

· 综述 ·

移植肾功能丧失受者的临床管理策略

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【摘要】 随着肾移植手术技术的成熟和新型免疫抑制药的引入以及免疫抑制方案的改进，肾移植受者的短期生存率已显著提高，但长期生存并未得到显著改善。肾移植受者通常可能面临移植肾功能丧失。移植肾功能丧失后的医疗管理较为复杂，包括免疫抑制药的调整、移植肾的处理以及后续肾脏替代治疗方式的选择。这些医疗管理直接影响移植肾功能丧失患者的预后，但目前仍缺少相关指南或共识，往往根据临床医师的自身经验决定。本文对目前移植肾功能丧失后免疫抑制药的调整、移植肾的处理和后续肾脏替代治疗方式的选择等进行综述，旨在为延长患者的生存期和提高生活质量提供参考。

【关键词】 肾移植；移植肾功能丧失；群体反应性抗体；免疫抑制药；肾脏替代治疗；致敏；移植肾切除术；经导管血管栓塞术

【中图分类号】 R617, R692 **【文献标志码】** A **【文章编号】** 1674-7445 (2024) 01-0018-07

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【Abstract】 With the maturity of kidney transplantation, introduction of new immunosuppressive drugs and improvement of immunosuppressive regimen, the short-term survival rate of kidney transplant recipients has been significantly improved, whereas the long-term survival rate has not been significantly elevated. Kidney transplant recipients may have the risk of renal graft loss. Clinical management after renal graft loss is complicated, including the adjustment of immunosuppressive drugs, management of renal graft and selection of subsequent renal replacement therapy. These management procedures directly affect clinical prognosis of patients with renal graft loss. Nevertheless, relevant guidelines or consensuses are still lacking. Clinical management of patients after renal graft loss highly depend upon clinicians' experience. In this article, the adjustment of immunosuppressive drugs, management of renal graft and selection of subsequent renal replacement therapy were reviewed, aiming to provide reference for prolonging the survival and improving the quality of life of these patients.

【Key words】 Kidney transplantation; Renal graft loss; Panel reactive antibody; Immunosuppressive drugs; Renal replacement therapy; Sensitization; Allograft nephrectomy; Transcatheter vascular embolization

慢性肾功能不全终末期患者需要进行肾脏替代治疗（renal replacement therapy, RRT），其中主要包括腹膜透析、血液透析以及肾移植。目前普遍认为，从经济和疗效两方面考虑，肾移植是最优的选择^[1-4]。

近年来，随着肾移植手术技术的成熟和新型免疫抑制药的引入以及免疫抑制方案的改进，肾移植受者的短期生存率已显著提高，但长期生存并未得到显著改善^[5]。因此，肾移植受者通常可能面临移植肾功能丧失^[6-7]。

DOI: [10.3969/j.issn.1674-7445.2023149](https://doi.org/10.3969/j.issn.1674-7445.2023149)

基金项目：国家自然科学基金（82000712）

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对于移植肾功能丧失患者的治疗较为复杂,并且缺乏相关指南或共识。

1 移植肾功能丧失后的免疫抑制药调整

对于移植肾功能丧失患者,免疫抑制药的调整较为复杂,目前的研究较少且多数为回顾性研究^[8-10],往往根据临床医师自身经验决定。通常认为,移植术后早期由于原发性无功能、血栓、超急性或早期难治性急性排斥反应等原因行移植肾切除术后,免疫抑制治疗应立即中断^[11-12]。然而,多数情况下,移植肾功能丧失是由慢性排斥反应导致,这种患者免疫抑制药的调整存在较大争议。

1.1 持续维持免疫抑制的影响

目前多数研究认为移植肾功能丧失后维持免疫抑制治疗有利于保留患者残余肾功能^[12-13]。且Knoll等^[10]的研究发现,移植肾功能丧失患者继续维持免疫抑制超过1年并不会增加住院感染及死亡风险。

移植肾功能丧失后撤除免疫抑制会增加致敏的风险^[9, 14-15],而致敏会增加患者再次肾移植时早期排斥反应发生率、整体移植失败率和全因病死率^[16]。在一项单中心研究中,119例移植前群体反应性抗体(panel reactive antibody, PRA)水平较低的患者在移植肾功能丧失6~24个月后复测PRA,其中56%的患者高度致敏(I/II类PRA $\geq$ 80%),多因素分析结果显示撤除免疫抑制药是导致患者致敏的独立危险因素^[17]。因此,有研究认为,对于期待再次进行肾移植的患者,可以考虑晚期转换为以贝拉西普为基础的免疫抑制方案,从而降低致敏的发生率,并可能延缓肾功能下降的速度,有利于酸中毒和其他代谢参数的改善^[18-19]。

移植肾功能丧失患者中约40%会发生移植植物不耐受综合征,主要表现为发热、贫血、乏力、血尿、疼痛、移植肾肿胀、消瘦、腹泻等^[20]。目前多数观点认为,当移植肾功能丧失患者出现移植植物不耐受综合征时,应及时行移植肾切除术。至于移植肾功能丧失后免疫抑制药的调整对移植植物不耐受综合征的影响,目前研究较少且存在较大争议。一些研究认为移植肾功能丧失患者持续低剂量维持免疫抑制可以降低移植植物不耐受综合征的发生率^[21],但也有研究认为移植肾功能丧失患者移植植物不耐受综合征的发生率与维持免疫抑制无关^[13]。

移植肾功能丧失患者持续维持免疫抑制具有较高

的并发症发生风险,如感染、心血管疾病、高血压、糖尿病、血脂代谢异常以及恶性肿瘤等^[11, 22]。既往研究显示,维持免疫抑制可以直接降低患者移植肾功能丧失后6个月的存活率^[13]。在以上并发症中,感染、心血管疾病及恶性肿瘤对患者的存活影响最为显著^[11, 23]。

1.2 调整免疫抑制药的方法

肾移植受者移植肾功能丧失后免疫抑制药的调整方案差异较大,且缺乏相关指南或共识^[24]。免疫抑制方案的调整受到多种因素影响,如移植肾功能丧失发生时间、移植肾残余功能、是否计划进行再次肾移植以及恢复透析的紧迫性等^[25]。

对于1年内有再次移植计划的患者,目前主流观点认为应继续服用免疫抑制药^[24, 26]。Davis等^[27]认为,当移植肾功能丧失患者预计在1年内能够进行再次肾移植时,可以维持原免疫抑制方案或将抗代谢药物的使用剂量减半,以降低致敏风险。此外,根据笔者中心调查研究显示,58%的临床医师会对1年内有再次移植计划的患者维持免疫抑制药使用。

对于短期内无再次肾移植计划的移植肾功能丧失患者,通常在恢复透析后的1年内停用免疫抑制药。目前,多数研究采取逐步减少免疫抑制药剂量的方法,即先停用抗代谢药物,然后逐渐停用钙调磷酸酶抑制剂(calcineurin inhibitor, CNI),最后减少糖皮质激素的使用。Gómez-Dos-Santos等^[12]认为,对于非早期移植肾功能丧失患者可以首先停用抗代谢类药物,然后在6~8周后停用CNI类药物,并开始每月减少2.5 mg糖皮质激素直至停用。此外,部分文献采用了类似的免疫抑制药调整方案^[11]。

目前指导移植肾功能丧失患者免疫抑制药管理的研究较少,这可能是由于每例移植肾功能丧失患者的管理具有较大的特异性且影响因素较多。笔者认为移植肾功能丧失患者免疫抑制方案的调整首先应确定患者是否有短期内再次行肾移植的计划,然后再针对不同的情况采用个体化的免疫抑制方案,以最大限度改善患者预后。

2 移植肾功能丧失后的切除手术

2.1 移植肾切除适应证

移植肾功能丧失患者进行移植肾切除手术的适用性存在较大争议,主要依赖于医师的自主决定,目前缺乏足够的临床证据。移植肾切除手术的抉择与移植术后的时间长短有关。研究显示,在接受移植肾切除

手术的移植肾功能丧失患者中,移植术后 3~6 个月的患者最多^[25-28]。另有研究表明,移植肾存活时间<6 个月的移植肾功能丧失患者进行移植肾切除手术可以显著降低患者产生抗体的风险^[29]。

Budhiraja 等^[30]认为,大多数无并发症的移植肾功能丧失患者不需要进行移植肾切除手术,也没有明确的证据表明移植肾功能丧失患者进行移植肾切除手术能改善预后。部分研究显示,移植肾功能丧失患者恢复透析后保留移植肾与切除移植肾的预后差异无统计学意义^[8,31]。移植肾切除手术主要用于早期原发性无功能、超急性或早期难治性急性排斥反应、动静脉血栓、移植肾严重感染或恶性肿瘤^[30]。然而,也有部分研究认为,保留异体移植肾可能是潜在的并发症来源,因此建议常规进行移植肾切除手术,以改善患者的预后^[11,32]。

目前普遍认为,当移植肾功能丧失患者出现移植物不耐受综合征时,自身长期处于炎症状态,也应进行移植肾切除手术^[33]。López-Gómez 等^[34]的研究显示,保留失功移植肾的患者贫血更严重、血清白蛋白水平更低、炎症标志物水平更高、红细胞生成素抵抗的发生率更高,其中 2/3 的患者最终需要进行移植肾切除手术,且在切除后上述症状得到了显著改善。

2.2 移植肾切除风险

移植肾切除手术是一种高风险手术,具有较高的并发症发生率与病死率。并发症主要包括术中和术后出血以及感染,发生率可达 4.3%~82.0%,而病死率可达 1.2%~39.0%,甚至更高^[12,35]。多数研究表明,患者进行移植肾切除手术在生存方面并无明显获益,且移植肾切除手术可能增加患者致敏的风险,因此建议无症状的移植肾功能丧失患者保留丧失功能的肾脏^[36-38]。

移植肾切除手术具有较多并发症,最常见的是出血和感染,其他并发症包括弥散性血管内凝血、淋巴结肿大、深静脉血栓形成、肠梗阻和缺血等^[10,12]。

2.3 移植肾切除手术方式

传统的移植肾切除手术术式主要包括被膜外切除和被膜下切除。被膜外切除是指在移植肾被膜外进行解剖、游离,从而切除包括肾被膜、输尿管和大部分移植血管在内的移植肾。当肾移植术后短期内(3~6 周)需要切除移植肾时,通常会采用这种方法。然而,术后远期肾被膜与周围组织往往粘连严重,不适合采用被膜外切除技术。此时,通常需要采用被膜下切除技术,即在肾被膜内进行解剖、游离并

切除移植肾。

近些年,出现一种新兴的经腹腔入路切除移植肾的术式,即进入腹腔切除腹膜外的移植肾。该术式的优势在于可以更完整地切除移植肾;另外,由于移植肾所处的腔隙与腹膜之间存在开口,腔隙中的液体会被动引流,并将血肿和脓肿形成的风险降至最低^[39]。此外,该术式不会显著增加手术时间,还可以通过减少整体并发症的发生率和病死率,从而降低再次干预的发生率并缩短住院时间。

2.4 经导管血管栓塞术

经导管血管栓塞术(transcatheter vascular embolization, TVE)是指通过导管向移植肾血管内注入栓塞物质,从而阻塞血流以达到预期治疗目的的技术。大多数研究证实,相比于移植肾切除手术,TVE 是一种创伤较小的替代技术,适用于发生移植物不耐受综合征的情况,其并发症较少且预后较好^[40-41]。

Takase 等^[42]回顾性分析了移植肾切除和 TVE 对移植肾功能丧失患者的治疗效果,发现移植肾切除组的病死率明显高于 TVE 组,但需要注意的是,TVE 不能用于移植肾破裂或移植肾血管血栓形成的患者。

另有研究表明,在进行移植肾切除手术前进行 TVE 可以减少手术失血量、术后输血量并缩短手术时间,从而降低手术风险^[43-44]。

3 移植肾功能丧失后的肾脏替代治疗

3.1 恢复透析的预后

既往主流观点认为,移植肾功能丧失后恢复透析治疗的患者预后较初次透析患者更差。这可能与移植肾功能丧失后透析前准备不足(例如血管通路管理不当等)^[45]、医疗管理不良(包括高血压、贫血、低白蛋白、低碳酸氢盐、高磷酸盐等)^[34,46]、移植后免疫相关并发症^[47],以及移植肾功能丧失后进入透析的时机较晚有关^[48]。然而,目前也有研究发现,在将原发性肾衰竭患者群体与移植肾功能丧失患者群体匹配后,两组患者的预后差异并无统计学意义^[4,49]。

3.2 恢复透析的时机

目前尚无足够的证据指导肾移植受者移植肾功能丧失后恢复透析的时机。研究显示,在估算肾小球滤过率(estimated glomerular filtration rate, eGFR)>10.5 mL/(min·1.73 m²)时恢复透析的移植肾功能丧失患者预后较差^[50]。目前多数研究认为,应在恢复透析前几个月决定透析方式并进行透析管路的规划,之

后根据患者的症状及相关个人情况决定开始透析的时机^[51]。对于拟行血液透析的患者,应在重新透析前至少3个月进行动静脉瘘成型术;对于拟行腹膜透析的患者,应在重新开始透析前2~3周放置腹膜透析管,以便伤口愈合和导管固定。

3.3 恢复透析后的科室转诊

研究认为,移植肾功能丧失患者接受移植科与肾内科的多学科合作治疗,可改善RRT的预后^[52]。移植科医师应重点关注移植肾及患者的预后、免疫抑制药管理并及时将移植肾功能丧失患者重新列入移植等待名单,而肾内科医师则确保患者得到最佳的透析管理,并指导患者完成透析计划。

通常认为,在透析治疗开始前的3个月内转诊至肾内科属于晚期转诊。一项研究比较了移植肾功能丧失患者早期与晚期转诊至肾内科治疗的病死率,发现晚期转诊群体的全因死亡风险约为早期转诊群体的2倍^[52]。另有研究发现,移植肾功能丧失患者在透析第1年具有较高的住院率与病死率,并且与转诊至肾内科的时机相关^[53]。因此,笔者认为早期转诊至肾内科可以减少移植肾功能丧失患者住院与死亡的风险。

3.4 透析方式的选择

透析方式主要分为血液透析与腹膜透析,目前并无明确的指导方案帮助移植肾功能丧失患者选择恢复透析的方式。多数研究认为,这两种透析方式对移植肾功能丧失患者的生存并无显著影响^[5, 23, 54]。同时,Perl等^[55]发现,移植肾功能丧失患者选择不同透析方式,虽然总生存率相似,但是腹膜透析患者早期(1年内)生存率更高,晚期生存率更低。此外,部分研究推荐移植肾功能丧失患者选择腹膜透析,并且发现其预后与未进行肾移植而初次进行腹膜透析的患者差异无统计学意义^[56-57]。虽然多数研究认为两种透析方式在总体生存期上差异无统计学意义,但笔者认为需要根据患者的情况有针对性地选择合适的透析方式,例如患者的年龄、慢性病、传染病、移植前透析方式等,以获得更好的生存预期。

3.5 血液透析中通路的选择

目前的指南和相关研究均显示,在血液透析过程中使用自体动静脉内瘘的优势要大于人工血管内瘘,同时二者的优势大于中心静脉导管^[58-59]。然而,多项研究发现,移植肾功能丧失患者在恢复规律血液透析后,超过一半的患者使用中心静脉导管进行血液透析^[45, 47]。由于目前较多移植肾功能丧失患者在恢复规

律血液透析后仍会维持一定程度的免疫抑制,因此移植肾功能丧失患者使用中心静脉导管进行血液透析更易导致导管相关性血流感染,并对移植肾功能丧失患者的预后产生不良影响^[47]。综上所述,笔者认为恢复血液透析的移植肾功能丧失患者应尽量使用自体动静脉内瘘或人工血管内瘘,并避免长期使用中心静脉导管。

4 移植肾功能丧失后的二次肾移植

普遍认为,对于移植肾功能丧失患者,进行二次肾移植是最佳的RRT方式,即使二次肾移植使用的供肾为扩大标准供肾^[60-64]。同时,研究显示,首次和二次肾移植的10年移植物存活率差异无统计学意义^[65]。因此,笔者认为移植肾功能丧失患者应尽早准备进行二次肾移植,以达到更好的生存预期。

5 小 结

随着我国肾移植事业的发展,接受肾移植的患者数量逐年增加,因此面临移植肾功能丧失的患者数量也将会持续增加。目前,对于肾移植受者移植肾功能丧失后的管理尚缺乏相关指南和共识,通常根据临床医师的经验决定治疗方案,但患者的预后往往较差。本文从免疫抑制药的调整、失功移植肾的处理及后续RRT等方面回顾并总结了目前肾移植受者移植肾功能丧失后管理的现状。临床上应重视移植肾功能丧失患者的个体差异,需根据患者的具体情况制定个体化的管理方案,以延长患者的生存期和提高生活质量。在未来的研究中,需要进一步探索和完善移植肾功能丧失患者的管理策略,以优化患者的预后。

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(收稿日期: 2023-07-31)

(本文编辑: 林佳美 鄢加佳)