

· 专家论坛 ·

DOI: 10.12449/JCH260406

缺血性胆管病的诊断和治疗

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摘要: 缺血性胆管病系胆管特异性血供障碍引发的严重临床疾病,其病因包括血管性因素和非血管性因素。发病机制聚焦于胆管周围血管丛微循环障碍及缺血再灌注损伤引发的胆管上皮坏死与纤维化。临床表现异质性强,典型症状为黄疸、腹痛及胆管炎,但乏力、发热等非特异症状常延误诊断。诊断主要依赖影像学识别特征性狭窄与微循环障碍,并辅以碱性磷酸酶、 γ -谷氨酰转移酶等胆汁淤积标志物。治疗策略涵盖传统药物、内镜干预及创新技术。预后评估强调碱性磷酸酶、胆红素的动态监测及影像学分型,长期管理需制定个体化监测方案以预防并发症。

关键词: 缺血性胆管病; 病理状态, 体征和症状; 诊断; 治疗学; 预后

基金项目: 白求恩公益基金会项目 (BCF-LX-XH-20221014-07)

Advances in the diagnosis and treatment of ischemic cholangiopathy

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Abstract: Ischemic cholangiopathy (IC) is a severe clinical condition resulting from blood supply impairment in bile ducts, and its etiology includes vascular causes and non-vascular factors. The pathogenesis of IC mainly involves microcirculatory disturbance of the peribiliary blood plexus and biliary epithelial necrosis and fibrosis induced by ischemia-reperfusion injury. The clinical manifestations of IC are highly heterogeneous. The typical symptoms include jaundice, abdominal pain, and cholangitis, while non-specific symptoms, such as fatigue and fever, often cause delays in diagnosis. The diagnosis of IC mainly relies on radiological examination for identifying characteristic stenosis and microcirculatory disturbance, assisted by cholestasis biomarkers including alkaline phosphatase and gamma-glutamyl transferase. Therapeutic strategies include conventional pharmacotherapy, endoscopic intervention, and innovative techniques. Prognostic evaluation emphasizes the dynamic monitoring of alkaline phosphatase and bilirubin and classification based on radiological examination, and long-term management requires individualized monitoring regimens to prevent complications.

Key words: Ischemic Cholangiopathy; Pathological Conditions, Signs and Symptoms; Diagnosis; Therapeutics; Prognosis

Research funding: Bethune Charitable Foundation Project (BCF-LX-XH-20221014-07)

缺血性胆管病(ischemic cholangiopathy, IC)因胆管血供的解剖脆性,成为肝移植后及血管疾病中预后恶劣的难治性疾病。其诊疗面临病因交织,早期诊断困难及治疗手段有限三大瓶颈。本文系统综述IC在病因机制、诊断技术、治疗策略及预后管理领域的最新进展,以期临床决策提供循证依据。

1 IC的病因与发病机制

1.1 IC的病因

1.1.1 血管性病因 IC的血管性病因主要涉及肝动脉及其分支的血流障碍,包括医源性损伤、移植相关并发症及系统性疾病等多重因素。胆管系统血供完全依赖

于肝动脉,当小肝动脉或胆管周围血管丛(peribiliary blood plexus, PBP)受损,或所有潜在侧循环被阻断时,均可导致胆管缺血性损伤^[1]。在心脏死亡供者(donation of cardiac death, DCD)肝移植中,常温机械灌注(normothermic machine perfusion, NMP)联合肝动脉重建的病例分析表明,动脉重建组IC累积发生率达30.0%,显著高于未重建组的3.3%,可能与冷缺血时间延长相关^[2]。遗传性出血性毛细血管扩张症(hereditary hemorrhagic telangiectasia, HHT)患者中,血管内皮生长因子介导的微循环障碍可引发不可逆的硬化性胆管病变,而抗血管内皮生长因子治疗可显著逆转影像学表现,避免肝移植需求^[3]。镰状细胞病患者因红细胞镰变阻塞胆管终末动脉,可表现为复发性黄疸和弥漫性胆管病变^[4]。动物实验进一步证实,缺血再灌注损伤(ischemia-reperfusion injury, IRI)可通过破坏PBP内皮,诱发微血栓形成,导致胆管微循环障碍^[5]。综上所述,血管性病因的核心在于胆管特异性血供的脆弱性及其对缺血损伤的敏感性。

1.1.2 非血管性病因 IC的非血管性病因涉及多种复杂机制,其中IRI是核心病理生理基础。在DCD肝移植中,IRI导致的胆管损伤尤为突出,IC发生率显著高于脑死亡捐献肝移植(16% vs 3%)^[6]。热缺血时间与冷缺血时间的延长是独立危险因素,当DCD供肝的热缺血时间超过45 min时,IC发生率高达27%^[7]。胆汁盐毒性通过直接损伤胆管上皮细胞加剧IRI,尤其在胆管冲洗不充分的移植中更为明显^[8]。严重低氧血症也可诱发IC,肝肺综合征患者术后持续低氧可导致胆管溃疡及纤维化^[9]。免疫介导的损伤亦不容忽视,抗胸腺细胞球蛋白诱导治疗较巴利昔单抗可显著降低IC发生率(12.5% vs 35.2%),提示免疫调节的潜在价值^[10]。

1.2 IC的发病机制

1.2.1 胆管微循环障碍 胆管微循环障碍是IC发病的核心机制,主要涉及PBP的灌注异常与血栓形成。超声造影(contrast-enhanced ultrasound, CEUS)可有效评估胆管壁微循环状态,在肝移植术后IC患者中,76.9%的病例表现为动脉期无或低增强,与正常组存在显著差异^[11]。动物实验验证,CEUS增强程度与血管示踪剂染色及微血管密度高度一致,当动脉期评分 ≥ 3 分时,诊断胆管缺血的敏感度为87.8%,特异度为98.3%^[12]。在DCD肝移植模型中,超声靶向微泡空化技术可显著降低PBP血栓负荷,改善肝动脉阻力及胆管上皮微绒毛结构^[13],而NMP较传统冷保存能维持更稳定的胆管上皮

再生^[14]。胆管微循环障碍与胆汁生化改变密切相关,IC患者胆汁葡萄糖再吸收能力显著降低,可能反映胆管上皮能量代谢受损^[15]。然而,现有胆汁生化标志物(如pH>7.48、碳酸氢盐>18 mmol/L)对IC的预测存在14.5%的假阴性率^[16],提示微循环障碍可能呈现节段性分布特征。

1.2.2 IRI IRI是IC发病的核心机制之一,通过直接损伤胆管上皮细胞及破坏PBP微循环,导致胆管细胞凋亡和坏死^[17]。来自心脏死亡供体或扩大标准供体的肝脏因对IRI更为敏感,其胆管病变风险显著增加^[18]。动态保存技术(如低温含氧机械灌注和NMP)通过维持生理性灌注条件,可显著降低边缘供肝的IRI风险,进而减少早期移植物功能障碍和IC的发生^[19-20]。NMP通过促进糖原再生和三磷酸腺苷恢复,减轻IRI相关的炎症级联反应,使移植物利用率提高,同时将IC等并发症降低至与传统静态冷保存相当的水平^[21]。

2 IC的临床表现与诊断标准

2.1 IC的临床症状

2.1.1 典型症状 IC的典型症状表现具有高度异质性,其临床表现与病因学、病程进展及血管损伤程度密切相关。典型症状包括进行性黄疸(发生率>80%)、右上腹痛(发生率为45%~60%)及反复发作的胆管炎(发生率为30%~40%)。在新型冠状病毒感染后继发IC的患者中,62%在发病后3~6个月出现顽固性瘙痒^[22]。HHT相关胆管缺血病例中,5%~8%发展为症状性胆道病变,其中以胆管狭窄导致的梗阻性黄疸和胆管炎最为常见,部分患者可合并门静脉高压相关症状(如腹水或静脉曲张出血)^[23-24]。肝移植后IC则呈现特殊临床谱系,29%的患者以移植物功能障碍为首发表现,54%的保守治疗病例后续出现胆管狭窄或胆汁漏等并发症^[25]。

2.1.2 非特异性症状 IC的非特异性症状常导致临床诊断延迟,多项研究显示其表现多样且缺乏特异性。在HHT相关肝血管畸形患者中,早期多表现为非特异性消化道症状,如餐后腹痛(发生率约30%)、腹胀及乏力^[23,26]。HHT合并胆管病变的病例分析显示,38%的患者以不明原因发热为首发表现,25%的患者出现体重下降,这些症状与胆道梗阻或胆管炎相似但缺乏典型胆道症状^[27]。相较之下,肝移植后IC患者更易出现非特异性胆汁淤积,而典型胆管炎表现仅占18%^[28]。这种症状学差异可能与原发病因导致的胆管微循环障碍程度相关,但现有数据缺乏大规模队列研究的统计学支持。

2.2 IC的诊断

2.2.1 影像学检查方法 影像学检查在IC的诊断中具有核心地位。磁共振胰胆管成像(magnetic resonance cholangiopancreatography, MRCP)作为无创性检查的首选,可清晰显示非吻合性狭窄的4种特征性分布模式:弥漫性坏死型、多灶进展型、汇合区优势型及轻微型,这些模式与移植预后显著相关,敏感度达87%~92%^[29]。CEUS在评估胆管壁微循环障碍方面展现出独特优势,临床研究进一步证实该技术在肝移植术后IC患者中的阳性预测值达76.9%^[11,30]。对于复杂病例,计算机体层成像(computed tomography, CT)与MRCP联合应用可鉴别胆管坏死与单纯胆管扩张,前者特征性表现为T₁加权像高信号及“管中管”征象^[31],而内镜逆行胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)虽非首选诊断手段,但在早期原发性硬化性胆管炎与IC的鉴别中仍具不可替代的组织获取优势^[32]。影像学评估需特别注意肝动脉血栓(磁共振血管造影检出率>95%)^[33]及门静脉血栓等血管并发症,上述因素可加速胆管缺血进程并影响治疗决策。

2.2.2 实验室检查指标 血清碱性磷酸酶(alkaline phosphatase, ALP)和 γ -谷氨酰转移酶升高是胆管损伤的特征性表现,其水平与胆管炎活动度呈正相关^[34]。2024年肝胆疾病囊性纤维化共识特别强调, γ -谷氨酰转移酶/血小板比值对早期胆管病变的识别价值可能优于传统肝酶检测,因其能同时反映胆道损伤和门静脉高压进程^[35]。天冬氨酸氨基转移酶/丙氨酸氨基转移酶升高更多提示继发性肝细胞损伤,在胆管缺血后期可能出现显著异常。持续性肝功能异常(>3~6个月)较短暂性升高更具病理意义^[35]。

3 IC的治疗策略与进展

3.1 IC的传统治疗方法

3.1.1 药物治疗的临床应用与局限性 药物治疗在IC中的效果有限,其临床应用主要针对改善胆管微循环障碍及控制继发性炎症反应,适用于症状早期控制和移植前桥接治疗。现有方案多采用抗凝治疗联合血管扩张剂(如前列腺素E1),但临床观察显示其仅能缓解早期缺血症状,对于已进展至胆管坏死的病例有效率不足30%。HHT患者中出现的急性胆道/肝坏死病例^[23]更凸显药物治疗的局限性,常规药物难以逆转血流动力学异常。针对门静脉高压继发的胆管缺血, β 受体阻滞剂虽可降低门静脉压力,但对胆管特异性缺血损伤的改善无

统计学意义^[23]。

3.1.2 内镜介入治疗的技术特点与疗效评估 内镜介入治疗作为IC的重要治疗手段,其技术选择与疗效评估需基于病变特征及患者个体化因素。对于局灶性缺血性胆管狭窄,内镜下球囊扩张联合支架置入具有显著疗效。DCD肝移植受者中,25%出现胆道并发症,局灶性狭窄患者经内镜治疗后预后良好,而弥漫性病变则需再次移植^[36]。胆管铸型综合征ERCP治疗中,最终60%达到完全狭窄缓解^[32,37]。影像学引导对治疗决策至关重要,MRCP与超声内镜检查在胆管异常检测等效性方面已获共识,术前通过磁共振成像评估肝体积引流比例(>50%)可显著降低感染风险并延长生存期^[38-39]。经皮经肝胆管引流术可有效处理胆漏及复杂狭窄^[28]。

3.2 IC的新型治疗进展

3.2.1 血管重建技术的创新与应用前景 在血管重建技术的创新与应用方面,近年研究揭示了动脉重建对IC预后的复杂影响。血管内介入技术(如支架置入)虽能短期改善血流,但其长期效果仍存在争议。病例报告显示,肝动脉狭窄经支架植入恢复再通后3周仍可出现肝脏梗死、脓肿及胆汁瘤等致死性并发症^[40];而经导管动脉内溶栓治疗的再通率仅为46%,且42%的成功再通患者仍需在2个月内行血管重建或再移植^[41]。相较之下,选择性非移植治疗策略在特定患者中展现出优势,血管重建后的移植5年内IC完全缓解率达100%,显著高于非重建组的17%^[42]。对于复杂解剖病例,两阶段手术策略可能比即时动脉重建更具安全性^[43]。NMP可显著降低IC总体发生率,但其中接受动脉重建的亚组却表现出更高的IC累积发生率(30.0% vs 3.3%),这可能与动脉重建组更长的冷缺血时间相关^[2]。上述数据提示,对于肝移植患者,未来血管重建技术需重点优化冷缺血时间控制与围手术期抗凝方案,尤其对于高凝状态患者^[44]。

3.2.2 生物材料支架在胆管修复中的研究突破 生物材料支架技术在胆管修复领域展现出突破性进展,其通过仿生结构与细胞重编程的协同作用实现功能性组织再生。采用双相聚己内酯支架(内层纳米纤维促进细胞附着分化,外层微孔泡沫增强机械稳定性)联合化学重编程肝细胞构建的人工胆管,在兔急性胆总管损伤模型中成功恢复胆汁流动,实验组存活率显著优于对照组^[45]。基因表达谱证实,经2周分化培养后,特异性肝祖细胞可完全分化为胆管上皮表型并覆盖支架表面,双层结构融合强度达 $(15.3 \pm 2.1) \text{ N/mm}^2$,满足抗断裂需求^[45]。相较之下,无支架三维多谱系球体模型虽能模拟

胆管病早期纤维化,但主要适用于药物筛选^[46]。生物材料支架技术通过精确调控微观拓扑结构与细胞微环境,为IC提供了兼具解剖重建与功能恢复潜力的治疗新策略。

4 IC的预后评估与随访管理

4.1 预后评估指标

4.1.1 临床生化指标评估 IC的预后评估依赖多项生化指标,但其临床解读需注意各自的应用场景与局限。ALP和胆红素作为IC及移植失功的早期预测指标已获得多项研究验证。一项针对89例DCD肝移植的回顾性分析显示,术后2个月的ALP水平与IC发生呈显著相关性:ALP<100 U/L时对IC的阴性预测值达97%,而>300 U/L时则成为IC发生的强预测拐点^[47]。同期数据表明,术后60 d胆红素>2.5 mg/dL的患者1年内移植失功发生率达100%^[47]。在离体肝灌注评估领域,胆汁pH值可作为胆管完整性的敏感指标:发生IC的肝脏胆汁峰值pH均<7.4,而无IC者pH>7.5^[48]。当前研究争议集中于各指标临界值的标准化,未来需整合多参数建立综合评估体系^[49]。

4.1.2 影像学评估 影像学检查为IC预后的关键评估方法,其模式识别与定量分析对临床决策具有重要指导价值。IC在肝移植后患者中可表现为4种特征性影像模式,其中弥漫性坏死型与移植物预后不良显著相关^[29,50]。MRCP可早期识别胆管铸型综合征,该征象患者5年移植存活率仅为42.9%,显著低于非吻合口狭窄组(56.3%)及吻合口狭窄组(80.6%)^[37]。多普勒超声不仅能区分肝静脉与门静脉分流类型,其标准化血流量参数与心脏衰竭及门静脉高压并发症的发生风险呈线性相关^[24]。将动态影像模式分析与血流动力学参数相结合,有助于建立更精确的IC预后分层体系。

4.2 长期随访管理策略

4.2.1 定期监测方案 在长期随访管理策略中,定期监测方案的制定需基于多模态影像学与生化指标的综合评估。研究显示,肝移植术后IC患者的5年肝动脉通畅率为81%,但32%的患者在58个月的中位随访期内仍出现IC影像学特征^[51]。IC发生与肝动脉并发症出现的时间显著相关:术后3个月内发生肝动脉并发症的患者IC发生率高达42%,而3个月后发现率仅为12%^[51]。这提示早期(术后3个月内)应加强监测频率,MRCP联合多普勒超声可提高IC检出率,即使超声检查正常者仍有19%(10/53例)存在MRCP证实的胆管病变^[51]。对于确

诊IC患者,非诺贝特治疗可使ALP在90 d内下降63.9%,并减少内镜逆行胆管造影频次^[52]。综上所述,IC监测方案需个体化设计,重点监测术后3个月内的肝动脉血流动力学变化,并持续评估胆道树形态与功能至少1年。

4.2.2 并发症预防与干预 在IC的长期随访管理中,并发症的预防与干预策略需基于多模态监测与风险分层。肝移植后3个月内发生肝动脉并发症的患者IC发生率显著增高(42% vs 12%)^[51],提示早期动脉事件是IC的独立危险因素。对于DCD肝移植,Meta分析证实其IC发生率较脑死亡供体升高10.8倍^[6],通过优化供体选择及缩短热缺血时间(功能性热缺血时间从21 min降至17 min),IC发生率可从25%降至3%^[53]。对于已发生IC者,血运重建后的5年胆管通畅率达81%,但需警惕肝脓肿等继发感染^[42,54]。体外NMP在DCD移植中可能降低IC风险^[52],而严重低氧血症亦可诱发胆管缺血性损伤,需加强氧合监测^[9]。综上,IC的并发症管理需结合动态影像评估、个体化血运干预及新兴器官保存技术,以实现精准化随访。

5 总结与展望

IC的发病核心在于PBP微循环障碍及IRI的双重打击,血管性与非血管性因素通过终末胆管动脉闭塞导致不可逆损伤,同时免疫介导损伤及细胞毒性疏水性胆盐等因素也参与其中。当前临床面临早期诊断和精准治疗两大挑战,未来的突破方向在于通过CEUS、MRCP分型联合生化指标构建早期预警体系,依托NMP、靶向血管重建及双层仿生支架等创新技术,推动治疗模式从“损伤控制”向“功能再生”转变。然而,上述新型治疗策略仍需进一步开展大样本研究予以验证。

利益冲突声明: 本文不存在任何利益冲突。

作者贡献声明: 胡天慧、黄志寅负责撰写论文;魏波负责拟定写作思路,指导论文撰写并修改论文。

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收稿日期: 2026-02-26; 录用日期: 2026-03-21

本文编辑: 刘晓红

引证本文: HU TH, HUANG ZY, WEI B. Advances in the diagnosis and treatment of ischemic cholangiopathy[J]. *J Clin Hepatol*, 2026, 42(4): 771-776. 胡天慧, 黄志寅, 魏波. 缺血性胆管病的诊断和治疗[J]. *临床肝胆病杂志*, 2026, 42(4): 771-776.