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儿童造血干细胞移植后闭塞性细支气管炎综合征研究进展

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摘　要

闭塞性细支气管炎综合征(BOS)是造血干细胞移植(HSCT)后最常见的非感染性肺部并发症，该病通常起病隐匿，早期诊断困难，且病理改变不可逆，治疗效果差，导致显著的非复发性死亡率。目前关于儿童HSCT后BOS的研究有限，其临床诊疗仍然面临巨大挑战。本文将综述儿童HSCT后BOS的发病率、危险因素、发病机制、诊断标准及治疗进展，旨在为促进该疾病的早期诊断和有效治疗提供理论支持，推动临床实践的发展。

关键词

闭塞性细支气管炎综合征，造血干细胞移植，儿童

Research Advances of the Bronchiolitis Obliterans Syndrome Following Hematopoietic Stem Cell Transplantation in Children

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Abstract

Bronchiolitis obliterans syndrome (BOS) is the most common non-infectious pulmonary complication following hematopoietic stem cell transplantation (HSCT). The disease typically presents with an insidious onset, making early diagnosis challenging. Pathological changes are irreversible, treatment responses are poor, and it leads to significant non-relapse mortality. Currently, research on BOS in pediatric patients post-HSCT is limited, and clinical management remains a substantial challenge. This review summarizes the incidence, risk factors, pathogenesis, diagnostic criteria, and treatment advances of BOS following pediatric HSCT, aiming to provide theoretical support for early diagnosis and effective treatment of the disease, and to promote the advancement of clinical practice.

Keywords

Bronchiolitis Obliterans Syndrome, Hematopoietic Stem Cell Transplantation, Children

1. 引言

造血干细胞移植(Hematopoietic Stem Cell Transplantation, HSCT)是治疗儿童恶性和非恶性血液疾病的重要手段，目前，全球每年有超过 5000 名儿童接受异基因造血干细胞移植(Allogenic Hematopoietic Stem Cell Transplantation, allo-HSCT) [1] [2]。尽管移植技术的进步显著提高了生存率，肺部并发症仍是导致移植后患者非复发死亡的主要原因[3] [4]。闭塞性细支气管炎综合征(Bronchiolitis Obliterans Syndrome, BOS)是移植后最常见的非感染性肺部并发症，其在儿童中的发生率为 1.3%~21.7% [5] [6]，病死率高达 14%~100% [7] [8]。BOS 通常起病隐匿，早期诊断困难，且病理改变不可逆，治疗反应差，极大地影响移植后儿童的生存时间和生活质量[9]-[11]。目前国内外对于 BOS 的研究多集中于成人，儿童相关研究较为匮乏。2024 年美国胸科协会(American Thoracic Society, ATS)首次发布了针对儿童 HSCT 后 BOS 监测和诊断的指南，为早期诊断 BOS 提供了重要参考[12]。本文将综述儿童 HSCT 后 BOS 的发病率、危险因素、发病机制、诊断标准及治疗进展，旨在促进儿童 HSCT 后 BOS 的早期识别与干预。

2. BOS 定义和发病率

BOS 是一类临床特征为慢性持续性咳嗽、喘息、呼吸急促、劳力性呼吸困难、活动耐量下降及低氧血症，影像学表现为气体潴留，肺功能提示阻塞性通气功能障碍，病理改变为终末性细支气管和呼吸性细支气管的炎症细胞浸润、管壁纤维化、小气道管腔进行性不可逆狭窄或闭塞的临床综合征[11] [13]-[15]。BOS 通常发生于移植后 100 天至 2 年之间，中位发病时间为移植后 15 个月，少数病例可能在移植后 5 年以上出现[14] [16]。BOS 主要见于 allo-HSCT 受者，而在自体移植后较为罕见[17]-[19]。当合并慢性移植物抗宿主病(Chronic Graft-versus-Host Disease, cGVHD)时，BOS 发生率显著升高[20]-[23]。由于缺乏统一的诊断标准，BOS 的发病率在不同的研究中差异较大。在成人和儿童的混合研究中，BOS 的发病率为 0~48% [24]，在儿科患者中的发病率为 1.3%~21.7% [5] [6]。成人 BOS 发病率高于儿童，这可能与较高的移植物抗宿主病风险以及现有 BOS 诊断标准在儿童中的适用性较差有关[7] [12] [25] [26]。

3. BOS 发生及预后不良危险因素

儿童 HSCT 发生 BOS 的重要危险因素是 cGVHD，尤其是活动性、广泛性或中重度 cGVHD，其他危险因素包括：原发疾病高危、移植前气流受限、移植前或移植后肺部疾病、移植时年龄较大、II~IV 级的急性移植物抗宿主病(Acute Graft-versus-Host Disease, aGVHD)、外周血干细胞移植、无关供者、女性供者或受者、ABO 血型不匹配的 HSCT、人类白细胞抗原不匹配的 HSCT、低血清免疫球蛋白水平、血清巨细胞病毒阳性以及包含白消安、全身照射或环磷酰胺的清髓性预处理方案[21]-[23] [27]-[30]。研究还表明，脐带血移植、减低毒性的预处理方案或者包含抗胸腺细胞免疫球蛋白的预处理方案可能有助于降低儿童 HSCT 后 BOS 的发病率[28]-[30]。

BOS 不良预后相关因素包括：移植后早期(6~12 个月)确诊 BOS、确诊时第 1 秒用力呼气量(Forced Expiratory Volume in One Second, FEV1)低于 30%预测值、合并 aGVHD 及肺外 cGVHD、确诊早期肺功能急剧下降等[15] [31]-[33]。Chien 等研究表明，HSCT 后 100 天至 1 年内 FEV1 快速下降(每年 > 10%)与较高的病死率相关，该研究还发现部分患者的早期小气道阻塞具有可逆性，提示早期肺功能监测对于 BOS 的防治具有重要意义[33]。

4. 发病机制

BOS 发病机制尚未完全明确，现有研究表明免疫细胞间的相互作用在 BOS 的发生和进展中起着关键作用，特别是巨噬细胞、中性粒细胞、嗜酸性粒细胞、Th1 细胞、Th17 细胞以及 B 淋巴细胞。这些免疫细胞通过分泌细胞因子调节效应细胞的活性，从而影响气道和肺组织的损伤与修复过程。

免疫细胞在 BOS 中的作用和机制主要包括以下几个方面：1) 巨噬细胞：作为重要的免疫细胞，巨噬细胞在先天免疫、组织稳态和修复中发挥重要作用[34]。肺泡巨噬细胞(Alveolar Macrophages, AM)主要负责保护气道和肺泡免受病原侵袭，而肺间质巨噬细胞则在血管系统和肺间质的免疫监视中发挥关键作用[35]。巨噬细胞可分为 M1 型和 M2 型。M1 型主要参与免疫反应，如微生物清除和抗肿瘤作用，而 M2 型则参与免疫抑制和组织修复[36]。研究显示，BOS 的早期阶段常见 M1 型 AM 出现，提示 M1 型 AM 可能与 BOS 发病的早期相关，而 M2 型 AM 则通过分泌血小板衍生生长因子(PDGF)促进晚期肺纤维化的形成[37]。2) 中性粒细胞：在慢性炎症反应中，中性粒细胞起着核心作用，其通过释放蛋白酶、形成中性粒细胞外陷阱(NETs)等途径促进炎症反应[38]。在 BOS 的发病机制中，中性粒细胞通过替代受损的气道上皮、降解基质及胶原沉积，引起气道纤维化[39]。研究表明，BOS 患者的支气管肺泡灌洗液(Bronchoalveolar Lavage Fluid, BALF)、痰及肺组织病理学检查中，中性粒细胞的比例显著增高[40] [41]。3) 嗜酸性粒细胞：嗜酸性粒细胞通过分泌促纤维化细胞因子(如 IL-6)，促进成纤维细胞增殖与分化，最终导致过度的细胞外基质沉积，加剧肺纤维化的进程[42]。研究发现，嗜酸性粒细胞的增多可能是 cGVHD 的早期预警标志，而白三烯受体拮抗剂孟鲁司特则能够显著降低嗜酸性粒细胞水平，缓解 BOS 的临床症状[43] [44]。4) Th1 和 Th17 细胞：Th1 细胞通过分泌干扰素(IFN)和肿瘤坏死因子(TNF)促进免疫反应，而 Th17 细胞则通过分泌 IL-17 等细胞因子，引发各种自身免疫和炎症性疾病(如慢性阻塞性肺病、哮喘、肺纤维化) [45]-[47]。两者在 BOS 的免疫反应中均发挥重要作用。研究显示，BOS 患者的外周血、BALF 和肺组织中的 Th1 细胞因子显著升高，抑制 Th17 细胞的功能可减轻气道纤维化的严重程度[48]-[50]。5) B 淋巴细胞：B 淋巴细胞通过产生抗体介导体液免疫，并通过分泌细胞因子调节免疫反应[51]。在 BOS 中，B 淋巴细胞的异常激活与成熟可能促进疾病的进展。一项研究显示，与无 cGVHD 的患者相比，BOS 患者血清中 B 淋巴细胞激活因子(B Cell Activating Factor, BAFF)和 BAFF/B 淋巴细胞比率明显升高[52]。目前靶向 B 淋巴细胞的治疗策略(如利妥昔单抗)已显示出一定的治疗潜力[53]。

总之，BOS 的发病机制是一个复杂的免疫反应网络，涉及多种免疫细胞的协同作用。尽管免疫细胞在 BOS 的发生与发展中起着重要作用，但各细胞群体的具体机制仍需要进一步研究，以更好地指导临床治疗策略的制定。

5. 辅助检查

5.1. 肺功能检查

肺功能检查(Pulmonary Function Tests, PFT)是诊断 BOS、监测病情发展和治疗效果的主要手段之一。BOS 的典型特征是不可逆的阻塞性通气功能障碍[54]，表现为 FEV1 及 FEV1/用力肺活量(Forced Vital Capacity, FVC)比值显著下降，而 FVC 可能维持在正常范围或轻度下降，肺总量(Total Lung Capacity, TLC)通常正常或轻度增加，其他包括：残气量(Residual Volume, RV)增加，RV/TLC 比值增高，一氧化碳弥散能力(Diffusing Capacity of the Lung for Carbon Monoxide, DLCO)下降，25%~75%用力呼气流速(25%~75% Forced Expiratory Flow, FEF25-75)下降，支气管舒张试验呈阴性等。然而，目前针对 HSCT 后 BOS 的 PFT 标准尚无统一共识。大多数研究者认为，当 FEV1/FVC 比值小于 0.7 且 FEV1 相较移植前下降超过 20%时，应高度怀疑 BOS 的发生；另有研究者认为，如果 FEV1/FVC < 0.7 且 FEV1 低于 75%预测值，则应考虑存在 BOS；部分研究指出，若 FEV1 和 FVC 的预测值均低于 80%，且 TLC 的预测值超过 80%，则可诊断为 BOS。还有研究显示，FEV1 下降超过 10%且 FEF25-75 下降超过 25%可以早期识别出向 BOS 发展的患者，提示 FEF25-75 的下降是反映小气道阻塞的早期指标[55] [56]。

多次呼吸冲洗(Multibreath Washout, MBW)是一种新型的肺功能检查方法，与传统的 PFT 相比，在检测儿童 HSCT 后 BOS 方面具有两个显著优点。首先，MBW 在潮汐呼吸期间进行测试，相较于传统的 PFT 更易于完成，特别适用于学龄前儿童和婴[57]-[59]。其次，MBW 对周围气道的变化具有更高的敏感性，能更早捕捉到小气道的变化[60] [61]。肺清除率指数(Lung Clearance Index, LCI)是 MBW 的主要测量指标，较高的 LCI 阈值可以有效提高 BOS 检测的灵敏度和特异性[60] [62] [63]。因此，在具备足够技术能力的医疗中心，ATS 建议将 MBW 与传统的 PFT 共同作为移植前后肺功能评估的一部分，如果传统的 PFT 不可行，MBW 可作为其补充工具，或在特定情况下单独使用[12]。

5.2. 胸部高分辨率 CT

胸部高分辨率 CT (High-Resolution Computed Tomography, HRCT)被认为是一种评估肺实质的无创检查方法，能够为无法进行 PFT 的患者提供有效的呼吸评估[64]。HRCT 可发现大部分 BOS 患者的异常影像学表现，但早期 BOS 患者，CT 表现可能接近正常[11]。BOS 的影像学异常通常集中在双侧下肺及胸膜下区域。BOS 的直接 CT 征象包括外周细支气管壁增厚、小气道扩张和小叶中心性支气管结节影；间接征象则包括空气潴留症、马赛克衰减征、中央型气道扩张以及过度通气等。相较于吸气相，呼气相 HRCT 更能清晰地观察到空气潴留征和马赛克衰减征[11] [65]。ATS 建议，所有接受 HSCT 的儿童，特别是那些怀疑患有 BOS 的儿童，应在移植前进行吸气相和呼气相的胸部 CT 扫描[12]。

5.3. 纤维支气管镜肺泡灌洗

纤维支气管镜肺泡灌洗(Bronohoalveolar Lavage, BAL)是临床上常用的诊断和治疗手段，BAL 通过提高病原体检出率，能够有效排除肺部感染性疾病，对于免疫功能低下及血小板较低的移植后儿童具有较好的耐受性[66] [67]。此外，感染与 BOS 可能同时存在。一项研究发现，在接受 BAL 治疗的疑似 BOS 患者中，许多患者实际上存在无症状的肺部感染[68]。BAL 不仅能够为疑似 BOS 患者提供病原学诊断依据，还可以通过检测分子标志物辅助 BOS 的诊断。ATS 建议，所有 PFT 结果下降的疑似 BOS 患儿都应

进行 BAL 检查，以评估是否存在感染。然而，针对以下两种情况需要特别注意：1) 如果由于技术原因导致 PFT 结果不可靠，可以在 1~2 周后重复检测，只有在持续怀疑 BOS 的情况下才进行支气管镜检查。2) 如果感染是通过侵入性较低的方法(如鼻咽拭子或痰液)诊断出来的，可以在治疗感染和/或等待感染消退的同时推迟支气管镜检查，只有临床上持续怀疑 BOS 的情况下，才进行支气管镜检查[12]。

5.4. 肺组织活检

肺组织活检是诊断 BOS 的金标准。BOS 的肺组织病理特征分为淋巴细胞性细支气管炎或缩窄性细支气管炎两种类型。缩窄性细支气管炎的特征为明显的细支气管狭窄，细支气管黏膜下或细支气管旁纤维化及上皮增生，而淋巴细胞性细支气管炎则通常无纤维化、支气管扩张或上皮变薄、坏死、消失等改变。与缩窄性细支气管炎患者相比，淋巴细胞性细支气管炎患者通常具有较好的肺功能、更高糖皮质激素反应率及存活率[69] [70]。然而，肺活检作为一种侵入性检查，可能引发气胸、纵隔气肿、持续性气漏综合征，甚至致命等严重并发症，因此在临床应用时应谨慎[71]。ATS 建议，对于疑似 BOS 但无法确诊且活检风险低于不确定风险的患儿，应考虑进行肺活检。诊断不确定性的情况包括：1) 临床证据，如临床表现、CT 扫描和肺功能检查不一致；2) 没有替代的诊断方法；或 3) 对其他疾病和/或合并症存在担忧[12]。

6. BOS 诊断标准的演变

BOS 的诊断标准经历了多次修订。1982 年由 Roca 等人首次报道了闭塞性细支气管炎是一种与 cGVHD 相关的渐进性、不可逆的阻塞性通气障碍[72]。2005 年，美国国家卫生研究院(National Institutes of Health, NIH)提出了将 PFT、HRCT、无呼吸道感染以及肺组织活检相结合的 BOS 诊断标准[73]。然而，肺活检作为一种侵入性检查，存在较高的临床风险，并且由于取样量有限，容易出现漏诊，因此，2014 年 NIH 对该标准进行了修订，修订后的标准简化了肺功能评分，仅通过 FEV1%预测值即可实现肺功能评估，此标准强调了 PFT 的重要性，而不再过度依赖病理活检[74]。2014 年 NIH 共识标准被认为是评估 cGVHD 的最全面标准，在成人群体中得到了较好的验证，但其在儿童群体中的适用性尚不明确。

目前发现 2014 年 NIH 共识标准在诊断儿童 BOS 时存在一些局限性，主要包括：该标准的筛查方法主要是基于成人数据推导的，过于依赖 PFT (年幼、发育迟缓以及无法进行测试的儿童无法可靠完成 PFT)，使用过时的 PFT 参考方程，采用固定的 FEV1 阈值，并且未能认识到 BOS 可以与感染共存，省略了 MBW 测试，以及许多经肺活检确诊的 BOS 并不符合 PFT 诊断标准等[12]。

2024 年，ATS 发布了儿童 HSCT 后 BOS 监测与诊断的新指南，并根据儿童是否能够进行 PFT，分别制定了相应的诊断标准[12]。对于能够进行 PFT 的儿童，使用全球肺倡议参考方程(Global Lung Initiative, GLI)来评估 PFT 结果，若 FEV1%预测值与移植前基线相比下降超过 15%，且这种下降在至少间隔两周的两次测试中持续存在，同时符合以下两个或更多条件，则可以诊断为 BOS：1) FEV1/VC 低于正常下限；2) 呼气相 CT 有空气潴留表现；3) PFT 有空气潴留表现，如 RV 或 RV/TLC 高于正常上限；4) LCI > 8.0；5) 存在肺外 cGVHD (活动性或既往病史)。对于无法进行 PFT 的儿童，若存在喘息、活动时呼吸急促的临床症状，并且满足以下两个或更多条件，则应考虑 BOS 的诊断：1) 呼气相 CT 有空气潴留表现；2) LCI >8.0；3) 存在肺外 cGVHD (活动性或既往病史)。同时，在已确诊感染并进行治疗或预期解决后，若仍持续怀疑 BOS 的存在，应进行感染评估，包括依据临床症状进行的检查，如胸部 X 光片、CT 扫描或微生物培养(例如鼻窦抽吸、上呼吸道病毒检测、痰培养、BALF 培养)。

7. 定期监测

关于 BOS 的监测，既往多认为在移植后前 2 年至少每 3 个月复查 1 次肺功能，随后可每 6 个月或每

年复查[67] [74]。对于儿童群体，ATS 建议移植前后都应积极进行肺功能监测，包括肺活量、静态肺容量和 DLCO 测定。若条件允许，应从 HSCT 后的第 3 个月开始监测静态肺容量和 DLCO，而不仅仅依赖肺活量测定来评估有症状的患者；对于 BOS 风险较低的患者，建议在移植后第一年每 3 个月进行一次肺活量测定，第二年则每 3 至 6 个月进行一次肺活量测定，并在可能的情况下增加静态肺容量和 DLCO 的测定。对于高风险的肺部并发症患者或其他器官存在 cGVHD 的患者，可能需要更频繁地监测。对于无症状患者的长期随访，建议在第 3 年每 6 个月进行一次肺活量测定(尽可能同时增加静态肺容量和 DLCO 的测定)，并在 3 年后每年进行一次监测，直至移植后 10 年。对于有持续症状的患者，可能需要每 3 至 6 个月进行一次肺活量测定，直到肺功能稳定性得到确认[12]。

8. 治疗进展

8.1. 糖皮质激素

BOS 是一种治疗难度较大的疾病，管理重点包括及时处理 BOS 诱发因素、潜在疾病以及优化患者的免疫抑制方案。目前，指导 BOS 特定治疗的证据有限，在国内外均尚未形成规范化诊疗路径。

糖皮质激素仍然是治疗 BOS 的主要药物。包括口服、静脉及吸入三种途径，常联合其他免疫制剂共同治疗 BOS，目前包含糖皮质激素的治疗方案主要有：1) 糖皮质激素(泼尼松 1 mg/kg/d，最大剂量为 100 mg/d)单药治疗或联合钙调磷酸酶抑制剂(环孢素/他克莫司)治疗：是当前国内外治疗 cGVHD 的常规一线方案，有效率约为 50% [75] [76]。但研究显示，该方案在 BOS 中反应率欠佳，仅为 20%~40% [77]。2) 布地奈德/福莫特罗联合吸入治疗：可用于治疗轻中度的 BOS 患者，一项多中心随机对照试验表明，与基线相比，布地奈德/福莫特罗组 1 个月时的 FEV1 和 FVC 在统计学上明显高于安慰剂组，且在 6 个月的研究期间内维持良好疗效[78]。3) 全身应用糖皮质激素：是治疗移植后中重度 BOS 的基石，常联合 FAM 方案(吸入氟替卡松 + 口服阿奇霉素和孟鲁司特)治疗[79]。一项研究表明，中重度 BOS 患者接受大剂量脉冲式甲泼尼龙(10 mg/kg/d，连续给药 3 天/4 周，共 16 周)治疗后，第 25 周时 7/9 患者的 FEV1 有所改善，病情趋于稳定[80]。欧洲血液和骨髓移植学会建议全身性糖皮质激素与 FAM 联合作为 BOS 的初始治疗方案[81]，该建议基于一项小规模非随机前瞻性研究，结果显示该方案 3 个月时能使 94%的患者病情稳定或明显改善，减少了激素用量，且有较好的安全性和耐受性[82]。此外，部分研究表明，短期至中期使用阿奇霉素可有效改善肺功能[14] [83]-[85]，但需要注意的是，allo-HSCT 后使用阿奇霉素可能与复发和肿瘤风险增加相关，因此应谨慎使用[86]。

8.2. 其他免疫调节治疗

目前许多免疫调节药物及治疗方法已在临床试验中显示出一定的疗效，包括：1) 芦可替尼：作为一种高选择性非受体酪氨酸激酶(JAK1/2)抑制剂，通过阻遏 JAK1/2 信号传导途径，抑制促炎细胞因子和效应 T 细胞的生成。芦可替尼已在美国获批用于治疗类固醇难治性 GVHD，是目前研究最多的治疗 HSCT 后 BOS 的药物[87]-[89]。一项研究表明，芦可替尼联合糖皮质激素在儿童 cGVHD 初始治疗中起效快，且耐受性良好，对以关节、肝脏、肺为靶器官的 cGVHD 疗效显著[90]。2) 伊马替尼：作为一种高选择性的小分子酪氨酸激酶(TKI)抑制剂，通过阻断 TGF-β 或 PDGF 信号通路抑制组织纤维化的发生。研究显示，伊马替尼治疗儿童 HSCT 后 BOS 总缓解率可达到 76.9%，能够有效抑制 BOS 患者肺功能的恶化，并显著改善患者的预后[20]。3) 依他奈西普：作为肿瘤坏死因子 α (TNF-α)拮抗剂，通过与 TNF-α 的特异性结合，减少 TNF-α 对气道上皮的炎症损伤。有研究表明，依他奈西普能使三分之一 BOS 患者的 FEV1 或 FVC 绝对值改善 $\geq$ 10% [68]。4) 甲磺酸贝舒地尔：作为一种选择性 Rho 关联卷曲螺旋蛋白激酶 2 (ROCK2)抑制剂，目前被认为是 BOS 挽救治疗的新选择。DeFilipp 等人对 59 名使用甲磺酸贝舒地尔治

疗的 BOS 患者进行回顾性分析，结果显示，39%的患者 FEV1 改善 ≥5%，22%的患者 ≥10%。基于肺功能的最佳整体反应率为 24%，基于肺功能和症状的最佳总体反应率为 32%，2 年总生存率为 82% [91]。5) 利妥昔单抗，作为靶向 CD20 的单克隆抗体，可抑制 B 细胞的活化，但目前关于其在 HSCT 后 BOS 治疗中的应用尚缺乏系统性数据和大规模临床研究支持[92]。现有研究表明，移植后采取预防性或早期干预性应用利妥昔单抗，可在一定程度上降低 cGVHD 的发生率及其严重程度。然而，其对于 HSCT 后 BOS 患者肺功能的具体影响仍不明确，亟需进一步的针对性研究以填补这一领域的知识空白[93]。6) 吡非尼酮和尼达尼布，作为已获批用于治疗慢性纤维化性肺疾病的抗纤维化药物，研究表明这两种药物可在部分患者中维持肺功能稳定，并可能作为桥接治疗为二次肺移植提供支持[94]。目前，多项临床试验正在进行，以进一步评估这两种药物在移植后 BOS 管理中的潜在治疗价值[95] [96]。7) 间充质干细胞输注(MSC)，可通过促进调节性 T 细胞增殖活化、上调 CD27+记忆 B 细胞数量，发挥免疫调节作用及诱导免疫耐受。MSC 已广泛用于治疗炎症及免疫性疾病，可以改善激素耐药性 BOS 的肺功能，研究显示，MSC 治疗 HSCT 后 BOS 患者的缓解率可达到 71%，3 年总生存率为 70.6% [97]。8) 体外光分离置换法(ECP)，是一种基于白细胞分离置换的光化学疗法，主要用于难治性 cGVHD 的治疗。研究表明，ECP 能够改善或稳定 FEV1，减少口服糖皮质激素的剂量，并提高总生存率，且仅出现轻微的不良事件[98]-[101]。

8.3. 终末期治疗

对于那些治疗无效且不伴有其他部位严重活动性 cGVHD、无复发迹象的严重 BOS 患者，肺移植可能是唯一的治愈手段[11] [102]。研究表明，BOS 患者在进行肺移植后总体生存率较为理想，1 年生存率为 78%~90%，5 年生存率为 75%~80% [103]-[106]。然而，肺移植同样存在诸多弊端，包括巨大的经济负担、肺组织供体的稀缺以及移植后 BOS 复发的风险等。因此，尽管肺移植为部分患者提供了生存的希望，但其依然面临诸多不确定性和风险。

目前 BOS 的治疗仍充满挑战，除免疫调节或抗炎治疗外，还应重视全身性对症支持治疗，具体措施包括合理使用疫苗接种和免疫球蛋白进行感染治疗和预防、呼吸功能康复训练、营养支持、胃食返流病治疗、以及对肺功能严重受损患者实施持续氧气治疗等[107] [108]。

9. 总结与展望

儿童 HSCT 后 BOS 具有显著的发病率和死亡率，目前发病机制尚不明确，早期诊断和治疗仍面临诸多挑战，未来需要开展更多针对儿童的多中心前瞻性研究，明确发病机制，探索新的监测技术、生物标志物及治疗方法。同时，应根据儿童的风险特征制定个性化的监测计划，进一步优化治疗方案，力求在提高患儿生存率和生活质量的同时，尽可能减少治疗负担和相关风险。

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