

肝移植术后合并感染及免疫支持治疗的研究现状

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[摘要] 肝移植是终末期肝病治疗的有效方法, 而合并感染是其术后病死率增高的重要原因。由于肝移植术后感染的临床症状缺乏特异性, 对包括细菌、真菌及病毒在内的不同病原感染的发生率、高危因素、诊断及治疗均需要进一步深入认识。此外, 了解肝移植术后免疫功能的变化特点, 及时有效地防治移植术后并发的感染, 可降低围手术期病死率, 改善患者结局。目前, 在移植后感染患者中应用胸腺肽 α_1 、静脉注射用人免疫球蛋白及乌司他丁等免疫调节药物均取得了一定的疗效。本文就肝移植术后合并感染的特点、免疫功能变化及免疫支持治疗的现状进行综述。

[关键词] 肝移植; 感染; 免疫监测; 免疫支持

Current state of research on immunosupportive treatment of infection after liver transplantation

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[Abstract] Liver transplantation is currently an effective treatment for end-stage liver disease. Postoperative infection is the main important cause of death in patients after liver transplantation. Due to the lack of specificity of clinical symptoms of postoperative infections, further insight is needed into the incidence, risk factors, diagnosis and treatment of different infections, including bacterial, fungal and viral. In addition, it could reduce the perioperative mortality that understanding the characteristics of changes in immune function after liver transplantation and timely prevention and treatment of post-transplant complications of infection, which would ultimately improve the outcome of patients. Nowadays, the use of immune-supporting drugs such as thymosin α_1 , intravenous immunoglobulin and ulinastatin have also shown some efficacy in patients with post-transplant infections. This article reviews the characteristics of infection, the changes of immune function and the feasibility of immunosupportive therapy after liver transplantation.

[Key words] liver transplantation; infection; immune monitoring; immunological support

自1963年Starzl等^[1]在美国实施了第1例肝移植(liver transplantation, LT)手术以来, LT技术发展至今已逐渐成熟, 成为治疗急慢性肝衰竭及肝脏恶性肿瘤等终末期肝病的有效方法^[2-3]。免疫抑制剂的广泛应用使得LT术后住院病死率降至6%左右^[4-5]。据统计, 欧洲肝移植登记处的LT术后1年生存率

为86%, 日本为87%, 美国为85%; 欧洲的LT术后5年生存率为74%, 美国及日本登记处的LT术后10年生存率为53%~76%^[6-9]。在中国较大的肝移植中心, LT术后1年生存率可达90%, 10年生存率可达70%^[10]。感染是导致LT受者围手术期死亡的主要原因之一, 不同研究中的感染发生率差异很大, 为

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21.0%~48.4%^[11-12], 感染所致死亡占LT术后死亡总数的30%以上^[13-14], 需引起临床医师的重视。本文就LT术后感染的特点、免疫功能变化及其监测手段、免疫治疗的效果等的研究现状进行综述。

1 LT术后合并感染的特点

LT术后早期是感染的高峰期, 终末期肝病模型(model for end-stage liver disease, MELD)评分高、移植前感染、采用Roux-en-Y胆道吻合方式、合并胆道并发症及围手术期输血史均是LT术后感染的独立危险因素^[15-16]。因为免疫抑制剂的使用使术后感染的临床症状缺乏特异性, 导致早期对病情进展进行准确判断有一定的难度, 因此对高度怀疑合并感染的患者, 即使缺乏明确的病原学依据, 也应根据当地的感染致病菌谱尽早预防性及经验性地应用广谱抗生素或联合应用抗生素预防感染, 以改善LT患者的预后^[17]。

1.1 细菌感染 细菌感染为LT术后病死率增高的的重要因素。国外文献报道, 在十余年前, 移植术后感染的病原菌为革兰阳性者占70.6%, 革兰阴性者占28.4%^[18]; 而吴金道等^[19]对2012—2015年1380株LT术后感染病原菌进行分析发现, 革兰阴性菌占70%, 革兰阳性菌占20%。近年国内外研究均表明, 革兰阴性菌已超过革兰阳性菌成为LT术后感染的主要病原菌^[20-21]。不同移植中心的移植术后感染率及病原体分布差异可能与地区间医疗水平、病原菌流行病学特征有关, 而暴露的强度、时间以及病原菌的毒力均会影响发病率及病死率, 日益增多的多重耐药菌也给移植术后抗感染治疗带来了巨大挑战^[22-23]。此外, 有研究发现长期肾脏替代治疗、术后胆漏、门静脉血栓形成、高龄、术后严重的高血糖、重症监护病房(ICU)停留时间长、机械通气时间长等均是导致移植术后感染的高危因素^[24]。

1.2 真菌感染 尽管在肝移植患者中侵袭性真菌感染的发生率不高于细菌感染, 但其病死率可高达80%。引起感染的真菌多为条件致病性真菌, 因术后免疫抑制剂的使用, 患者免疫功能下降, 导致真菌突破免疫防御, 从而造成真菌感染的发生。Phoompong等^[25]对成人肝移植受体的侵袭性真菌感染情况进行荟萃分析发现, 侵袭性真菌的感染率为1.4%~32.7%。来自韩国的一项多中心回顾性临床研究显示, LT术后患者的侵袭性真菌感染率为4.77%, 最常见的是白色念珠菌, 占55.2%, 其次为曲霉菌, 占30.4%^[26]。国内的流行病学研究发现, LT术后侵袭性真菌感染率达18.8%, 其中白色念珠菌占55.2%, 曲霉菌占8.4%, 其他非白色念珠菌占36.4%^[27]。广谱抗生素治疗、肠外营养、中性粒细胞

减少、ICU停留时间长、糖尿病、移植前定植、肾脏替代治疗、巨细胞病毒感染、再次手术、胆总管空肠吻合是肝移植后早期发生侵袭性念珠菌病的危险因素^[28-29]。术前类固醇药物的使用、急性肝衰竭及肾脏替代疗法与移植后早期发生侵袭性曲霉菌病相关^[30-31]。而在移植术后(>4个月), 泼尼松的大量使用及肾衰竭也易诱发曲霉菌感染^[32]。对侵袭性真菌进行早期诊断及治疗很有必要, 因其与术后并发症、移植体失功密切相关^[33], 以1,3-β-D-葡聚糖检测(G实验)、曲霉半乳甘露聚糖抗原检测(GM实验)、下一代测序技术(next generation sequencing, NGS)为代表的非侵袭性实验室技术的广泛应用, 提高了真菌感染诊断的阳性率^[34]。

1.3 病毒感染 肝移植后最常见的病毒感染类型是巨细胞病毒(cytomegalovirus, CMV)感染^[35-36]。供者体内潜伏的CMV可通过移植肝转移到受者体内。CMV感染的治疗主要包括免疫调节及抗病毒治疗两个方面, 且二者同等重要。在CMV感染的早期阶段, 主要是增强患者的免疫功能, 特别是CMV肺炎, 在不导致急性排斥反应(acute rejection, AR)的前提下, 尽可能减少抗排斥药物的用量, 甚至全部停用, 必要时还可加用增强免疫功能的药物(如胸腺肽 α_1 、人免疫球蛋白)^[37]。Wang等^[38]的研究显示, 胸腺肽 α_1 治疗CMV肺炎安全有效, 且不会增高AR的发生率。常用的抗病毒药物如更昔洛韦、伐昔洛韦等均可用于预防及治疗CMV感染。

EB病毒(Epstein-Barr virus, EBV)可导致一种免疫缺陷相关的淋巴增生性疾病, 即移植后淋巴组织增生性疾病(post transplant lymphoproliferative disease, PTL), 在LT术后的发生率小于5%^[39-40], 但因其具有一定的侵袭性, 也是导致LT术后高病死率的危险因素。目前, EBV相关PTLD的治疗标准尚缺乏高质量的循证医学证据^[40]。有研究显示以西罗莫司为基础的免疫调节方案可提高此类患者的生存率^[41]。

微小病毒B19(parvovirus B19, B19V)是一类无包膜单链DNA病毒, 在器官移植后免疫功能低下的患者中, B19V的感染率约为2%^[42], 受体感染B19V的途径主要包括3个方面: 供体, 污染的血液及其制品, 以及受者的围手术期感染^[43]。B19V可抑制骨髓红细胞系统增生, 常导致以严重的红细胞贫血为主要临床表现的慢性纯红细胞再生障碍性贫血^[44]。目前, 免疫球蛋白输注联合包括输血在内的对症治疗均能有效中和B19V并改善贫血状况, 可取得满意的治疗效果^[44-45]。

2 LT术后炎症指标及免疫功能的变化与监测

肝脏除了具有较强的局部固有免疫功能外,

也是T细胞介导的局部及全身适应性免疫的主要场所。肝脏通过两个机制来调节免疫系统的稳态：首先，通过肝脏双重血供防御血源性病原体，可避免来自肠道微生物抗原的全身性播散，发挥其免疫监视作用；其次，肝脏能够通过合成免疫相关可溶性分子来调节免疫稳态^[46]。此外，肝脏通过多种定植的抗原递呈细胞(包括库普弗细胞、肝窦内皮细胞、树突状细胞)及淋巴细胞发挥其抗菌监视作用。肝细胞可通过表达多种模式识别受体(pattern recognition receptors, PRRs)识别不同类型的病原菌，这些PRRs与其配体结合，在免疫细胞中可发挥信号转导及活化作用，在与某些特殊的细菌产物结合的情况下，可促进核因子 κ B(nuclear factor kappa-B, NF- κ B)活化^[47]。对于LT术后患者，在使用免疫抑制剂的过程中动态监测免疫功能有助于制定更精准的免疫调控方案，快速达到免疫耐受状态，减少使用免疫抑制剂引起的继发感染等并发症，改善最终结局。多个淋巴细胞亚群参与了免疫调节及免疫抑制的过程，对淋巴细胞亚群进行监测是移植术后免疫状态监测的主要方法^[48]。

2.1 免疫细胞数量的变化及监测 既往研究发现，LT术后免疫耐受者外周血中的调节性T细胞(regulatory cells, Tregs)、树突状细胞(dendritic cells, DC)、 $\gamma\delta$ T淋巴细胞等均明显增多^[49]，这几类细胞可作为LT术后患者免疫功能的“监视器”。王勤拯等^[50]通过分析LT术后合并感染与未感染的各19例患者外周血淋巴细胞亚群，发现早期监测外周血淋巴细胞亚群百分比及绝对计数变化可对感染风险进行有效评估。董家勇等^[51]通过比较肝癌LT术后复发与未复发患者的CD4⁺T淋巴细胞三磷酸腺苷(ATP)含量及亚群计数发现，复发患者的免疫细胞数量随时间延长逐渐降低，在一定程度上也能反映肝癌LT术后复发患者的免疫状态。一项纳入105例小儿肝移植病例的回顾性研究发现，LT术后合并感染者的CD4⁺T淋巴细胞ATP值及CD4⁺/CD8⁺比值明显降低，这两个指标能较好地反映小儿LT术后的免疫状态^[52]。

2.2 免疫功能变化及监测 CD14⁺单核细胞人白细胞DR抗原(CD14⁺/HLA-DR)能激活多种免疫细胞，可作为急性胰腺炎等常合并感染疾病患者病情诊断、评估、发展及预后判断的生物学指标^[53-54]。文强等^[55]对83例LT术后患者CD14⁺/HLA-DR水平的变化进行分析发现，术后当天感染组与非感染组间无显著差异，感染组患者在感染程度最重时，CD14⁺/HLA-DR水平下降到最低，当感染逐步得到控制后，CD14⁺/HLA-DR水平逐渐升高，因此动态监测CD14⁺/HLA-DR的变化有助于判断LT术后感染

的发生以及评估预后。

2.3 其他免疫指标的监测 Ruiz等^[56]研究发现，Torque Teno病毒(一种广泛存在于人类的病毒)可用于LT术后早期免疫抑制状态的监测。黄小慧等^[57]用ImmuKnow免疫细胞功能测定试剂盒检测发现，以CD4⁺T淋巴细胞ATP含量 $\leq 225 \mu\text{g/L}$ 作为术后感染和急性排斥反应的监测及诊断标准具有一定的应用意义。一项纳入6项研究的meta分析发现，ImmuKnow免疫细胞功能测定试剂盒预测感染的总体准确性较高，其结果呈阳性的移植受者发生感染的概率比阴性受者高14.6倍^[58]。但也有研究发现ImmuKnow的结果并不能完全反映移植术后受者的免疫状态^[59]。

2.4 炎性相关指标的变化及预测价值 降钙素原(procalcitonin, PCT)是全身细菌感染的特异性标志物，研究显示其可用于评估LT术后是否合并感染^[60]；Hara等^[61]的研究显示，移植前血清PCT $>0.5 \text{ ng/ml}$ 是移植后脓毒症的唯一独立危险因素。Kaido等^[62]发现当PCT为 2.0 ng/ml 时，菌血症的阳性预测值为83.3%，阴性预测值为97.4%。Mahmoud等^[63]研究发现，术后第1天PCT $<9 \text{ ng/ml}$ 可排除83.7%的感染。上述研究均表明，PCT在预测LT术后感染方面具有一定的价值。但也有研究显示PCT高并不是LT术后感染的独立危险因素，而C-反应蛋白(C-reactive protein, CRP)水平升高是感染的危险因素^[64]，可作为LT术后30 d细菌感染的独立预测因子^[65]，在预测LT受者6个月及12个月病死率中具有一定作用^[66]。一项回顾性研究发现，白细胞介素-6(IL-6)水平升高与终末期肝病患者的3个月及1年病死率相关，其对预后的预测价值与MELD评分及MELD-Na评分相当，高于CRP的预测价值^[67]。在LT患者中，IL-6及肿瘤坏死因子 α (TNF- α)被认为是早期移植体再生成功的重要介质^[68]，也有研究认为IL-6可作为活体肝移植患者发生急性肾损伤(acute kidney injury, AKI)的预测因子^[69]，而再灌注时的IL-6水平可作为预测长期存活率的有效生物标志物^[70]。

3 LT术后合并感染的免疫治疗

临床上，对LT术后患者危重状态与移植体功能平衡的准确把握可帮助临床医师制定个体化的治疗方案，但受者的感染风险会因免疫抑制剂的使用而明显增加，因此，肝移植后各种感染性并发症的发生率大大增高。目前临床上常用的免疫调节药物包括胸腺肽 α_1 、静脉注射用人免疫球蛋白及乌司他丁等。

3.1 胸腺肽 α_1 胸腺肽 α_1 在固有性免疫及获得性免

疫治疗中均发挥着重要的免疫调节作用,是目前临床上最常使用的一种免疫调节剂^[71]。胸腺肽 α_1 可以活化树突状细胞,提高自然杀伤细胞活性,直接作用于巨噬细胞,增强其吞噬杀菌能力,促进单核细胞HLA-DR及抑制程序性死亡分子配体1(PD-L1)的表达,从而增加T细胞的数量及活性,增强Th1细胞的抗菌作用^[72-74]。胸腺肽 α_1 的免疫调节活性及治疗作用已在多种疾病中得到证实,包括慢性乙型肝炎、慢性丙型肝炎、原发性及获得性免疫缺陷性疾病等^[75]。有报道胸腺肽 α_1 并不会增加使用免疫抑制剂患者的急性排斥反应发生率^[76-77]。有研究采用西罗莫司联合胸腺肽 α_1 及槐耳冲剂以预防LT术后肝细胞癌复发,结果发现并无明显的不良事件发生。此外,在治疗LT术后机会性致病菌感染(如CMV肺炎)方面,撤减免疫抑制剂的同时加用胸腺肽 α_1 也显示出了较好的疗效^[78]。亦有研究发现,胸腺肽 α_1 联合乌司他丁治疗可提高碳青霉烯耐药菌腹腔感染脓毒症患者的存活率^[79]。上述研究均表明LT术后应用胸腺肽 α_1 可能不仅不会增加急性排斥反应的发生率,还可对T淋巴细胞数量进行调节,增强了患者的抗感染能力,从而改善预后。

3.2 静脉注射用人免疫球蛋白 静脉注射用人免疫球蛋白(intravenous immunoglobulin, IVIG)具有抗多种病原体的作用,因为其含有多价抗原特异性的IgG抗体^[80]。为预防及治疗LT术后乙型病毒性肝炎,目前使用的免疫球蛋白多为乙型肝炎人免疫球蛋白(hepatitis B immunoglobulin, HBIG),将IVIG用于治疗LT术后合并其他感染的情况较少。Kerensky等^[81]通过静脉注射西多福韦联合IVIG治疗1例LT术后继发感染腺病毒肝炎患者,取得了良好的效果。Sridhar等^[82]应用IVIG成功救治了1例肝移植受者并发副流感病毒4B期鼻病毒C的严重肺炎病例。还有个案报道应用IVIG治疗肝移植后继发西尼罗河病毒(WNV)脑炎患者1例,结果显示患者完全康复^[83]。但也有研究显示,移植后使用IVIG抗感染治疗的效果有限,其剂量、频率、持续时间及疗效仍有待确定^[84]。

3.3 乌司他丁 乌司他丁作为一种可抑制胰蛋白酶等各种胰酶活性的糖蛋白,其抗炎及抑炎反应与淋巴细胞的凋亡相关^[85],因此临床上常将乌司他丁作为一种有效的免疫调节药物使用^[86]。亦有报道乌司他丁能减轻LT患者的炎症反应,其机制为抑制CD11b/CD18表达的上调^[87],而进一步研究发现,使用高剂量乌司他丁的患者术后感染发生率更低^[88]。此外,多项研究显示乌司他丁能显著改善LT术后患者肺、肾、心脏等多个器官的功能,并可改善凝血功能,减轻缺血再灌注损伤等^[89-93]。

4 LT术后合并感染时免疫抑制药物剂量的调整

LT术后合并感染时,免疫抑制剂方案的调整仍存在较大争议,不同的中心存在一定的差异,暂无统一的调整方案。中华医学会器官移植学分会认为应通过评估感染患者的免疫功能及病原微生物的情况,加强对免疫抑制剂血药浓度的监测,由联合用药调整为单一用药,并及时调整钙调磷酸酶抑制剂(CNI)或西罗莫司的剂量。感染严重时可考虑暂时撤除免疫抑制剂,并酌情使用免疫增强药物^[94]。李瀚等^[95]认为感染患者可考虑停用免疫抑制剂,待感染逐渐得到控制及免疫状态逐步恢复后,再缓慢恢复使用免疫抑制剂。笔者根据本中心的临床经验认为,在严重感染的患者中,可考虑完全或部分停用免疫抑制剂,并根据天然免疫及获得性免疫功能情况,增加免疫增强剂胸腺肽的使用,可取得不错的治疗效果,且不会增加急性排斥反应的发生率。但上述调整方案的应用指征还需要通过进一步的临床及基础研究进行探讨。

5 总结与展望

LT术后合并感染是围手术期死亡及远期预后的重要影响因素,临床上应予以重视。术后服用免疫抑制剂期间,精准高效的免疫监测手段有利于更好地评估患者的免疫状态,目前的监测手段与患者整体的免疫状态之间缺少必然的内在联系,仍需进一步研究。LT术后因免疫功能低下而合并机会性感染的患者越来越多,对此类患者停用免疫抑制剂甚至予以免疫支持治疗也逐渐成为一项新的治疗策略,但仍需开展大量高级别的临床研究以获得更可靠的证据支持。

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