

急性胰腺炎肝损伤的发病机制和治疗

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Pathogenesis and treatment of acute pancreatitis with liver injury

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Abstract

Acute pancreatitis is a frequent acute abdomen in clinic, causes damages not only to pancreas, but also to distant organs. Liver is one of the mainly involved organs. The development of liver injury may aggravate pancreatitis. The pathogenesis of acute pancreatitis with liver injury is mainly related to cytokines, pancreatic enzyme, oxidative stress, microcirculation disturbance, apoptosis and pancreatitis-associated ascitic fluid, etc. Its treatment is also to eradicate these factors. However, more methods are still under animal studies. Their clinical application requires further study.

Key Words: Acute pancreatitis; Liver injury

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摘要

急性胰腺炎(acute pancreatitis, AP)是临床常见的急腹症, 常常引起胰外器官损伤, 肝脏是主要受损器官之一, 其损害的不断加重可导致胰

腺炎病情恶化, 目前认为肝脏损伤的机制主要有细胞因子、胰酶、氧化应激、微循环障碍、细胞凋亡和胰腺炎相关性腹水等。目前AP肝损伤的治疗也主要从上述各方面着手, 但更多的方法仍仅仅局限于动物实验, 临床应用还需进一步研究。

关键词: 急性胰腺炎; 肝脏损伤

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0 引言

急性胰腺炎(acute pancreatitis, AP)是临床常见的急腹症, 其发病机制尚未完全阐明。而急性重症胰腺炎(severe acute pancreatitis, SAP)常常并发肝、肾、肠道等胰外器官损伤, 进而发生多器官功能障碍(MODS), 死亡率较高。在一项对178名SAP相关MODS患者的回顾性研究中, 具有最高死亡率的是肝衰竭患者(83%); 而联合器官衰竭中, 又以肝肾衰竭死亡率最高(91%)^[1]。围绕急性胰腺炎相关肝损伤的机制和治疗有着众多的研究, 现将目前研究进展作一综述。

1 急性胰腺炎肝损伤的发病机制

1.1 细胞因子的作用 目前研究表明, AP时中性粒细胞分泌大量细胞因子, 在AP的病理生理变化中起着重要的作用。常见的致炎因子主要有TNF- α 、IL-1 β 、IL-6、IL-8等, 他们参与了局部炎症和全身炎症级联反应, 不仅引起胰腺水肿、出血坏死等, 还导致了胰外器官的损伤^[2-3]。Pastor *et al*^[4]发现, 在雨蛙肽诱导的大鼠AP中, 给予抗中性粒细胞血清后胰腺等器官损伤减轻, 肝脏中IL-6、IL-10水平明显降低, 认为中性粒细胞的激活是AP时器官损伤的原因之一。Zhang *et al*^[5]在牛磺胆酸钠诱导的大鼠AP中发现, AP时TNF- α 、IL-6、IL-10等炎症因子水平明显升高, 且与胰腺炎严重程度和器官损伤程度密切相关, 给予生长抑素后TNF- α mRNA的表达降低,

背景资料

急性胰腺炎是临床常见的急腹症, 肝脏是主要受损的胰外器官之一, 其损害的不断加重可导致胰腺炎病情恶化。肝脏损伤的机制目前认为主要有细胞因子、胰酶、氧化应激、微循环障碍、细胞凋亡和胰腺炎相关性腹水等方面, 而治疗方法大多局限于动物实验, 临床应用还需进一步研究。

同行评议者

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创新盘点

本文总结了近7年来国内外对于急性胰腺炎肝脏损伤的研究情况,探讨了急性胰腺引起肝脏损伤的诸多原因以及针对不同原因采取的治疗方法。

细胞因子水平也下降,推测TNF- α 在疾病的进展中可能起很重要的作用。另外,有人在胆碱缺乏和乙硫氨酸补充饮食(choline-deficient/ethionine-supplemented diet, CDE)诱导的C57BL/6大鼠SAP中,在实验36 h监测到肝脏中NF-kappa B的激活并且随之出现IL-6、MIP-2和转氨酶的显著升高,认为NF-kappa B依赖的细胞因子参与了AP时的肝损伤^[6-7]。

1.2 胰酶的作用 AP时在致病因素作用下大量胰酶在胰腺内激活,胰蛋白酶原激活成胰蛋白酶,继而激活糜蛋白酶、弹力蛋白酶、磷脂酶A2等,造成胰腺局部损伤,刺激中性粒细胞产生大量炎性介质。这些介质入血后进一步引起机体炎性介质释放形成瀑布似的连锁反应,形成全身的炎症反应造成多器官的损伤^[8]。Zhang *et al*^[9]从人体和大鼠的胰液中分离出一种甘露糖结合蛋白,他曾从血清、肝脏、肺等器官分离出来,证实在急性宿主防御反应第一线发挥重要作用。而该蛋白属于一种胰弹性蛋白酶,可以引起巨噬细胞激活、增强TNF- α 的表达,推测其可能在急性胰腺炎和全身炎症反应中起中介作用。Jaffray *et al*^[10]的实验证实了AP胰弹性蛋白酶造成了肝脏的炎症反应和损伤。而胰腺炎时胰酶的多少影响着胰腺炎的严重程度,这已得到Coelho *et al*^[11]实验证实:在牛磺胆酸钠诱导的AP中,造模前通过给予生理剂量的雨蛙肽[0.133 mg/(kg·h)]以降低胰酶和胰蛋白酶原的含量,从而减少了AP时致炎细胞因子的生成以及肝细胞线粒体功能障碍的发生。胰腺炎相关蛋白(pancreatitis-associated protein, PAP)是一种胰弹性蛋白,AP时过度表达。Folch-Puy *et al*^[12]在牛磺胆酸钠诱导的大鼠AP中,经腔静脉外源注入PAP(400 mg/kg),发现3 h后肝脏中NF-kappaB激活、肝细胞中TNF- α mRNA过度表达、TNF- α 含量异常增加,胰腺组织中的中性粒细胞浸润、氧化应激程度均较对照组明显升高,说明AP时PAP由胰腺释放后引起肝细胞TNF- α 过度表达, TNF- α 生成增加引起炎症造成组织损伤。

1.3 氧自由基的作用 在AP的发展中,被损坏的腺泡细胞与激活的白细胞、巨噬细胞产生大量的氧自由基及其衍生物,氧自由基的失衡导致了细胞的损伤,这些自由基不仅仅局限在胰腺内,也影响到身体的其他器官,特别是在肝、肺等器官中^[13]。Esrefoglu *et al*^[14]在雨蛙肽诱导的大鼠AP中发现,肝细胞出现变性、空泡化、血管充血、血窦膨大、炎症性浸润等病变同时伴有

显著的丙二醛(malondialdehyde, MDA)升高、过氧化氢酶(catalase, CAT)和谷胱甘肽过氧化物酶(glutathione peroxidase, GPx)的活动降低。给予抗氧化剂褪黑素或N-乙酰半胱氨酸+维生素C后可以明显改善肝脏的损伤。认为氧化损伤在AP肝损伤中起重要作用。Szabolcs *et al*^[15]采用L-精氨酸(3.2 g/kg, 2次ip)诱导大鼠坏死性胰腺炎模型,发现精氨酸引起肝脏脂质过氧化物反应水平升高,随过氧化物酶激活,造模24 h后Cu/Zn过氧化物歧化酶(Cu/Zn-SOD)以及CAT和GPx显著增加。Czako *et al*^[16]在L-精氨酸诱导的大鼠AP模型中也发现了胰腺、肝脏等器官中MDA浓度升高,而肝脏中Mn过氧化物歧化酶(Mn-SOD)和GPx的活动在发病初降低,胰腺腺泡细胞、肝细胞出现坏死等病变,认为在精氨酸诱导的AP早期,胰腺、肝脏等器官产生的氧自由基造成了器官的损害。但也有研究显示,小剂量L-精氨酸对AP具有治疗作用, Dobosz *et al*^[17]在雨蛙肽诱导的AP大鼠中,以L-精氨酸作为NO底物(100 mg/kg)给予大鼠后,发现可以改善胰腺、肝脏等脏器的微循环灌注。

1.4 微循环障碍 微循环的改变是AP早期重要的病理生理过程,他不仅仅发生于胰腺,而是涉及到众多器官诸如肝脏、肺脏和肠道等。肝脏中微循环的变化参与了肝组织损伤和肝功能障碍的发生发展过程^[18]。Foitzik *et al*^[19]通过活体显微镜检查法(intravital microscopy)和计算机图像分析发现,肝脏、胰腺等的微循环障碍在大鼠SAP模型早期发生,持续存在48 h以上,不仅影响毛细血管血流量,还影响毛细血管渗透性和白细胞内皮细胞的相互作用,认为微循环障碍可能与胰腺炎相关的MODS发生有关。Forgacs *et al*^[20]在雨蛙肽诱导的AP大鼠中,也观察到造模6 h后,与对照组相比, AP大鼠肝脏毛细血管流量显著降低,给予雨蛙肽拮抗剂可以明显改善肝血流灌注。Dobosz *et al*^[17]的实验也证实了AP造成了肝脏微循环灌注的显著下降,而给予L-精氨酸后,能够改善肝脏微循环,减轻器官损伤。

1.5 肝细胞凋亡 各种原因造成的肝损伤都可以出现肝细胞凋亡。肝细胞的凋亡是AP肝脏受损的表现之一,大量的肝细胞凋亡可造成肝功能障碍,严重时可进展至肝衰竭。Takeyama *et al*^[21]在大鼠SAP模型中发现肝细胞凋亡的存在,同时用SAP时产生的胰腺炎相关性腹水培养体外大鼠肝细胞时发现细胞的死亡是通过凋亡实现的,给予转化生长因子 β 1的(TGF β 1)中和

抗体可以部分阻止凋亡的诱导, 推测凋亡产生可能部分与胰腺炎相关性腹水(pancreatitis-associated ascitic fluid, PAAF)中的TGF β 1有关. Hori *et al*^[22]和Nakamura *et al*^[23]也发现, 大鼠AP时TGF β 1在血浆、PAAF、肝组织和腹膜巨噬细胞中的水平都升高, 其中和抗体可以减少肝细胞的凋亡、降低血清谷丙转氨酶, 而巨噬细胞的清除明显降低了血浆和PAAF中TGF β 1蛋白的水平, 且明显抑制了肝组织中TGF β 1的激活, 因此认为AP肝损伤与巨噬细胞引起的凋亡有关, 而其衍生的TGF β 1是诱导肝细胞凋亡的重要因子. 研究发现AP时Kupffer细胞衍生的Fas配体(FasL)、p38-促分裂原活化蛋白激酶(p38-mitogen-activated protein kinase, p38-MAPK)、细胞凋亡蛋白酶-3(caspase-3)表达增加并且诱导了肝细胞的凋亡损伤^[24-25]. Gallagher *et al*^[26]又进一步发现, 在Fas/FasL基因敲除大鼠中, AP诱导的p38-MAPK表达显著降低, 肝细胞的凋亡也明显减少, 推测Fas/FasL在AP肝细胞的凋亡中起关键作用. Peng *et al*^[27]通过CDE诱导大鼠AP模型, 并用胰弹性蛋白酶在p65 siRNA转染的大鼠离体Kupffer细胞株中模拟AP损伤模型. 实验发现, CDE胰腺炎引起p65 NF-kappa B/RelA核转位、Fas/FasL和caspase-3表达增加以及大鼠肝细胞核内DNA断裂. 而在体外实验中, p65 siRNA的转染减弱了弹性蛋白酶诱导的p65 NF-kappa B/RelA核转位和Kupffer细胞的凋亡, 证明AP通过NF-kappa B途径诱导Kupffer细胞凋亡, 并推测Kupffer细胞衍生的Fas/FasL诱导的肝细胞凋亡和NF-kappa B途径诱导的Kupffer细胞凋亡之间的平衡失调决定了AP时肝脏损伤的程度.

1.6 胰腺炎相关性腹水(PAAF)

AP时形成腹水不仅作为一种损伤体征出现, 而且具有很强的致病性, 可以促使AP病情进一步加剧, 并造成胰外器官的损害. Murr *et al*^[28]用PAAF灌注健康大鼠肝脏60 min后, 发现血清中AST、ALT、LDH水平升高15倍以上, 且不能被蛋白抑制因子所抑制. 而将人肝细胞株(CCL-13)暴露于PAAF后, 死亡细胞达到了15%而且PAAF的这一作用不受蛋白酶抑制因子或热灭活所影响. 推测PAAF对AP时肝脏的影响并不是通过其含有的胰酶或者局部Kupffer细胞诱导的细胞因子, 而是通过一种热稳定因子实现的. Yang *et al*^[29]又进一步发现, 向大鼠ip灭菌的PAAF, 同时将离体人肝细胞株(CCL-13)暴露于PAAF, 24 h后, 大鼠血清ALT、AST、LDH水平和肝细胞凋亡的数量都明显增

加. 在CCL-13中检测到p38-MAPK的激活, 细胞凋亡出现了时间和剂量的依赖性, 而caspase-3抑制剂II可以减少凋亡, 故而认为PAAF通过p38-MAPK的激活和caspase-3依赖的途径引起肝细胞凋亡从而造成了肝损伤. Ueda *et al*^[30]认为PAAF通过其含有的细胞毒性物质造成了肝细胞凋亡, 并发现PAAF还可引起肝细胞酸中毒、细胞内钠滞留、线粒体内ATP衰竭等, 认为PAAF中含有的血色素可能是造成肝脏损伤的细胞毒性物质之一. 而此前Ueda *et al*^[31]认为PAAF可造成肝细胞内钙超载, 这也可能是AP时肝脏受损以及AP造成多器官功能损伤的原因之一.

1.7 其他

AP发病初期, 病损的胰腺组织作为抗原或炎症刺激物激活巨噬细胞等炎症细胞释放各种细胞因子等, 他们对肝脏的损伤被认为是重要的引发效应和第一次打击, 继之而来的瀑布级联反应引发的全身炎症反应以及细菌移位、内毒素血症等具有感染性的打击构成了对肝脏的第二次打击. Okabe *et al*^[32]用雨蛙肽诱导大鼠AP模型形成第一次打击, 之后造成内毒素血症以形成第二次打击. 实验发现雨蛙肽+内毒素血症组的大鼠, 其肝脏对吲哚花青绿的血浆清除率较其他组显著降低, 提示肝脏功能受损严重, 而单纯的内毒素血症组该指标变化较轻微, 认为AP时的第一和第二次打击对造成肝脏损伤都具有重要作用. Gray *et al*^[33]用雨蛙肽诱导大鼠AP模型后注射内毒素, 24 h后发现肝脏NF-kappa B激活, 推测内毒素通过肝脏NF-kappa B引起器官损伤.

2 急性胰腺炎肝损伤的治疗

AP相关肝损伤的治疗与AP的治疗密切相关, 因为胰外器官的损伤程度取决于胰腺炎的严重程度. 根据AP肝损伤的机制, 进行抗炎、抗氧化、改善微循环、抑制凋亡、促进肝细胞再生以及支持疗法等.

2.1 抗炎治疗

一些细胞因子参与了肝脏炎症反应并造成损害, 故抑制这些细胞因子发挥作用或者阻断其激活和表达都可以起到保护作用^[34]. 抑制细菌移位以阻止其诱发炎症反应, 有人应用血小板活化因子抑制剂以及血小板活化因子受体抑制剂-BN52021, 降低了大鼠AP时细菌移位的发生并减轻了器官损伤^[35-36]. Cevikel *et al*^[37]发现, NO对AP时细菌移位可能具有调节作用, 通过每日给予NO合酶作用底物-L-精氨酸(100 mg/kg)2 d后, 细菌移位的发生明显低于对照组, 器官损害亦较轻. Chen *et al*^[38]经静脉给予AP大鼠表皮生长因子(epidermal growth factor,

应用要点
对于急性胰腺肝损伤的机制, 国内外研究涉及到诸多方面. 肝脏损伤的治疗也有不同方法, 但大多集中于动物实验的研究. 本文可以为今后急性胰腺炎肝损伤机制和治疗的研究提供一个借鉴和参考.

名词解释

胰腺炎相关性腹水(PAAF): 是指胰腺炎时含有胰酶的胰液渗漏进入腹腔, 引起慢性炎症, 导致大量液体在腹腔内聚集。

EGF)后, 可以改善肠道的渗透性从而阻止细菌移位发生, 保护胰腺、肝脏等器官. IL-10作为一种内源性抗炎细胞因子, 可以抑制单核巨噬细胞合成和表达TNF- α 、IL-1 β 、IL-6、IL-8等, 减轻AP严重程度, 改善预后. Zou *et al*^[39]进行了针对人IL-10(hIL-10)基因治疗的研究, 给AP大鼠ip一种“阳性脂质体/质粒-hIL-10(pcDNA3-hIL-10)复合物”后, 胰腺、肝脏、肺脏hIL-10水平升高, TNF- α 水平降低和组织学改善, hIL-10基因治疗组的死亡率较对照组明显降低, 7 d存活率分别为70%和10%, 认为该疗法可能具有积极的临床意义. Wang *et al*^[40]在大鼠SAP实验中, 用阳性脂质体介导的pcDNA3-IL-10基因治疗也证明能够有效降低SAP严重程度和死亡率. Ueno *et al*^[41]给AP大鼠造模前注射重组大鼠IL-18(rmIL-18)蛋白, 降低了AP时血清淀粉酶、脂肪酶、腺泡细胞空泡化水平, rmIL-18还增加了胰腺、肝脏等器官NO水平和iNOS基因表达, 认为rmIL-1在AP早期的保护作用可能是通过引起iNOS来源的NO释放形成的, 可能对AP具有治疗作用. 早期给予抗生素治疗也可以减少肝脏的损伤, Miyahara *et al*^[42]在狗胆汁反流性AP实验中, 造模6 h后, 经肠系膜上动脉持续给予抗生素亚胺培南治疗, 发现治疗组存活率较对照组明显升高, 血清转氨酶和门静脉内毒素水平显著降低, 发病24 h后, 对照组肝细胞和Kupffer细胞损伤加剧, TNF- α 表达急剧增加, 而治疗组的损伤则轻微. 认为抗生素可以控制内毒素易位, 从而减少肝损伤. Onok *et al*^[43]实验也证实抗生素具有治疗效果, 并发现喹诺酮类的药物效果要优于 β -内酰胺类抗生素.

2.2 抗氧化治疗 应用氧自由基清除剂可以降低AP时肝脏的氧化损伤. 褪黑素(melatonin)具有很强的抗氧化作用, Szabolcs *et al*^[15]发现褪黑素可以降低AP大鼠血清淀粉酶、过氧化氢酶的水平, 降低脂质过氧化反应程度, 减少器官损害. 褪黑素还具有抑制中性粒细胞浸润作用, Barlas *et al*^[44]发现其在胰管梗阻性胰腺炎中可以保护肝脏等胰外器官, 认为通过其清除氧自由基和抗氧化剂活性抑制了嗜中性白细胞对组织的浸润. 白藜芦醇(resveratrol)是葡萄属植物产生的一种植物抗毒素, 为多酚类物质, 具有很强的抗氧化和抗炎作用. Szabolcs *et al*^[45]发现, 在胆囊收缩素诱导的大鼠AP中, 白藜芦醇可以增加肝脏还原性谷胱甘肽含量并减少肝过氧化氢酶的激活. 此外还有维生素C, N-乙酰半胱氨酸等也具有抗

氧化的作用^[46-47]. Esrefoglu *et al*^[14]在其实验中发现, 维生素C联合N-乙酰半胱氨酸可以增加大鼠肝脏中GPx和CAT的活性, 减少了胰腺和肝脏的损伤.

2.3 改善微循环 Dobosz *et al*^[48]通过激光多普勒血流仪发现, 大鼠AP时各个器官微循环灌注都显著降低, 而肝素钠增加了微循环灌注, 具有一定的治疗作用. Machado *et al*^[49]发现AP时平均动脉压显著降低, 而高渗盐水(7.5% NaCl)治疗可以升高动脉压, 改善血液动力学并且降低IL-6、IL-10等细胞因子水平和髓过氧化物酶(myeloperoxidase, MPO)活性, 减轻肝脏等器官损伤, 死亡率降低. Chen *et al*^[50]发现, 给予大鼠ip褪黑素(2或10 mg/kg)后, 可以减轻全身动脉压降低的程度, 维持器官灌注水平, 大剂量组对于AP的治疗效果要优于小剂量组, 能够降低促炎介质-前列腺素的水平, 使之趋于正常.

2.4 生长抑素 生长抑素对AP的治疗疗效较为确切, 能够进一步减轻肝脏的损伤^[51]. 研究发现, 生长抑素能够抑制AP大鼠血清TNF- α mRNA的过度表达, 减轻胰腺和肝脏组织的损伤^[5, 52-53]. Tang *et al*^[54]对39名SAP患者, 于发病早期给予生长抑素(250 μ g/h)治疗持续72 h, 发现可以减少炎症应答, 恢复细胞免疫功能, 改善患者一般状况, 但对于死亡率的疗效还需进一步研究. Xia *et al*^[55]对60名SAP患者应用生长抑素治疗后, 血清C-反应蛋白水平降低, APACHE II评分明显有改善, 器官功能障碍的发生率较常规药物治疗组降低.

2.5 糖皮质激素 糖皮质激素的使用存在有争议, 研究显示, 给予地塞米松或者氢化可的松后, 大鼠肝脏中ATP水平明显升高, MPO、细胞间黏附因子-1(ICAM-1)水平降低, 认为糖皮质激素在AP早期炎症反应中发挥重要作用^[56-59]. Cosen-Binker *et al*^[60]则发现糖皮质激素对AP大鼠具有预防损伤作用且与给药时间和剂量相关, 在诱导AP前30 min给予氢化可的松4 mg/kg效果最佳, 过高或过低则效果欠佳. Zhang *et al*^[61]观察到地塞米松可以明显降低AP大鼠血清中淀粉酶、内毒素、TNF- α 的水平, 但并没有改变大鼠的死亡率.

2.6 血液滤过 血液滤过作为一种净化血液的方法, 在AP以及相关器官损伤的治疗中可能具有重要意义. Yang *et al*^[62]对猪SAP模型使用高容量零差额(high-volume and zero-balance)的血液滤过疗法, 与对照组相比, 治疗组的平均

动脉压、动脉血氧分压显著增加, 而尿蛋白含量、血清ALT水平则显著下降, 造模6 h后, 血清TNF- α 、IL-1 β 水平降低, IL-10/TNF- α 比率更高, 认为早期血滤可以有效清除猪血液中TNF- α 、IL-1 β , 升高IL-10/TNF- α 比率, 改善血流动力学, 减轻肝、肾等器官损伤. Yang *et al*^[63]对37名SAP患者的随机分组实验, 采用连续性静脉-静脉血液滤过(continuous veno-venous hemofiltration, CVVH)组的治疗效果明显优于常规治疗组, 死亡率低(18.2% vs 33.3%)、住院天数少(18.3 \pm 5.7 d vs 27.5 \pm 8.6 d), 认为该法对SAP造成的组织和器官损伤具有显著的保护效果.

2.7 其他 研究证实, 肠内营养的方法可以有效减少细菌移位的发生, 降低了血清淀粉酶、转氨酶^[64-65]. 但Alhan *et al*^[66]却发现肠道内营养和静脉营养联合疗法对AP大鼠并没有显著效果. Yol *et al*^[67]对大鼠采用胰胆管结扎法诱导AP, 并于造模开始给予大量聚乙二醇持续灌肠6 h, 结果显示72 h后, 灌肠组血清淀粉酶、ALT、LDH、乳酸水平和肝损伤的发生率均显著低于对照组. Alhan *et al*^[68]在大鼠AP实验中发现, 给予Omega-3(ω -3)脂肪酸可以减少胰腺、肝脏等器官的细菌感染, 降低血清TNF- α 、IL-6含量, 减少氧自由基的破坏, 降低死亡率. Ueda *et al*^[69]发现肝细胞生长因子在AP损伤器官中表达增加, 肝细胞生长因子具有一定营养作用, 并且可以抑制PAAF引起的肝细胞凋亡.

3 结论

AP肝损伤机制仍未完全阐明, 目前研究认为与炎性细胞因子、胰酶活性、氧化应激、微循环障碍、肝细胞凋亡、胰腺炎相关性腹水等损伤因素有关, 这些方面相互影响, 构成了一个复杂的病理生理过程. 治疗上包括抗炎、抗氧化、改善微循环、应用生长抑素、糖皮质激素和血液滤过等方法, 目前AP肝损伤治疗的研究主要为动物实验, 其临床疗效有待进一步证实.

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同行评价
本文之前虽有报道, 但该文的参考文献较新, 且信息量大, 有一定的参考性.

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