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乙型肝炎相关慢加急性肝衰竭发病机制及治疗进展

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摘要：乙型肝炎相关慢加急性肝衰竭（hepatitis B virus-related acute-on-chronic liver failure，HBV-ACLF）是一种短期病死率极高的临床综合征，其发病机制尚不完全明确，除肝移植外尚无有效的治疗措施。肝移植常受限于肝源不足、治疗费用高昂等因素，因此内科综合治疗（包括人工肝支持系统）就成为提高患者短期生存率的重要手段。本文将重点阐述HBV-ACLF的发病机制及内科综合治疗相关进展。
关键词：肝炎，乙型；肝衰竭，慢加急性；肠道菌群

Progress on pathogenesis and medical treatment of hepatitis B virus-related chronic and acute liver failure

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Abstract: Hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF) is a complicated syndrome with extremely high short-term mortality. The pathogenesis of HBV-ACLF has not been fully elucidated, and there is no effective treatment except for liver transplantation. Liver transplantation is limited by the shortage of donor livers and high costs of the treatment. Thus, the comprehensive medical treatment (including artificial liver support systems) emerged as an important intervention for improving short-term survival of patients with HBV-ACLF. This paper focuses on the pathogenesis of HBV-ACLF and recent progress of comprehensive medical treatment.
Key words: Hepatitis B virus; Liver failure, acute-on-chronic; Fecal microbiome

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[1]，进展期间可出现肝脏和（或）肝外多器官衰竭，短期病死率极高。亚太地区慢性肝病主要由乙型肝炎病毒（hepatitis B virus，HBV）感染引起，HBV再激活是ACLF发生的主要诱因[2]，而欧美地区慢性肝病主要以酒精性肝硬化为主，酗酒及细菌感染是ACLF的主要诱发因素[3]。因此世界范围内ACLF定义及诊断标准尚不统一。有研究表明，乙型肝炎相关慢加急性肝衰竭（hepatitis B virus-related acute-on-chronic liver failure，HBV-ACLF）患者的总胆红素及INR显著高于其他类型ACLF[4]。

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大量肝细胞坏死是肝衰竭的主要病理特点，肝细胞坏死程度与患者预后显著相关，其发病机制尚不完全明确。除病毒因素外，近年来发现系统性炎症、免疫-代谢紊乱等在促进HBV-ACLF疾病进展中发挥关键作用。ACLF治疗目前尚缺乏特效药物和手段，早诊断、早治疗，积极采取内科综合治疗、防治并发症等对改善ACLF预后非常重要[5]。肝移植（liver transplantation，LT）是改善ACLF患者预后的有效方式[6]，但肝脏供体缺乏、治疗费用高昂且ACLF进展极为迅速，大部分患者无法进行LT治疗。因此内科综合治疗对HBV-ACLF患者显得尤为重要。本文就当前HBV-ACLF发生机制以及内科综合治疗进展进行总结。

1 HBV-ACLF发病机制

1.1 病毒因素

迄今为止，全球已报道的HBV基因型

有10种，我国最为常见的基因型为B型和C型[7]。HBV基因型是否对HBV-ACLF发生发展有影响尚存在争议，有学者发现HBV B基因型患者更易发生HBV-ACLF[8,9]，而另有研究发现HBV-ACLF的发生与发展和基因型无明显关联[10,11]。此外，HBV前C区和C区突变也与HBV-ACLF发生相关，多项研究表明HBV-ACLF患者A1762T / G1764A、A1846T和G1896A突变点位明显高于慢性乙型肝炎患者，且A1846T点位与HBV-ACLF患者短期高病死率显著相关[8 9,12]。但HBV基因突变是否可能因增加HBV复制或增强宿主对HBV免疫应答而影响HBV-ACLF的发生发展尚不清楚。

1.2 *系统性炎症反应* 全身炎症反应被认为是以酒精性肝病为主的欧美国家驱动ACLF发生发展的主要原因。当感染作为诱发因素时，病原体可以通过病原相关分子模式（pathogen-associated molecular patterns，PAMPs）激活天然免疫应答；当非感染性因素诱发时，肝脏内受损的细胞释放损伤相关的分子模式（damage associated molecular patterns，DAMPs）可激活天然免疫应答，进而可能引发过度免疫反应。随着疾病进展，抗炎反应与促炎反应失衡，产生细胞因子风暴以及全身炎症反应综合征，最终引起全身多器官衰竭。在ACLF发生发展期间，抗炎反应逐渐占据上风，可发生“代偿性抗炎反应综合征（compensatory anti-inflammatory response syndrome，CARS）”，导致免疫功能降低，对感染易感性增加从而引起全身感染[13-15]。HBV再激活常导致HBV特异性免疫应答过度激活，因此所致的炎症细胞因子急剧增多而致免疫病理损伤是诱发 ACLF 的重要因素。已有研究发现无论在外周或肝内，均可发现炎性细胞因子如IL-6、IL-8、IL-10、IL-12、IL-17、IL-21、IL-22、IL-27和IL-33水平均显著高于CHB患者[16-20]。还有研究发现HBV-ACLF患者相关炎症因子受体上调与肝病严重程度显著相关，例如IL-23R在Th17细胞表达增加[21]，无论是炎症因子产生增多还是炎症因子受体上调，均与体内过度炎症反应有关，多种炎症因子综合作用最终导致HBV-ACLF的发生。

1.3 *HBV激活引起免疫-代谢紊乱* 最近COSSH研究组利用COSSH-ACLF中国标准研究的多中心、前瞻性、开放性大队列生物样本库进行的研究提示：慢性乙型肝炎或肝硬化患者在向HBV-ACLF进展过程中，天然免疫相关（干扰素、中性粒细胞、单核细胞、树突状细胞）基因表达显著增加，而适应性免疫相关（T细胞、B细胞）基因表达显著降低，与此同时，自噬、胆固醇、氨基多糖生物合成、过氧化物酶体增殖物激活受体等代谢信息失衡，这意味着与全身炎症反应相比，HBV再激活所致的免疫-代谢失衡可能是HBV-ACLF发生发展及重症化转归的关键机制[22]。

1.4 *肠道菌群失衡* 已有研究表明ACLF患者肠道菌群发生显著改变，主要表现为拟杆菌门相对丰度显著降低，而莫拉氏菌、硫氧化菌、单胞菌和伯克霍尔德菌显著升高[23,24]，这提示肠道菌群在ACLF发展中可能发挥重要作用。肠道菌群失调可与慢性肝病相互促进，进而导致慢性肝病发展为ACLF。慢性肝病患者随着疾病进展，肠道神经功能发生改变，不仅导致肠道屏障受损，而且降低抗菌肽分泌，从而加剧肠道炎症[25-28]，而肠道炎症及屏障受损则可导致肠道通透性增加，使肠道菌群发生移位[28-30]。此外肠道菌群失调可增加肠道屏障通透性，从而使微生物组分和（或）其分泌的有害物质（例如短链脂肪酸、次级胆汁酸等）穿过肠道屏障进而引起或加重全身炎症反应，导致ACLF发生[31]。

2 内科治疗策略

2.1 *抗病毒治疗* 对于HBV DNA阳性的ACLF患者，早期快速降低HBV DNA载量是治疗关键[5]。大量研究证实核苷（酸）类似物可降低CTP评分和MELD评分，有助于提高HBV-ACLF患者的短期及长期预后、延缓疾病进展或降低HBV-ACLF患者康复后复发的概率[32-35]。随着抗病毒药物的不断更新，目前强效高耐药屏障的核苷（酸）类似物包括恩替卡韦（entecavir，ETV）、替诺福韦酯（tenofovir disoproxil fumarate，TDF）和丙酚替诺福韦酯（tenofovir alafenamide，TAF），已被推荐为一线的抗HBV药物，然而上述药物对于HBV-ACLF患者预后的影响尚有待研究。与目前临床较多使用的ETV相比，有研究发现接受TDF治疗的HBV-ACLF患者累积生存率较高[36,37]，但也有研究发现ETV、TDF和TAF在HBV-ACLF患者中具有相似的疗效和安全性[38]。针对ETV、TDF和TAF肾功能影响的问题，研究发现与ETV治疗组相比，TAF治疗的HBV-ACLF患者似乎具有更好的肾功能[39,40]，而短期使用TDF也并未导致肾脏损害风险增加[41]。但上述多为小样本单中心研究，因此上述一线抗乙型肝炎病毒药物在HBV-ACLF的应用仍需大样本多中心临床试验数据加以证明。

2.2 *人工肝支持系统*（artificial liver support systems，ALSS） ALSS是治疗肝衰竭非常重要的内科治疗手段，主要通过体外装置暂时替代肝脏功能，清

除体内有害产物，补充体内所需因子，纠正内环境紊乱，为衰竭肝脏恢复争取时间并创造条件。目前临床常用的非生物型ALSS包括血液/血浆灌流、胆红素吸附、血浆置换、血液滤过和连续性血液透析滤过、双重血浆分子吸附等。多项临床研究表明，ALSS支持治疗可有效降低患者总胆红素，改善患者凝血功能障碍，减少患者短期病死率，改善患者长期生存预后[42-46]，对于合并器官衰竭或细菌感染的患者，ALSS也可降低病死率，改善生存预后[42, 47]，同时还可有效改善肝移植术后患者短期预后[48]。尽管ALSS可改善轻中度HBV-ACLF患者短期生存预后，但对于重度HBV-ACLF患者预后的改善似乎并不明显[46]。ALSS工作模式选择是否对患者预后有所影响，目前研究尚不完善，一项单中心临床研究显示血浆置换与双重血浆分子吸附相比，前者胆红素清除率高于后者，但两者短期预后并无显著差异[49]，而另一项研究则表明，血浆置换联合双重血浆分子吸附比单纯血浆置换更能改善中晚期HBV-ACLF患者的短期预后[50]，但需更大样本的研究队列加以验证。

2.3 间充质干细胞　间充质干细胞移植是一种理想的可替代肝移植的治疗方法，可从多种组织（骨髓、脂肪、滑膜、脐带、胎盘、血液等）中分离，并具有低免疫原性以及分化为肝细胞的能力[51]，多项研究表明来源于脐带、外周血或自体异体骨髓的间充质干细胞治疗可显著提高HBV-ACLF患者的短期生存率（90 d至72周），减少重症感染发生，除治疗期间发热更为频繁外未见其他明显不良反应[52-55]，但是否能显著改善长期生存率（例如延长至192周）还有待进一步研究[56]。此外间充质干细胞来源以及移植剂量、途径、时机等问题均需进行大样本多中心临床研究以进一步阐明。

2.4 糖皮质激素　迄今为止，糖皮质激素对HBV-ACLF患者的治疗效果尚具争议。多项关于糖皮质激素治疗HBV-ACLF的研究表明，糖皮质激素的早期使用可有效降低患者短期病死率，且未发现HBV DNA复制增加，但需注意患者真菌感染以及低蛋白血症发生风险、PT延长、住院时长及费用增加[57-60]。但也有研究表明，糖皮质激素的使用并不能降低短期病死率[61,62]，这可能与激素使用时机、剂量等相关，发病早期小剂量短期激素治疗或可及时抑制过度的免疫反应，从而减少肝细胞损伤，阻止ACLF快速进展。

2.5 调节肠道菌群　目前针对肠肝轴的治疗方式包括不可吸收的抗生素、粪菌移植（fecal microbiota transplantation，FMT）以及益生菌制剂等。利福昔明能有效治疗肝性脑病，但并未观察到其对肠道菌群的显著影响[63-66]。FMT是将健康人粪便中的功能菌群移植到患者胃肠道内，重建新的肠道菌群，已用于肠道及肠道外疾病的治疗，目前已有多项临床研究证实，无论通过灌肠还是口服胶囊，FMT受试者均可改善肝性脑病所带来的认知障碍，并减少肝性脑病的复发[67-70]，同时也有研究表明，FMT可改善酒精性ACLF患者的短期及中期生存率[71]。益生菌制剂也被证实可用于治疗肝性脑病以降低患者住院率[72-74]。大量证据证实靶向肠道菌群的治疗策略能用于肝性脑病的治疗，FMT也被证实能有效改善酒精性ACLF患者的预后，但其在HBV-ACLF治疗中的价值尚需进一步研究。

2.6 靶向肝细胞代谢　最近一项研究发现口服曲美他嗪能显著降低HBV-ACLF患者90 d病死率，其机制可能通过抑制肝细胞脂肪酸氧化和增强糖酵解来增加高血氨和缺氧微环境中的肝细胞存活率[75]。

3 小结

随着对HBV-ACLF研究的不断深入，HBV-ACLF发病机制不断被探索和完善，除病毒因素外，系统性炎症反应和HBV激活引起的免疫-代谢紊乱可能是重要驱动因素，但前者可能在酒精性ACLF中发挥更重要作用。近年来肠道菌群对肝脏疾病的影响越来越受到关注，但其在HBV-ACLF发生发展中的作用尚有待进一步研究。HBV-ACLF是一种临床高病死率的综合征，LT是患者的最终治疗手段，但考虑到肝源不足，患者经济情况以及医院手术开展情况，内科综合治疗仍是大部分患者延长生命的主要手段。HBV再激活是HBV-ACLF发生的重要因素，因此尽早快速抑制病毒复制能显著改善患者预后，如何选择一线口服抗乙型肝炎病毒药物尚需进一步研究。ALSS目前作为除肝移植外最有效的延长患者生命的治疗方式之一，多种工作模式联合使用或许是未来ALSS治疗的主要方向。此外间充质干细胞移植、早期小剂量激素使用、靶向肠道菌群、靶向肝细胞代谢等内科治疗策略也为HBV-ACLF治疗带来新的选择，但仍需进一步的临床队列或真实世界研究来明确其长期获益及探讨最佳方案。

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《中国肝脏病杂志（电子版）》表格规范

文内表格的设置应有助于简洁、明了、直观地表达结果。若表中的内容简单， 仅少数几个统计数字，用简洁文字可表达清楚的，可删去表格，选用文字描述； 若文字叙述冗长烦琐，而用表格表达便于理解，则建议作者选用表格。表、图、文字描述三者之间应无重复。

表格设计的基本原则是重点突出、简单明了，主谓分明、层次清楚，结构完整、有自明性。自明性即只看表，不阅读正文，即可理解统计或对比的意义。

表格一律采用三线表， 即以表顶线、表头线、表底线3条横线为基本线条构架的表。每个表均应有序号和表题，居中排印在表的上方。表的序号一律用阿拉伯数字。全文只有一个表时，表序号为“表1”。表题说明表的内容，应简明扼要，突出中心。

表头由主语横标目和谓语纵标目组成，表明表格内的项目。所谓主语、谓语，是根据表格所要表达的内容划分的。被研究的事物的主要标志，或者说是分组标志，一般作为主语；而各类统计指标，一般作为谓语。主语一般安排在表的左侧，谓语一般安排在表的右侧。尽量避免主谓语倒置，影响表格的表达效果。

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