Advances in Clinical Medicine 临床医学进展, 2026, 16(4), 2352-2358
Published Online April 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1641484

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儿童免疫介导坏死性肌病的治疗进展

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收稿日期：2026年3月8日；录用日期：2026年4月2日；发布日期：2026年4月10日

摘　要

儿童免疫介导坏死性肌病IMNM (Immune-Mediated Necrotizing Myopathy)是儿童特发性炎性肌病中的重要亚型，具有起病缓、易误诊及潜在预后不良的特点，目前该病的治疗尚缺乏基于儿科高质量证据的文献。传统免疫疗法如糖皮质激素、甲氨蝶呤、环磷酰胺等仍是一线治疗，但部分患者存在疗效不佳或无法耐受的问题。靶向治疗及新型细胞治疗的发展为难治性病例带来新希望。本文系统综述儿童IMNM及其治疗策略特别是新型治疗策略，并展望未来个体化精准治疗的研究方向。

关键词

儿童，免疫介导坏死性肌病，生物制剂，靶向治疗

Progress in the Treatment of Immune-Mediated Necrotizing Myopathy in Children

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Received: March 8, 2026; accepted: April 2, 2026; published: April 10, 2026

Abstract

Immune Mediated Necrotizing Myopathy (IMNM) in children is an important subtype of idiopathic inflammatory myopathy, characterized by slow onset, easy misdiagnosis, and potential poor prognosis.

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文章引用: 张欣, 洪思琦. 儿童免疫介导坏死性肌病的治疗进展[J]. 临床医学进展, 2026, 16(4): 2352-2358.
DOI: 10.12677/acm.2026.1641484

Currently, there is a lack of high-quality pediatric evidence for the treatment of this disease. Traditional immunotherapy such as glucocorticoids, methotrexate, cyclophosphamide, etc. are still first-line treatments, but some patients have poor efficacy or intolerance issues. The development of targeted therapy and novel cell therapies brings new hope to difficult-to-treat cases. This article provides a systematic review of IMNM in children and its treatment strategies, especially new treatment strategies, and looks forward to future research directions for personalized precision therapy.

Keywords

Children, Immune-Mediated Necrotizing Myopathy, Biological Agents, Targeted Therapy

1. 引言

免疫介导坏死性肌病(Immune-Mediated Necrotizing Myopathy, IMNM)是特发性炎症肌病(Idiopathic Inflammatory Myopathies, IIM)的重要亚型，其发病率约为 0.5~1/100 万，占儿童特发性炎症性肌病的 10%~20% [1]。临床以急性或亚急性起病的肌无力为主要特征，伴血清肌酸激酶(CK)水平显著升高，肌肉病理可见明显肌纤维坏死及再生，而炎症细胞浸润相对较轻，儿童中发病相对少见；该病与多发性肌炎、皮肌炎、包涵体肌炎及非特异性肌炎等其他类型肌病存在差异[2]。与成人相比，儿童免疫介导坏死性肌病(IMNM)患者的临床表现更为隐匿，部分患儿因起病缓慢，病程初期肌肉病理呈营养不良样改变，易被误诊为肌营养不良症[3]，使儿童 IMNM 诊断具有一定挑战性。儿童 IMNM 病情进展快，肌无力程度重，容易出现吞咽困难、呼吸肌受累等严重并发症[4]，早期诊断和积极治疗对改善预后具有重要意义，若治疗不及时，可导致显著功能障碍，严重影响生活质量及长期预后。近年来，随着对 IMNM 发病机制的深入认识和生物制剂的临床应用，儿童 IMNM 的治疗策略也在逐步发生变化。

2. 发病机制

近年来，随着肌炎特异性抗体检测的普及及研究的深入，我们对发病机制的认识正在历经变革。既往认为 IMNM 是以补体激活为核心的体液免疫反应是导致肌纤维损伤的主要途径，而最新研究表明 IMNM 发病机制以自身抗体驱动为核心病理环节[5]。

IMNM 根据血清学分为三个亚型：抗信号识别颗粒(anti-Signal Recognition Particle, anti-SRP)抗体阳性 IMNM、抗 3-羟基-3-甲基戊二酰辅酶 A 还原酶(anti-HMG-CoA Reductase, anti-HMGCR)抗体阳性 IMNM 和自身抗体阴性抗体 IMNM [6]。SRP 抗体主要靶向 SRP54 kDa 亚基，可干扰新生肽链向粗面内质网的转运，导致肌纤维蛋白合成障碍和细胞凋亡[7]；HMGCR 抗体识别胆固醇合成途径限速酶的胞内 C 末端区域，其结合可干扰肌细胞代谢并触发补体依赖性细胞毒作用[8]。上述抗体既可结合再生肌纤维表面异位表达的靶抗原，激活经典补体通路并形成膜攻击复合物(C5b-9)在坏死肌纤维表面沉积，也可内化进入肌细胞后抑制靶蛋白功能，干扰蛋白质转运或胆固醇合成等代谢过程，引发脂质堆积与肌纤维损伤[7]。

此外，免疫细胞失衡会放大损伤，巨噬细胞作为主要的炎症浸润细胞，其不同极化状态(M1, M2)与局部炎症微环境共同影响着疾病进程，通过释放促炎因子加剧肌纤维损伤，同时参与坏死碎片的清除和组织再生修复[9]。更重要的是，非免疫性机制如内质网应激和自噬细胞的激活是一把“双刃剑”，适度

的激活有助于细胞清除损伤蛋白，促进再生，过度激活则可能直接启动细胞凋亡程序，加剧肌纤维凋亡与肌萎缩[7] [9]。

遗传易感性与环境因素的交互作用构成抗 HMGCR 肌病的重要触发条件。主要组织相容性复合体(MHC)等位基因 DRB 1 * 11:01 与成人抗 HMGCR 肌病密切相关；而在抗 HMGCR 抗体阳性的儿童患者中 DRB 1 * 07:01 等位基因的频率则显著增加[10] [11]。就环境触发因素而言，他汀类药物可通过上调肌细胞中 HMGCR 的表达来增加自身抗原暴露[12]；此外，饮食中的天然他汀(如香菇、红曲米)、病毒感染及恶性肿瘤等因素也可能直接启动异常的免疫应答[8]。

3. 治疗进展

儿童免疫介导坏死性肌病(IMNM)的一线治疗旨在快速控制疾病活动、改善肌力并维持长期缓解。目前，糖皮质激素被推荐作为一线治疗，根据疾病严重程度和治疗反应，可同时或一个月内加用其他药物，如甲氨蝶呤、利妥昔单抗和/或静脉注射免疫球蛋白(IVIG) [6]。

3.1. 糖皮质激素

在儿童免疫介导坏死性肌病(IMNM)的治疗中，糖皮质激素被视为一线基础药物，但其单药治疗往往疗效有限，多数患儿需联合使用其他免疫抑制剂或静脉注射免疫球蛋白(IVIg) [13] [14]。然而，长期或大剂量使用可导致生长迟缓、骨质疏松、感染风险升高等副作用，在儿童群体中需尤为警惕。

3.2. 免疫抑制剂

为减少激素用量及其副作用，常需联合使用免疫抑制剂。甲氨蝶呤是常用的激素助减剂，起效相对较快(约 4~8 周)，但需监测肝功能和骨髓抑制等不良反应，且部分患者疗效不佳或不耐受[13] [14]。对于重症或难治性患者，可考虑使用环磷酰胺[15]，其虽能有效改善肌力和疾病活动度[16]，但存在骨髓抑制、出血性膀胱炎及潜在远期肿瘤风险，在儿童中应用需严格评估获益风险比。此外霉酚酸酯也可用于难治性患者或伴多系统受累者[17] [18]，但其同样存在胃肠道反应、感染风险，且有文献提示可能诱发肌病[19]。他克莫司通过抑制 T 细胞活化，能促进 IMNM 患者的病情缓解与康复[20]，不良反应发生的严重程度与血药浓度相关。

3.3. 静脉注射免疫球蛋白(IVIG)

静脉注射免疫球蛋白(IVIG)是重要的辅助治疗，通常采用剂量为 2 g/kg，每 4 周 1 次，具体用量可根据患者实际情况进行动态调整[21]，特别是对于反复感染的患者，可评估是否需要 IVIG 辅助治疗[22]。通过多靶点免疫调节发挥作用，约 60%~70%的患者可获得治疗反应。但其疗效可能不持久，常需联合其他免疫抑制剂以维持病情稳定，且治疗成本较高[23]。

3.4. 靶向治疗

随着对发病机制研究的深入，针对不同细胞和介质的新型疗法为 IMNM 的治疗提供重要的补充选择。目前，IMNM 潜在的治疗靶点包括：B 细胞/浆细胞－作为自身抗体的来源，系 IMNM 的核心治疗靶点，长寿命浆细胞可持续产生自身抗体，是疾病复发的重要因素；补体系统-C5 抑制剂可阻断膜攻击复合物形成，保护肌纤维免受补体介导的损伤；FcRn-阻断 FcRn 可加速致病性 IgG 抗体的清除；JAK-STAT 通路－参与干扰素信号传导，调控多种促炎因子的表达[24] [25]。

(一) 抗 CD20 抗体

利妥昔单抗(Rituximab)是一种靶向 B 细胞表面 CD20 抗原的单克隆抗体，通过结合 B 细胞表面的

CD20 抗原，可诱导 B 细胞凋亡或通过抗体依赖性细胞介导的细胞毒作用(ADCC)清除 CD20+ B 细胞，从而耗竭外周血 CD20+ B 细胞。该疗法可通过减少自身抗体生成及影响 B 细胞的抗原呈递等功能，进而多层面调节异常免疫反应[26] [27]。在难治性儿童 IMNM 中，利妥昔单抗可作为诱导缓解或联合治疗使用，常用方案包括按体表面积 375 mg/m² 每周给药一次，连续 4 周，或采用固定剂量 1 g、间隔 2 周输注两次[28]。现有研究显示，多数患者在接受利妥昔单抗治疗后肌力改善、CK 水平下降，部分患者可实现完全缓解[27] [29]。其主要安全性风险与 B 细胞耗竭导致的体液免疫功能抑制有关。儿童和青少年使用利妥昔单抗与感染风险增加相关，低丙种球蛋白血症是重要的危险因素，需进行免疫监测[30]-[32]。

(二) 补体抑制剂

依库珠单抗(Eculizumab)是一种抗补体 C5 单克隆抗体，通过特异性结合补体 C5，阻止其裂解为 C5a 和 C5b，从而抑制膜攻击复合物(MAC, C5b-9)的形成；其机制旨在直接阻断抗体介导的补体依赖性肌纤维损伤，相关临床前研究已在体外及体内模型中得到证实[33] [34]。该药在难治性免疫介导坏死性肌病(IMNM)中的应用主要基于成人研究及个案报道，现有证据提示其对部分难治性病例可能有效。此外，同机制药物 zilucoplan 治疗 IMNM 的 II 期随机对照试验也显示其在改善肌力和降低肌酸激酶水平方面具有一定疗效[35]。主要安全性风险与补体系统受抑制相关，尤其需警惕脑膜炎球菌等严重感染风险的增加。在儿童患者中应用时，其长期安全性数据尚不充分，需予以关注。

(三) 蛋白酶抑制剂

蛋白酶体抑制剂是通过抑制 26S 蛋白酶体的活性，诱导终末分化的浆细胞凋亡。浆细胞是自身抗体的主要来源，且对常规免疫抑制剂和 B 细胞耗竭治疗可能不敏感。硼替佐米(Bortezomib)作为常用的蛋白酶抑制剂，可直接靶向并清除此类长寿命浆细胞，理论上为清除致病性自身抗体提供了另一途径，因此，该药适用于自身抗体滴度显著升高、且对 B 细胞耗竭疗法反应不佳的难治性 IMNM 病例[36] [37]。需要注意，硼替佐米有导致周围神经病变与骨髓抑制的风险[38]，其在儿童免疫性疾病领域应用经验有限，长期安全性数据尤其是对远期免疫系统发育及肿瘤风险的影响尚未明确，需进一步研究评估。

(四) FcRn 拮抗剂

FcRn 拮抗剂通过竞争性阻断 FcRn 与 IgG 的相互作用，从而抑制 IgG 的再循环过程，加速致病性 IgG 抗体的清除。一项回顾性病例研究发现使用艾加莫德(Efgartigimod)治疗难治性 IMNM 可有效降低血清总 IgG 及特异性自身抗体滴度，并伴随肌力改善[39]，目前针对儿童 IMNM 的艾加莫德治疗经验有限，需要更多临床研究验证其疗效和安全性，通过广泛降低 IgG 发挥作用，需关注潜在的感染风险，尤其是可能诱发的低丙种球蛋白血症及其相关影响[40]。

(五) JAK 抑制剂

托法替尼(Tofacitinib)、巴瑞替尼(Baricitinib)、芦可替尼(Ruxolitinib)是小分子 Janus 激酶(JAK)抑制剂，通过抑制 JAK-STAT 信号通路，阻断多种炎症细胞因子(如干扰素、白细胞介素)的细胞内信号转导。该药在儿童风湿性疾病领域特别是幼年特发性关节炎和幼年皮肌炎中的临床应用经验逐渐积累。目前，托法替尼治疗难治性幼年皮肌炎可显著改善皮肤病变和肌力，减少激素用量[41] [42]。但其在儿童 IMNM 中的具体应用经验仍较少。此类药物的已知不良反应主要包括血脂异常、血栓及特定感染风险相关[43]。

3.5. 新型细胞治疗

嵌合抗原受体 T 细胞(CAR-T)治疗是一种通过基因工程修饰患者或供者 T 细胞，使其表达靶向特定抗原的 CAR 分子，从而精准识别并清除目标细胞的免疫疗法。2024 年发表的一项里程碑研究报道了异体 CD19 靶向 CAR-T 细胞(KYV-101)治疗重症肌炎和系统性硬化症的安全性数据，显示良好的耐受性和初步疗效[44]。此外，一例成人病例报告证实了其在难治性免疫介导坏死性肌病(IMNM)中的治疗潜力：

对多种免疫抑制剂无效的 IMNM 患者在接受 CD19 CAR-T 细胞治疗后，肌力获得显著改善，且自身抗体转为阴性[45]。目前，CAR-T 细胞治疗在自身免疫性疾病(尤其是儿童 IMNM)中的应用尚处于早期探索阶段，其安全性、对免疫系统发育的影响及疗效的持久性需长时间的观察随访。CAR-T 疗法可能引起严重的副作用，如细胞因子释放综合征、免疫效应细胞相关神经毒性综合征(ICANS)、长期 B 细胞再生障碍所致感染风险增加以及与基因整合相关的远期风险[46]。

对于难治性 IMNM，靶向治疗和 CAR-T 治疗通过干预特定免疫环节，可能带来更深层和持久的疾病控制。然而，长期或反复使用生物制剂易导致免疫监视功能受损，潜在增加远期感染、肿瘤发生风险。儿童患者处于免疫系统发育的关键期，长期使用生物制剂可能对免疫记忆形成、疫苗应答及远期安全产生未知影响[47]-[49]。在临床应用中需严格权衡其疗效与潜在风险，进行个体化治疗与长期监测。

4. 展望

儿童 IMNM 是一种严重的自身免疫性肌病，早期诊断和积极治疗对改善预后至关重要。目前尚无标准化的儿童用药指南，治疗需综合考虑患儿年龄、疾病严重程度、抗体类型、既往治疗反应、合并症及家庭意愿等相关因素。传统免疫抑制治疗仍是基础，靶向治疗和 CAR-T 治疗为难治性 IMNM 带来了新的希望。IMNM 治疗仍面临诸多挑战，现有证据主要基于回顾性病例分析和个案报道，缺乏针对儿童的前瞻性、对照研究。未来，基于抗体分型的个体化精准治疗将成为主流，期待在儿童 IMNM 中开展高质量临床研究，积累真实世界的数据，为儿童 IMNM 患者提供更加安全、有效的治疗选择。

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