ support, ADVOS)系统相比,两者在改善危重患者肝功能及短期死亡率方面差异无统计学意义^[46]。血液灌注可作为ACLF等终末期肝病患者的的重要支持治疗手段,但因吸附选择性低且生物安全性不足而在临床应用中受到限制,后续仍需大规模队列研究验证其安全性与有效性^[47]。Du等^[48]通过双键官能化二氧化钛纳米颗粒与苯乙烯间的悬浮聚合反应,设计了一种新型抗菌胆红素吸附剂,这种吸附剂具有较好的胆红素吸附能力和抗菌性能,确保在肝功能衰竭患者进行治疗时能高效清除胆红素,并预防细菌感染。Hu等^[49]开发了一种以壳聚糖为基础的HKUST-1气凝胶吸附剂,其选择性、生物安全性及抗菌性均较高。Yin等^[50]研发了一种有苯并三唑官能团化的超交联聚合物(hyper-cross-linked polymer, HCP),该材料作为血液灌注吸附剂在去除胆红素方面表现优异,最大吸附容量达877 mg/g,平衡容量为195 mg/g,为高效清除血液内源性毒素、促进肝衰竭患者肝脏恢复提供了新的吸附剂构建策略。Deng等^[51]利用相反转和静电喷雾技术制备了基于咪唑官能团化季铵盐的改良聚醚砜(polyethersulfone, PES)微球,制备的血液灌流吸附剂(PES/VI8-AANa)胆红素清除

率超过95%。这些表现出优异生物相容性的血液灌注吸附剂都将成为治疗肝衰竭的有力工具。

代谢组学比较分析显示,与血浆置换和标准药物治疗相比,血液灌注在改善血浆环境方面具有更大潜力^[52]。血液灌注联合血浆置换的临床耐受性较好,可有效促进肝功能恢复,显著逆转器官功能衰竭,延缓新发器官衰竭和并发症的发生,从而降低了ACLF患者的死亡风险^[53]。小容量血浆置换与血液灌注相结合不仅经济实用,还可缓解血浆资源有限的难题,具有广阔的临床应用前景^[54]。

3.1.3 双血浆分子吸附系统 采用中性大孔树脂和离子交换树脂的双重血浆分子吸附系统(double plasma molecular absorb system, DPMAS)对于胆红素和炎症介质的吸附效果更佳,降低了过敏反应和传染病的风险,但存在无法补充白蛋白和凝血因子等物质的缺点^[55]。DPMAS与血浆置换的结合既能有效清除毒素和炎症因子,又能补充所需物质,弥补了各自的不足。与单纯血浆置换治疗相比,DPMAS联合血浆置换治疗已经被证实在改善早期ACLF患者胆红素水平和28 d生存率方面更有效^[56]。Xu等^[57]将50例ACLF患者分为试验组(综合药物治疗联合低容量血浆置换和DPMAS)和对照组(综合药物治疗),结果表明,试验组和对照组患者的12周累计生存率分别为64%和36%($P=0.048$),试验组出血事件和过敏反应发生率分别为12%和4%,提示DPMAS联合低容量血浆置换对于中期ACLF患者安全有效。Lan等^[58]对239例ACLF患者的研究表明,ALSS组患者12周和1年的生存率显著高于标准药物治疗组,血浆置换组与DPMAS联合血浆置换组在12周和1年内的生存率无显著差异,且血浆置换组患者与ALSS相关的并发症相对较多。以上提示DPMAS联合血浆置换可作为临床治疗的更优选择。

3.1.4 多功能等离子净化系统 目前的非生物型人工肝系统主要采用膜式血液分离技术^[59],存在杂质分离效率不稳定、与导管相关的感染和出血风险。Dai等^[60]开发的多功能等离子净化系统(versatile plasma purification system, VPPS)是一种新型的非生物型人工肝,将膜式血液分离技术与离心血细胞分离技术相结合,克服了先前的局限性。在长期随访期间,接受VPPS治疗的患者再入院率和死亡率均有所降低,为ACLF患者的治疗提供了一种新的选择。

3.2 生物型人工肝 生物型人工肝支持系统的研发旨在成为肝移植的过渡方案,促进肝脏再生,预防

终末期肝病引起的严重并发症并提高患者生存率^[61],通过优化肝细胞来源和生物反应器模拟“功能完备的肝脏”。目前,多个大型生物医学研究中心正致力于生物型人工肝系统的临床试验,以验证其安全性和有效性^[62]。一种新型生物型人工肝系统将粒细胞和单核细胞血细胞分离柱与装载诱导多能干细胞衍生的类肝细胞(pluripotent stem cell-derived hepatocyte-like cells, iHLCs)的生物反应器整合,被命名为“UTOpia”(universal tandem optimized iHLCs with granulocyte and monocyte apheresis),该系统在提供肝脏支持的同时可减轻全身性炎症反应。研究人员利用ACLF大鼠模型评估UTOpia的治疗效果,结果表明,单次2 h UTOpia治疗后大鼠的存活率可达88.9%,充分体现了免疫调节与肝脏支持联合应用的协同价值。UTOpia系统是超越传统单功能生物型人工肝的重要发展方向^[63]。

近年来中国对生物型人工肝系统的研发已在世界前列。依托于基因工程改造的SynHeps-II细胞的血浆细胞连接生物型人工肝系统(plasma-cell contacting bioartificial liver support system, PCC-BAL)可高效代谢胆红素及氨,有效减少促炎细胞因子并改善肝脏微环境,有利于其再生。此系统可使约80%的急性肝衰竭患者规避急性死亡风险^[64]。基于人诱导肝细胞(human induced hepatocyte, hiHeps)的临床级生物型人工肝装置除发挥支持作用外,还可恢复残余肝脏功能,促进肝脏再生。对于7例接受广泛性肝切除术的患者,hiHep-生物型人工肝治疗耐受性良好,达到了安全性与可行性的主要研究终点^[65]。

4 肝移植

肝移植是目前挽救ACLF患者生命的根本手段。现有数据表明,肝移植术后ACLF患者1年生存率超过80%,5年生存率约为76%^[66]。然而,由于ACLF的高发病率、肝移植候选人病情危重及肝移植适应证不断扩展等原因,供肝持续短缺,仍需持续研究以优化临床实践。

4.1 肝移植进展 近年来,肝移植在利用器官保存装置扩大供体来源、使用延长移植植物以及重视活体供体移植等方面取得了较大进展^[67]。随着患者生存期的延长和供体资源的增加,一些长期并发症如移植后代谢综合征也逐渐显现出来。肝移植的临床实践正处于从单纯“免疫抑制”向“免疫-代谢综合管理”转变的关键阶段^[68]。归根结底,肝移植的持续发展将取决于临床技术创新、伦理分配实践以及健全的医疗基础设施的有机结合,从而优化患者预

后并实现社会效益最大化^[69]。

4.2 无缺血性肝移植 无缺血性肝移植(ischemia-free liver transplantation, IFLT)是肝移植领域的重大进展,可在持续常温体外循环(normothermic machine perfusion, NMP)条件下获取、保存和移植肝脏移植植物^[70],是一种避免缺血再灌注损伤的新型临床方法^[71]。Tang等^[72]对28例接受IFLT和51例接受传统肝移植的ACLF患者进行对比分析,结果显示,IFLT组患者6个月生存率显著高于传统肝移植组(100%比74.5%, $P=0.009$),且术后再灌注综合征发生率更低、手术时间更短、术中失血量减少、血制品使用量更少。尽管优势明显,但临床实施IFLT仍存在一定局限性。该方法依赖于院内脑死亡供体,地理上的灵活性受到限制,且因供体热缺血时间会导致整体损伤而无法应用于循环死亡供体^[73]。此外,延长NMP时间需要先进的灌注系统,目前仅在1例移植病例中得到临床应用^[74]。

4.3 ABO血型不合型活体供体肝移植 由于捐献者短缺,ABO血型不合型活体供体肝移植(ABO-incompatible living-donor liver transplantation, ABOi-LDLT)主要在亚洲国家展开研究^[75]。韩国的一项研究表明,对病情紧急的ACLF患者,通过2~3 d的快速脱敏治疗(包括预防性利妥昔单抗治疗和多次全血浆置换)可成功实施ABOi-LDLT。该方案在ACLF或严重肝硬化患者中可行且安全,且ABOi-LDLT组与ABO血型相容型(ABO-compatible, ABOc)LDLT组的术后并发症及感染性并发症发生率差异无统计学意义^[76]。无法否认的是ABOi-LDLT在短期和长期内都存在显著的抗体介导排斥(antibody-mediated rejection, AMR)风险^[77]。对AMR进行早期诊断和治疗是提高移植植物存活率和治疗效果的关键因素之一^[78]。同时脱敏治疗的强化免疫抑制方案使受者易出现严重感染性并发症,这些并发症大大提高了AMR的发病率和患者死亡率^[79],所以移植前的脱敏治疗仍需评估长期结局^[80]。

5 小结与展望

ACLF作为慢性肝病急性进展的危重状态,其高短期死亡率与复杂的病理机制决定了治疗的艰巨性。本文系统梳理了靶向治疗、人工肝支持系统及肝移植在ACLF治疗中的研究进展。靶向治疗方面,PDK4、let-7a-5p、SEMA6B、GalNAc-LNP-siMKK4等靶点展现出调控炎症反应、减轻肝损伤的潜力,但其临床应用仍面临靶向特异性、长期安全性等挑战。人工肝支持系统从非生物型人工肝到生物型人工肝的技术演进为ACLF患者提供了重

要的过渡性支持,尤其是血浆置换、DPMAS等技术的优化组合,在改善患者生存率方面显示出积极效果。肝移植技术的革新(如IFLT、ABOi-LDLT)为扩大供肝来源、改善移植预后提供了新思路。然而,ACLF的治疗仍面临诸多挑战:不同研究间ACLF定义存在差异,影响研究结果的可比性;人工肝治疗的启动时机、治疗频率、置换剂量尚未统一;靶向治疗多处于临床前或早期临床阶段,缺乏大规模循证医学证据;肝移植受制于供肝短缺,部分患者无法在最佳时机接受移植。未来,ACLF治疗的研究应重点关注以下方向:①建立统一的ACLF诊断与分层标准,为临床试验提供可比性基础;②开展大样本、多中心、随机对照试验,验证不同治疗策略的有效性与安全性;③探索靶向治疗与人工肝支持、肝移植的协同应用策略;④开发新型生物材料与生物反应器,提升人工肝支持系统的性能;⑤结合多组学技术与人工智能,实现ACLF患者的精准分层与个体化治疗。通过上述努力,有望在ACLF的早期干预、治疗优化和预后改善方面取得突破,最终降低患者死亡率、改善生活质量。

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收稿日期: 2026-04-28

李锦钰, 张耀武, 李玉, 等. 慢加急性肝衰竭治疗进展: 从靶向新策略到人工肝技术[J/CD]. *中国肝脏病杂志(电子版)*, 2026, 18(2): 44-51.