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·综述·

肝移植后感染的时间进程与流行病学特征

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[摘　要] 尽管手术技术与预防策略日趋规范,感染仍是肝移植受者发生并发症和死亡的主要原因。感染在移植后不同时期呈现特定的病原学特征:早期(移植后 1 个月内)以手术相关感染和供体来源感染为主,中期(2～6 个月)机会性感染风险达峰值,晚期(6 个月后) 则以社区获得性感染为主。本文通过综合分析近期研究,系统阐述肝移植后不同阶段感染的病原学特点、流行病学特征,以及不同地区人群的感染谱差异,旨在为优化感染监测与防控策略,改善患者预后提供理论依据。

[关　键　词] 肝移植;术后感染;机会性感染;流行病学

[中图分类号] R617　R563.1

Temporal progression and epidemiological characteristics of post-operative infection after liver transplant

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[**Abstract**] Despite the increasing standardization of surgical techniques and prevention strategies, infection still remains the main cause of complications and death in liver transplant recipients. Post-operative infection exhibits specific pathogenic characteristics at different stages after transplant: in the early stage (within 1 month after transplant), surgery-related infection and donor-derived infection are predominant, in the middle stage (2－6 months after transplant), the risk of opportunistic infection reaches its peak, and in the late stage (6 months after transplant), community-associated infection is predominant. Through comprehensive analysis of recent research, this paper systematically elaborates the pathogenic and epidemiological characteristics of infection in different stages after liver transplant, as well as the differences in infection patterns among populations in different regions, aiming to provide theoretical basis for optimizing infection surveillance as well as prevention and control strategies, and improving patients' prognosis.

[**Key words**] liver transplant; post-operative infection; opportunistic infection; epidemiology

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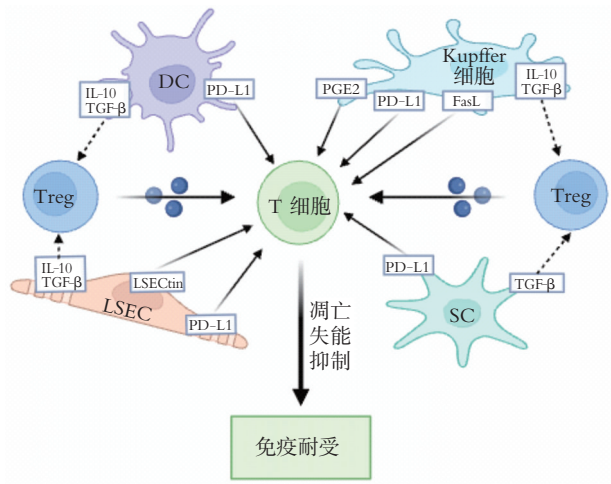
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肝移植是治疗终末期肝病的最有效手段。尽管手术技术、围术期感染控制及预防策略日益规范，感染仍是肝移植受者并发症和死亡的主要原因，位居移植后 1 年内死亡原因的首位[1]，约三分之二的肝移植患者至少经历过一次感染[2]。移植后感染的病原谱及感染类型随时间呈现规律性变化，主要取决于免疫抑制程度和流行病学暴露。免疫抑制治疗的具体方案、剂量及持续时间是决定感染风险的关键因素[3]。基于相对标准化的免疫抑制方案，Fishman 等[4]提出了广为接受的移植后感染时间分期：早期（≤1 个月）、中期（2～6 个月）及晚期（＞6 个月）。本综述旨在系统分析肝移植后感染的时间分期特征和流行病学规律，重点阐述不同时期感染的发生机制、临床特点，并比较中国与其他国家/地区感染模式的差异，以期为临床实践提供参考依据。

1　感染时间进程分期与发病机制

移植后感染的病原体谱和感染风险随时间呈现阶段性演变。移植后 1 个月内，感染主要源于手术相关并发症和供受体传播。此阶段尽管使用高剂量免疫抑制剂以预防急性排斥，但机会性感染相对少见。这可能与免疫抑制的累积效应尚未完全显现，且围术期预防性抗微生物治疗仍具保护作用有关[5]。移植后 2～6 个月是机会性感染的高峰期。免疫抑制累积效应导致 T 细胞功能显著受损、先天免疫识别能力下降，为巨细胞病毒（*cytomegalovirus*，CMV）、EB 病毒（Epstein-Barr virus，EBV）等病毒的再激活以及真菌感染创造了条件[6-7]。移植 6 个月后，受者免疫功能逐渐恢复，感染病原体谱向常见社区病原体转变，疫苗接种的有效性也显著提高，如流感疫苗的血清转化率从移植后 4 个月内的 14% 升至 12 个月后的 86%[8]。若发生急性排斥反应需强化免疫抑制治疗，上述感染时间进程将重置。国际肝移植协会建议，此时应重新开始为期 3～6 个月的机会性感染预防[9]。

肝移植后的感染时间模式还受其独特的免疫学特性影响。与其他实体器官移植不同，肝脏被称为“免疫特惠器官”。其肝窦内皮细胞（liver sinusoidal endothelial cell，LSEC）、树突状细胞（dendritic cell，DC）和星状细胞（stellate cell，SC）等低表达共刺激分子，并通过多种机制诱导 T 细胞耐受、凋亡和功能抑制[10]（图 1）。基于这种内在的免疫调节特性，20%～40% 的成人肝移植受者可逐步建立操作性免疫耐受，即在不使用免疫抑制剂的情况下，至少 1 年以上未出现移植物排斥反应，并实现移植器官长期存活[11-13]。此比率在儿童受者中甚至可达 60%[12,14]。临床研究显示，部分患者可在移植后 6～18 个月内逐步减停免疫抑制剂，成功者可在长达 49 个月的随访中保持稳定[15-16]。虽然完全停用免疫抑制剂目前仍限于临床试验阶段，但这体现了肝脏免疫耐受的逐步形成，使得移植晚期患者的整体免疫功能得以恢复，感染风险相应降低，从而构成了肝移植独特的感染时间演变模式。



注：耐受的实现依赖于 Kupffer 细胞、LSEC、DC 和 SC 的协同作用。这些细胞主要通过两条途径发挥作用：一是直接途径（实线箭头），通过表达免疫检查点分子等方式直接抑制效应 T 细胞，诱导其凋亡、失能或功能抑制；二是间接途径（虚线箭头），通过激活和扩增 Treg 细胞间接抑制效应 T 细胞。这些机制共同作用，最终建立了移植后的免疫耐受状态。

图 1　肝移植后肝脏免疫耐受的机制

2　基于时间进程的感染流行病学特征

2.1　移植后早期（移植≤1 个月）　移植早期感染发病率较高且相对集中，40%～50% 的感染发生在术后 1 个月内[17-18]，感染发病率达 16.4 例/1 000 移植日[17]，其中以细菌感染为主。感染类型主要分为供者相关感染和手术相关感染，后者包括手术部位、腹腔、导管、肺部及泌尿道感染。

2.1.1　细菌感染　75% 的细菌感染发生于术后 30 d 内，中位发生时间为 10 d[2]。腹腔内感染和血流感染居前两位，分别占早期细菌感染的 50%、19%～46%[19]。腹腔内感染占早期细菌感染的半数，术后 13～15 d 为发病高峰[20-21]。感染类型以腹

膜炎(28%～43%)和腹腔脓肿/胆管瘤(29%～58%)最为常见[20-21]。主要病原体包括肠杆菌(占 42%)、肠球菌(占 24%)和念珠菌(占 15%)[17,21-22]。胆漏和手术时间延长是主要危险因素[21];近年研究发现,供受者年龄差大于 10 岁也会显著增加风险[23]。

2.1.1.1　艰难梭菌感染　艰难梭菌感染作为一种特殊类型的腹腔感染,其发病率近年呈上升趋势(从 2004 年 23.1 例/1 000 人年升至 2017 年 46.7 例/1 000 人年)[24],约半数发生于术后 1 个月内[25-27]。值得注意的是,近期研究发现发病时间影响预后,晚发型艰难梭菌感染(≥90 d)的短期死亡风险(*OR* 为 4.26)和长期死亡风险(*HR* 为 2.49)均显著高于早期感染[24,28]。

2.1.1.2　血流感染　血流感染占肝移植后所有感染的 19%～46%,病死率接近 40%[28]。术后首月发病率为 8.28 例/100 受者月,随后快速下降[29]。同时,67.2%的血流感染发生在术后 1 个月内,其中 39.4%集中于术后前 10 d[30]。移植后不同时间段的感染病原体和来源各有不同(见表 1)。早期以革兰阳性菌为主(占 83%),主要来源于导管相关感染和腹腔感染;1 个月后革兰阴性菌逐渐占主导,胆道感染增加,这可能与患者后期出现胆管狭窄等慢性移植物并发症,进而发生复发性胆管炎有关[29-34]。值得注意的是,肝移植后血流感染的腹腔源性感染比率(27%～47.6%)显著高于导管相关感染(4.8%～18%),此特点有别于其他实体器官移植[28,30,32,35]。不同时期细菌感染的主要危险因素见表 2。

表 1　肝移植术后不同时期血流感染特征比较

感染特征	早期(≤1 月)	中晚期(>1 月)
集中程度[30]	67%	33%
优势病原体[29-33]	革兰阳性菌	革兰阴性菌
革兰阳性菌[28]	金黄色葡萄球菌、屎肠球菌	粪肠球菌、链球菌
革兰阴性菌[28]	铜绿假单胞菌、厌氧菌	大肠埃希菌
感染主要来源[28,30,32,34-35]	导管相关感染(占 4.8%～18%):金黄色葡萄球菌、念珠菌;腹腔感染(占 27%～47.6%):肠球菌、肠杆菌	胆道感染增加

表 2　肝移植术后细菌感染危险因素

术后不同时期		危险因素
移植后早期	≤30 d[36-37]	女性、住院时间、机械通气时间、手术时间延长、肾脏替代治疗、腹部再次手术、VRE 定植、糖尿病、低白蛋白血症、供体肝脏质量与受体体重比降低、移植前 3 个月使用抗菌药物、Roux-en-Y
	<100 d[38]	门静脉血栓、ICU 住院时间延长、额外免疫抑制治疗
移植后晚期	>100 d[38]	复发性丙型病毒性肝炎、额外免疫抑制治疗
	>6 个月*[39]	女性、高龄、慢性同种异体移植物障碍、早期细菌感染(6 个月内)、抗 HCV 阳性血清状态
	>1 年[40]	Roux-en-Y、一年后的急性排斥反应发作

注:早期和晚期的时间定义因研究而异;* 表示为混合器官移植研究(941 例患者中肝移植 280 例)。

2.1.1.3　多重耐药菌(multidrug-resistant organism, MDRO)感染　MDRO 指对三个或以上抗菌药物类别中至少一种耐药的细菌。MDRO 在发生细菌感染的肝移植受者中检出率已超 50%[2,17,41-42],由其引起的血流感染呈增长趋势[33,35],其中产超广谱 β-内酰胺酶(extended-spectrum β-lactamases, ESBLs)肠杆菌尤为显著[43-44]。西班牙一项研究[33]显示,产 ESBLs 菌株引起的血流感染比率从 2007—2008 年的 7%上升至 2015—2016 年的 34%。首次 MDRO 感染的中位发生时间为术后 7～11 d[2,45]。MDRO 感染来源主要包括供体传播、术前定植激活和术后新发感染三种情况。在供体传播方面,约 50%接受 MDRO 阳性供体器官的受者会发生供体来源感染[46],其感染风险较阴性供体器官者高 3.8 倍[47]。其次是移植前已定植患者的感染激活,荟萃分析[42]发现,耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*, MRSA)定植率从术前的 11.8%升至术后的 13%,耐万古霉素肠球菌(vancomycin-resistant *Enterococcus*, VRE)定植率从 11.9%上升至 16.0%,术前 MRSA 和 VRE 定植者术后发生感染的风险分别增加 5.51、6.65 倍;术后新发感染则主

要与术后并发症相关，早期侵入性操作和医疗设备的使用增加了交叉传播风险[48]。近年来，关于MDRO定植和感染危险因素的研究取得了新进展。肠道微生态失调是重要的危险因素之一，美国一项纳入177例受者的前瞻性研究[49]显示，MDRO定植与微生物多样性降低独立相关（$P<0.001$），且术前微生物标志物可预测后续定植风险。在代谢层面，粪便中短链脂肪酸、次级胆汁酸和色氨酸代谢物浓度降低与术后感染风险显著相关[50]，提示粪便代谢物谱检测可用于识别高危患者。

2.1.2 念珠菌感染 念珠菌病是肝移植受者最常见的侵袭性真菌感染，占58.5%～93%[17,51-53]。在实体器官移植受者中，肝移植患者念珠菌病发病率最高，达39.9%[54]。念珠菌血症在术后1个月内达到高峰[17]，约占该时期所有血流感染的20%[29]。肝移植特有的危险因素包括MELD评分＞20分、暴发性肝衰竭、供体分裂肝、活体供肝和胆肠吻合术等[55-56]。病原体以白念珠菌为主（58.5%），热带念珠菌是最常见的非白念珠菌（11.9%）[51]。约34%和46%的侵袭性念珠菌病分别发生在术后1个月、3个月内，感染类型以念珠菌血症（57%）和腹腔内感染（43%）为主[51]。2022年世界卫生组织（WHO）发布了首个真菌优先病原体清单，将氟康唑耐药念珠菌列为“中度优先级”病原体[57]。西班牙一项多中心研究[58]发现，近平滑念珠菌对氟康唑的耐药率在2019—2022年从2.6%上升至36.6%。棘白菌素类药物因其肝毒性低，已成为肝移植患者念珠菌感染防治的一线用药，但近年耐药率升至5%～8%[51,59]。白念珠菌对棘白菌素耐药率仅0～0.9%，而光滑念珠菌则达2.1%～8.2%[60]。新兴的耳念珠菌呈现严峻的多重耐药特征：全球范围内对氟康唑耐药率超过90%，对两性霉素B耐药率为8%～35%，对棘白菌素耐药率为2%～10%且呈上升趋势，近4%的分离株对三类抗真菌药物均耐药[61-62]。移植后耳念珠菌感染的报道较少，但已有病例显示其高致死性：美国1例肺移植患者发生供者来源的耳念珠菌肺部感染，尽管术后预防性使用米卡芬净，仍于术后第8天死亡[63]。

2.1.3 曲霉感染 肝移植后侵袭性曲霉感染的发病率为0.94%～9%[52-53,64]，中位发病时间为术后18～25 d[52,65-66]，明显早于其他器官移植（通常＞100 d）[52,67]。烟曲霉是最常见的致病菌种（73%）[65]，下呼吸道是最常受累部位（66%～100%），其次为中枢神经系统（39%～42.9%）[52,64-66,68]。2024年一项国际多中心研究发现，术后3个月内发病的主要危险因素包括再次手术（调整后$OR=5.99$）和系统性使用抗菌药物（调整后$OR=5.03$）；整体危险因素还包括肺炎病史（调整后$OR=48.7$）[69]。肝移植受者的独特之处在于更易发生播散性疾病和中枢神经系统受累[66,70-72]，其中铁代谢异常可能是其重要影响因素[73]。中枢神经系统曲霉病通常发生在术后3个月内[72]，而病毒性中枢神经系统感染则多见于术后12个月以后[72]。此外，侵袭性曲霉感染常合并其他感染：42%的病例合并细菌感染，15%合并巨细胞病毒感染[70]。若不采取抗真菌预防措施，36%的移植受者会发生侵袭性真菌感染[53]，且侵袭性曲霉感染12周全因病死率可高达37%[69]。鉴于这一高风险特征，针对曲霉属的靶向预防策略在临床实践中备受重视[53]。

2.1.4 供体来源性感染 供者来源感染是移植后需重点关注的问题。美国疾病传播咨询委员会（DTAC）对81例供者来源感染的分析显示，67%的受者在术后30 d内出现症状，所有细菌感染均在45 d内被发现。不同病原体感染的发病时间存在差异：细菌感染的中位时间为14 d，真菌为18 d，病毒为48 d，寄生虫为50 d[74]。此外，供体传播的细菌病原体中，MDRO占36%，包括MRSA、VRE、不动杆菌属、伯克霍尔德菌属和假单胞菌属；供体重症监护病房（ICU）住院时间延长、血流动力学不稳定是供体携带MDRO的独立危险因素[74]。同时，供体ICU住院延长、机械通气和特定死因（如脑出血、溺水）也与丝状真菌传播风险增加相关，特别是毛霉属和赛多孢子菌属[75]。非预期供者来源疾病虽少见（发病率0.18%），但仍需要警惕。美国疾病预防控制中心（CDC）报告的20例意外乙型肝炎病毒（HBV）传播中，92.9%的供体合并丙型肝炎病毒（HCV）感染和注射吸毒史[76]，提示具有高危行为史的供体存在常规筛查未能检出的病毒传播风险。肝移植受者可能面临更高的供者传播菌血症风险，有病例报道显示，即使在抗菌药物预防下仍可发生感染，而同源的其他器官受者则未发现感染[77]。虽然疑似供者来源结核病可在术后30个月被发现，但大多数确诊病例在前3个月内出现症状[74,78]。因此，临床医生应根据供体特征，在术后前30～45 d内保持警惕，特别关注肝移植受者的不典型表现，如不明原因脓毒症、发热、肝酶升高或精神状态改变。

2.2 移植后中期（术后2～6个月） 术后30～180 d期间，感染发病率降至约3.3例/1 000移植日[17]，

但感染仍是死亡的主要原因[79]。此阶段细菌感染的频率和种类减少，导管相关感染、手术部位感染和腹腔感染显著下降。随着免疫抑制效应累积，感染类型转向机会性病原体和潜伏病毒重新激活，这些感染通常发生在术后 30 d～12 个月，或排斥反应治疗后 3 个月内[17,80-81]。真菌感染仍常见，特别是侵袭性念珠菌病和曲霉病。

2.2.1 CMV 感染 肝移植后 CMV 感染呈现供受体血清学依赖性分层，供受体血清状态是感染风险的主要决定因素[82]。在未采取预防措施的患者中，高危组合[供体阳性/受体阴性(D+/R-)]感染发病率达 78%～88%，而低危组合[供体阴性/受体阴性(D-/R-)]为 0～13%[83]。预防策略改变了感染时间分布：未预防时，感染主要发生在术后 1～6 个月[80,82,84-85]；抢先治疗组病毒血症集中在前 3 个月，而预防组则在预防结束后 3～6 个月出现迟发性 CMV 感染[86]。接受预防治疗患者的首年感染发病率存在地域差异，从哥伦比亚的 5.2%，到韩国、泰国和巴西的 40%～50%不等[87]，这可能与宿主合并症、免疫抑制方案、排斥反应及地域流行病学特征相关[82]。

2.2.2 EBV 感染 EBV 属于 γ 疱疹病毒，全球成人血清阳性率超过 90%[80,88]。在实体器官移植患者中，77%的 EBV 感染发生在肝移植受者[17]。术后首年常存在无症状病毒复制，临床感染多集中在前 150 d 内[17]。肝移植后可发生原发感染或病毒重新激活，并可导致移植后淋巴增殖性疾病(post-transplant lymphoproliferative disorder, PTLD)，其发病率在术后第一年内最高[89]。PTLD 的公认危险因素包括年龄小、D+/R- 血清状态、CMV 阳性和 T 细胞清除治疗[80-90]。大多数 PTLD 病例(60%～80%)与 EBV 感染相关，但 PTLD 也可在无 EBV 感染的情况下发生[91-92]。

2.2.3 单纯疱疹病毒(herpes simplex virus, HSV)/水痘-带状疱疹病毒(varicella-zoster virus, VZV)感染 成人移植受者的有症状 HSV/VZV 疾病主要由病毒重新激活引起。瑞士移植队列研究(Swiss Transplant Cohort Study, STCS)[93]发现，肝移植受者术后 1 年的 HSV 感染发病率为 8.4%，VZV 感染发病率为 1.6%，中位发生时间分别为 66、249 d。预防措施也会影响 HSV 的发病率。一项大型实体器官 STCS[94]报告显示，在移植后第一年内，接受抗病毒预防治疗的受体有症状 HSV 发病率为 3%，而未使用预防治疗的发病率为 9.8%。此外，与普通人群相比，实体器官移植受者 HSV 感染风险更高，在术后 1 年达到峰值，并表现出更频繁的病毒脱落，更严重的临床表现及更慢的治疗反应[93-95]。

2.2.4 其他罕见病原 类圆线虫感染在肝移植受者中较少见，仅占实体器官移植类圆线虫感染病例的 7.5%(肾移植占 74.7%)，中位发生时间为术后 10.8 周[96]。其中 34.7%为供体来源感染，这些供体中 95.8%来自流行区，且供体来源感染病死率高达 40.6%[96]。李斯特菌是一种罕见的食源性感染病原体，肝移植后感染发病率为 0.18%，总体病死率为 15%；若累及中枢神经系统，病死率则更高，达 20%～50%[97-98]。为预防李斯特菌病，应向患者提供食品安全指导，复方磺胺甲噁唑可能是一种有效的预防药物[98]。弓形虫感染同样值得关注，因感染者 6 个月生存率明显低于未感染者[99-100]。血清阳性受者发病时间较短(术后<4 个月)，血清阴性受者发病较晚(术后>4 年)[99,101]。诺卡菌感染在肝移植受者中发病率最低，为 0.1%～0.18%，显著低于肺移植(0.8%～3.5%)和心脏移植(1.0%～4.0%)[102-104]。其中位发生时间为术后 8.8～17.5 个月，25%～40%病例发生在术后 6 个月内，50%～60%出现在术后 12 个月之后[102-104]。肺部受累是最主要的临床表现(71%～89%)[102-103]，总体病死率为 16.2%～46%，且肝移植是死亡的独立危险因素(HR = 3.52)[103]。

2.3 移植后晚期(>6 个月) 移植术后 6 个月，移植物功能稳定的受者因免疫抑制剂已减至维持剂量，感染病原体谱转向常见病原体，但症状较普通人群更严重[80,105]。而移植物功能受损或持续接受大剂量免疫抑制治疗的受者，仍面临较高的机会性病原体感染风险。

2.3.1 隐球菌病 隐球菌感染是实体器官移植受者第三常见的侵袭性真菌感染(占 8%)，发病率为 0.2%～5%[52,106-108]。供者来源的感染最早可出现在术后 1 个月内[107,109]，而多数病例发生在移植后较晚期，中位发病时间 16～21 个月；肝移植和肺移植受者可能比肾移植受者发病更早(<12 个月)[108]。临床表现以中枢神经系统受累(45%)和肺部疾病(39%)为主。总体病死率为 5%～20%，但格特隐球菌的俄勒冈亚型病死率可达 70%[108]。

2.3.2 耶氏肺孢子菌病 耶氏肺孢子菌肺炎约占肝移植后所有肺炎病例的 7%，其病死率为 7%～88%[110]。预防策略可显著降低其发病率：在未预

防的情况下，发病风险在术后前 6 个月内最高，早期研究估计发病率为 5%～15%[111-113]。然而，近 10 年数据[112-114]显示，实际累积发病率仅 0.99%～1.15%。但预防措施并不能完全清除发病风险，即使预防 6～12 个月后，晚发型耶氏肺孢子菌肺炎仍可能在术后 1 年以上出现[113,115]，其危险因素包括淋巴细胞和 $CD4^+$ T 淋巴细胞计数低、CMV 感染、低丙种球蛋白血症、排斥反应和高龄[111]。

2.3.3 呼吸道病毒感染 社区获得性呼吸道病毒感染在非肺移植受者中累积发病率为 12%，发病率 30.6 例/1 000 人年，其中流行性感冒（简称流感）病毒是主要病原体（占 7.5%）[105]。多数感染发生在术后 1 年后（中位时间为 1.29 年）[105]，但早期感染危害更大，术后前 3 个月内确诊流感的患者发生严重疾病的风险比晚期感染者高 5 倍[116]。不同病毒呈现季节性分布：小 RNA 病毒全年可见，流感病毒、呼吸道合胞病毒、人冠状病毒和人偏肺病毒集中在冬季，人副流感病毒则在春秋季流行[105,117-118]。新型冠状病毒感染（coronavirus disease 2019，COVID-19）对肝移植受者的影响是近年关注的重点。多中心研究显示，肝移植受者 COVID-19 病死率与普通人群相似（$OR = 0.8$），年龄和合并症是预后的主要决定因素，而非肝移植状态本身[119-120]。感染后，约半数感染者调整了免疫抑制方案（主要为减停霉酚酸酯），但调整与临床结局无显著关联[120-121]。在供体来源方面，初步研究显示，新型冠状病毒阳性供体的肝移植受体传播风险极低，但需注意肝动脉血栓形成的风险可能增加[122]。

2.3.4 结核病 肝移植受者结核病主要由潜伏感染重新激活引起，中位发病时间为 9～18 个月，病死率高达 25%～40%[123-126]。与普通人群相比，移植受者活动性结核分枝杆菌感染风险高出 18 倍，病死率也高出 4 倍[127-128]。发病率存在显著的地理差异，流行区远高于非流行区。韩国术后第 1 年发病率达 2 261 例/10 万人年[129]，中国为 506 例/10 万人年[130]，而西班牙仅 18 例/10 万人年[131]。北美一项多中心研究显示，潜伏感染经充分治疗后可实现零发病[132]，提示预防性治疗的重要性。主要危险因素包括使用 mTOR 抑制剂、既往结核病史和肺部影像学异常[124,127,129-130]。中国研究还发现，死亡供肝移植会增加感染风险（$OR = 3.7$）[130]。

2.3.5 马尔尼菲篮状菌病 马尔尼菲篮状菌病是一种播散性真菌感染，常累及肺、肝、皮肤及淋巴结等多器官，具有明显的地域聚集性。该病的全球疾病负担主要集中于东南亚和中国南部，其中中国病例占 60.3%、泰国和越南占 38.8%[133]。在中国，病例主要分布在广西和广东两省，合计占比达 84%[134]。这些流行区的患病率为 0.1%～26.7%，病死率高达 8%～40%[134]。90% 的马尔尼菲篮状菌病患者是人类免疫缺陷病毒（HIV）感染者[134]，而全球报道的实体器官移植受者感染不足 30 例。这些患者几乎均来自流行区，中位发病时间为移植后 12 个月，76% 表现为播散性感染[135]。肾移植病例更常见，但肝移植受者病死率更高（75%，3/4）[135-136]。在调整免疫抑制强度时需警惕该病，多数感染发生在免疫抑制剂剂量增加阶段，而非低剂量维持期[137]。此外，由于该病与结核病的流行区域重叠且临床表现相似，13.4% 的非 HIV 感染患者曾被误诊为结核病[137]，这在器官移植受者中易导致诊治延误。

3 中外肝移植人群特征差异及其对感染的潜在影响

不同国家肝移植受者的感染流行病学存在差异。中国肝移植人群具有独特的临床特征（见表 3），其基础疾病以乙型病毒性肝炎为主（占 71.3%），而韩国和欧美国家则以酒精性肝硬化和丙型病毒性肝为主。供肝来源以死亡供肝（deceased donor liver transplantation，DDLT）为主（占 87%），与韩国、日本等以活体供肝（living donor liver transplantation，LDLT）为主的国家形成对比。

这些特征的临床意义值得关注。在基础疾病方面，意大利研究发现酒精相关性肝硬化是移植后感染的独立预测因子，而乙型病毒性肝炎和丙型病毒性肝炎受者未见此关联[41]。在供肝类型方面，尽管研究普遍认为 LDLT 具有更优的生存率[138-140]，但在感染风险方面，现有证据呈现复杂。DDLT 受者的主要风险在于细菌感染。多项研究显示，其围术期细菌感染发病率显著升高，韩国一项单中心研究显示，DDLT 组感染发病率达 71.1%，而 LDLT 组仅为 30.3%，死亡供肝本身即为术后感染的独立危险因素（$OR = 5.5$）[141]。LDLT 的感染风险则与手术技术并发症密切相关。由于 LDLT 的胆道并发症风险增加 2.23 倍、血管并发症风险增加 2 倍[139,142]，术后胆漏成为细菌感染的独立危险因素（$OR = 6.62$）[143]，导致移植后 1 年内腹内脓肿和胆道感染风险更高（LDLT 6% VS DDLT 3%）[139,142]。

侵袭性真菌感染风险也略有升高（*OR* = 1.78）[144]。但 LDLT 在病毒感染方面具有优势。韩国队列研究显示，LDLT 受者 3 个月 CMV 感染发病率仅为 15.2%[145]，远低于文献报道的 DDLT 感染发病率（40%～54%）。值得注意的是，尽管两种模式在特定感染类型上存在差异，一项纳入 19 项研究（其中 9 项来自中国）的大型 Meta 分析显示，LDLT 和 DDLT 的总体术后感染发病率差异无统计学意义[140]。见表 3。

表 3　各国肝移植人群基本特征和感染情况

项目	中国[16,95,144,146-148]	美国[149-151]	韩国[152-155]	瑞士[17,93,156-157]
人口特征				
数据库	CLTR	OPTN/SRTR	KOTRY	STCS
时间	2021 年	2019 年	2014 年 5 月 1 日—2017 年 12 月 31 日	2008 年 5 月 1 日—2020 年 9 月 30 日
研究人群	成人 + 儿童	成人	成人	成人
例数	5 834（成人 4 678）	8 345	2 563	1 158
男性（%）	73.2	63.70	72.20	68.40
年龄（岁）	41.6 ± 21.3	55.6 ± 12.7	53.9 ± 8.9	57.2（49.3～62.8）
移植前肝癌（%）	32.2	14.8	49.20	19.9
移植前肝病（%）				
乙型病毒性肝炎	71.3	–	55.9	7.7
丙型病毒性肝炎	1.1	7.8	7	16
酒精性肝病	5.3	31	24.3	16
活体供肝（%）	14.1（成人 1.54）	5.3	76.3	5.4
DCD（%）	20.0	8.5	–	12.4
DBD（%）	65.4	91.5	–	82.1
劈离式供肝（%）	10.0	1.2	–	–
感染特征				
细菌（%）	26.6	29.9	67.9	59.0
革兰阳性菌（%）	48.9	32.4	58.4	48.2
革兰阴性菌（%）	51.1	32.3	40.0	38.6
真菌（%）	11.9	5.2	4.8	8.0
念珠菌（%）	52.3	78.0	52.2	80.0
曲霉（%）	40.0	4.3	30.4	6.2
隐球菌（%）	4.8	8.6	4.3	0
CMV（%）	4.9	59.0	19.0	7.3
HSV/VZV（%）	1.4（仅 HSV）	42.0	7.7	8.4

注：CLTR 为中国肝移植注册系统，OPTN/SRTR 为美国器官获取和移植网络/科学注册移植受者，KOTRY 为韩国器官移植注册系统，STCS 为瑞士移植队列研究，DCD 为心脏死亡器官捐献，DBD 为脑死亡器官捐献。基线数据来自于各国移植注册数据库[146-148,151,155,157]；感染特征来自于已发表的文献，中国[16,95,144]，美国[149-150]，韩国[152-154]，瑞士[17,93,156]。– 表示数据未报告。

4　成人与儿童肝移植受体感染特征比较

儿童肝移植受者中，感染导致的病死率约为排斥反应的 9 倍（5.5% VS 0.6%）[158]，使感染成为影响儿童移植结局的首要因素。成人与儿童在感染类型、发病时间和危险因素方面均存在显著差异。

在细菌和真菌感染方面，儿童与成人的总体感染模式相似，现有儿童队列与成人数据的间接比较未发现显著差异[159]。但儿童群体内部存在差异，年龄本身是重要的风险分层因素。婴幼儿是移植后细菌感染的独立危险因素[158,160]；与青少年相比，婴

儿虽然排斥发生率降低 50%，但细菌或真菌感染风险却增加 3 倍[158]。

在病毒感染方面，儿童与成人呈现不同的流行病学特征。印度一项前瞻性研究显示，儿童受者 CMV 感染发病率远高于成人（71.4% VS 33.4%，$P=0.004$），且感染的时间分布模式截然不同（$P=0.003$）。儿童患者全部在移植后第 1 个月内发病，而成人感染时间分布分散：50%在第 1 个月，29.5%在第 2 个月，其余延续至第 6 个月[161]。这种差异主要源于儿童患者既往 CMV 暴露机会有限，多数儿童受者为血清学阴性，在移植时缺乏预存的 CMV 特异性细胞免疫，符合高危 D+/R- 组合的风险特征[82]。EBV 相关感染在儿童与成人间同样存在差异。PTLD 多发生在移植后 30 d 之后[158]，儿童发生率明显高于成人（4.3%～5.1% VS 1.5%～2.3%）[162-163]，且年龄越小风险越高，移植时小于 2 岁的患者风险尤其突出（$OR=3.53$），婴儿（<1 岁）的发生率是青少年（>12 岁）的 10 倍[158]。这可能与不同年龄组的血清学状态差异相关，63%的儿童在移植时为 EBV 血清学阴性，而成人的阴性比率不足 10%[158]。此外，儿童的 PTLD 在肝移植后发生更早[162]。相比之下，成人患者的危险因素还包括年龄超过 50 岁（风险增加 3.5 倍）和原发肝病类型，其中丙型病毒性肝炎肝硬化和酒精性肝硬化的风险分别增加 8.7、9.6 倍[164]。鉴于这些年龄相关的风险差异，预防策略也呈现年龄特异性：荟萃分析显示，儿童抗病毒预防可显著降低 PTLD 风险（$RR=0.58$，95%CI：0.43～0.79），而成人获益不显著（$RR=0.88$，95%CI：0.64～1.21）[165]。

5 结语

肝移植后感染遵循明确的时间演变规律，早期以手术相关感染为主，中期进入机会性感染高发阶段，晚期随着免疫功能逐渐恢复，感染风险显著降低。不同病原体呈现差异化的流行病学特征，并受多种宿主和环境因素影响。感染特征存在显著的年龄差异，儿童患者更易发生病毒感染。在中国，乙型病毒性肝炎是肝移植的主要原发病，供肝来源以死亡供肝为主，同时还需应对马尔尼菲篮状菌等地方性病原体的挑战，这些因素共同构成了独特的感染防控需求。然而，目前仍缺乏针对中外感染特征的直接对比研究。未来应建立基于时间进程和病原体特异性的个体化风险评估模型，并加强国际比较研究，从而为中国患者提供更精准的感染防控策略。

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