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儿童迁延性细菌性支气管炎的发病机制及治疗进展

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摘　要

儿童迁延性细菌性支气管炎是儿童慢性湿性咳嗽的主要病因之一，其与慢性化脓性肺疾病、支气管扩张被认为是同一疾病的不同发展阶段。该病发病机制尚不完全清楚，可能与细菌生物膜形成、气道软化、纤毛－黏液清除障碍以及免疫调节紊乱等因素有关。部分迁延性细菌性支气管炎患儿面临复发和难治的问题，而反复发作有进展为支气管扩张的风险，探索更加有效的治疗策略至关重要。为此，本文综述该病可能的发病机制及治疗进展，为临床诊治提供参考。

关键词

迁延性细菌性支气管炎，儿童，发病机制，细菌生物膜形成，治疗

Progress in Pathogenesis and Treatment of Protracted Bacterial Bronchitis in Children

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Abstract

Protracted bacterial bronchitis in children is one of the main causes of chronic wet cough in children. It is considered to be different stages of the same disease as chronic suppurative lung disease and bronchiectasis. The pathogenesis of it is not fully understood, but may be related to some factors such as bacterial biofilm formation, airway malacia, ciliary-mucus clearance disorders and immunomodulatory disorders. Some children with protracted bacterial bronchitis face the problem of recurrence and refractory, and repeated attacks of the disease have the risk of progression to

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bronchiectasis, so it is crucial to explore more effective treatment strategies. Therefore, this article reviews the possible pathogenesis and treatment progress of the disease to provide a reference for clinical diagnosis and treatment.

Keywords

Protracted Bacterial Bronchitis, Children, Pathogenesis, Bacterial Biofilm Formation, Treatment

1. 引言

儿童迁延性细菌性支气管炎(protracted bacterial bronchitis, PBB)位居我国儿童慢性湿性咳嗽病因的第四位[1]，以幼儿和学龄前期儿童多见[2]，主要表现为持续性慢性湿性咳嗽。随着对呼吸道微生物组认识的加深，该病逐渐受到国内外儿科医师的重视[3]。目前 PBB 的发病机制尚不完全明确，可能与细菌生物膜的形成、气道软化、纤毛–黏液清除障碍以及免疫调节紊乱等因素有关。该病咳嗽通常可通过 2 周的抗生素治疗缓解，推荐阿莫西林克拉维酸钾为首选治疗[4] [5]。然而，临床实践和研究报告显示，部分 PBB 患儿在经过足够疗程的抗生素治疗后，咳嗽仍难以控制，且存在复发和难治的问题。此外，若不进行早期诊治，PBB 有可能进展为支气管扩张[6]，结合目前 PBB 的治疗现状，亟待探索更为有效的治疗策略。因此，本文将对 PBB 患儿发病机制及治疗进展进行综述，希望为临床诊治 PBB 患者提供参考。

2. 发病机制

2.1. 细菌生物膜形成

细菌生物膜是导致持续性细菌感染和抗生素耐药性增加[7]的主要原因，特别是在慢性感染中，高达 80%的病例被证实与细菌生物膜的形成有关[8]。PBB 患儿气道中也发现了细菌生物膜的存在[9]，PBB 是儿童细菌生物膜相关最常见疾病之一[10]。国内学者鲍燕敏等人的研究表明，PBB 患儿气道中假单孢菌属、流感嗜血菌属等条件致病菌数量增加，菌群多样性显著降低[11]。国外研究报告 PBB 患儿的气道微生物群落主要由嗜血杆菌和奈瑟氏菌构成[12]，表明 PBB 气道微生物群落是由一种或多种病原体主导的微生物群落，微生物组多样性降低，细菌生物膜因此形成并占据主导地位，为 PBB 细菌的定植以及相关的慢性中性粒细胞炎症特征提供了合理的解释。目前的研究已经发现不少细菌生物膜形成的机制，例如，肺炎链球菌和未分型流感嗜血杆菌等细菌的生物膜形成依赖于特定的酶和菌毛等结构，这些结构在调节群体感应分子生物合成和促进病原体黏附中发挥关键作用[10]。另外，在动物模型实验中，当肺炎链球菌及流感嗜血杆菌细菌共同生长时，肺炎链球菌的存活率被提高及生物膜生成显著增加[13]，表明呼吸道微生物之间的相互作用可能影响生物膜的产生。细菌生物膜形成后通过生物膜结构(如胞外聚合物基质)阻挡抗生素和免疫细胞的渗透，此外，生物膜内细菌代谢减缓，对抗生素的敏感性降低；细菌表达抗性基因，抗生素耐药性增加可高达 1000 倍[14]。有学者提出体内生物膜的产生和厚度与抗生素渗透和抗生素敏感性直接相关的观点[15]，但是目前尚无诊断生物膜的标准化方案，使用不同技术的研究结果可能有很大差异，这使得比较困难且结果值得商榷，需要进一步研究探索一种可快速准确检测生物膜的方案。

2.2. 气道软化

部分 PBB 患儿通过支气管镜检查发现气管、支气管软化等表现。一项为期 5 年的国外前瞻性研究结果显示，PBB 患者中有 45%合并气管软化，31%合并支气管软化[16]，国内研究也报道东北地区 PBB 患者中婴儿气管支气管软化比例高于年长儿[17]，一项回顾性研究显示，当治疗效果不理想时需考虑是否存在潜在的其他病因[18]。尽管尚缺乏直接证据确立气道软化与 PBB 之间的发病机制联系，但已有研究表明，气道软化的患儿面临无效咳嗽、分泌物滞留以及呼吸道感染风险增加的挑战[19]。呼吸运动过程中，气道壁的反复振动、黏膜刺激以及咳嗽时的呼吸道塌陷，可共同导致分泌物清除障碍，进而诱发反复或慢性呼吸道感染，还可能促使气道黏膜发生鳞状上皮化生，进一步损害纤毛–黏液清除系统的功能[20]。此外，随着时间和治疗的推进，部分年长儿童的气道软化症状通常会伴随气道直径的扩大及黏液清除能力的提升而自然缓解，为气道软化与 PBB 之间潜在的致病关联提供了支持。

2.3. 纤毛–黏液清除障碍

呼吸道防御系统与纤毛–黏液清除功能之间存在紧密的联系，这一机制在维护呼吸道健康中起着至关重要的作用。多种因素(如呼吸道病毒感染、慢性炎症、香烟烟雾、室内空气污染等)可导致纤毛–黏液清除功能受损，鼻病毒、呼吸道合胞病毒和流感病毒可能会下调与纤毛形成有关的关键基因[21]，影响纤毛的正常功能。此外，呼吸道病毒感染可能导致纤毛上的血管内皮细胞脱落[22]，进一步减弱纤毛–黏液功能并增加继发性细菌感染的风险。实验模型显示，未分型流感嗜血杆菌通过表达特定的表面成分，如高度保守的表面脂蛋白、蛋白-D 和 LOS 分离物等抑制纤毛的功能，直接干扰纤毛–黏液系统的清除机制[23]。此外，感染引发氧化应激和氧化–抗氧化失衡[23]导致呼吸道黏膜蛋白质、脂质和 DNA 损伤，进一步破坏纤毛–黏液系统的完整性，不仅维持了气道的炎症反应，还促进感染的恶性循环，最终影响 PBB 的发生、发展及预后。

2.4. 免疫调节紊乱

研究发现，PBB 患儿存在持续中性粒细胞炎症和先天免疫激活。Marchant 等发现 PBB 患儿气道中性粒细胞增多和细胞因子中位数水平升高，巨噬细胞显著降低，toll 样受体-2 和 toll 样受体-4 mRNA 表达值显著升高[24]在细菌感染的反应中起关键作用，参与慢性气道炎症的形成。Ntesou 等报道 PBB 患儿支气管黏膜活检标本在显微镜下观察到嗜酸性粒细胞、中性粒细胞和淋巴细胞聚集，支气管肺泡灌洗液标本中防御素-2 和甘露糖结合凝集素水平升高[25]，进一步强化了 PBB 中性粒细胞炎症及肺部先天免疫被激活的观点。

值得注意的是，在 PBB 的发生发展过程中，上述机制不是孤立存在，细菌生物膜的形成和气道软化导致黏液滞留和细菌增殖，纤毛–黏液清除功能障碍进一步加剧了这一过程，宿主和呼吸道微生物组之间相互作用，这些因素共同形成了 PBB 的病理基础，未来需要更多的研究探讨它们之间具体的相互作用机制和联系，有助于开发更有效的治疗策略。本文将重点综述以下包括抗感染、抗细菌生物膜、调节免疫功能及纤毛–黏液清除功能等治疗方案。

3. 治疗

3.1. 抗感染

PBB 目前的治疗方案主要是抗生素的应用，临床实践中常根据临床表现、致病菌药敏实验结果等选取适当的抗生素进行个体化的治疗。指南[4] [26] [27]推荐口服阿莫西林克拉维酸钾作为抗感染治疗的首选方案，此外可选取头孢类抗生素作为替代方案。针对用药疗程，不同指南存在一定差异，英国胸科学

会(BTS)发布的指南[28]建议抗生素的使用时间为 4 周至 6 周，旨在通过相对较长时间的持续抗菌彻底清除感染；而多数其他指南推荐标准治疗时长为 2 周，同时强调若患儿在初始 2 周治疗结束后咳嗽症状无明显缓解，可再使用 2 周。一项多中心 RCT 研究显示抗生素使用 2 周与 4 周两组咳嗽缓解率无显著差异，但使用 4 周抗生素治疗可延长复发间隔时间[29]。既往高质量证据表明 2 周的抗生素疗程通常足以治疗 PBB [30]，然而在临床实践中部分 PBB 患儿反复恶化、频繁复发。一项研究报道约 43.5%的患者在 1 年内反复发作次数超过 3 次[31]，而且 4 周抗生素治疗后咳嗽症状仍未缓解，则未来进展为支气管扩张的风险增加[32]；另一项前瞻性队列研究随访结果显示 PBB 儿童复发的比例呈逐年下降趋势[16]，表明部分 PBB 患儿常规抗感染治疗效果不尽人意，早期诊断及治疗尤为重要。针对疗效不佳的这部分患儿，除了常规抗感染治疗外，还可选择以下包括抗细菌生物膜治疗、调节免疫及纤毛－黏液清除功能等策略，以改善 PBB 患儿的预后，降低远期并发症的发生。

3.2. 抗细菌生物膜治疗

细菌生物膜形成不仅可抑制抗菌药物的扩散和隔离抗菌药物，还可通过嵌入高水平的耐药性细菌进一步增强抗菌药物耐药性[33] [34]，针对细菌生物膜的治疗对于控制持续性细菌感染和提高抗生素治疗效果具有重要意义[35]。现阶段，各种抗生物膜策略在体外和动物研究中都显示出良好的前景，但在人体的应用有限，如分散素 B、脱氧核糖核酸酶 I 和藻酸裂解酶等工程酶可有效破坏细菌生物膜[10]。将藻酸裂解酶与环丙沙星相结合，由于抗生素对生物膜的渗透性提高，可有效降低生物膜中铜绿假单胞菌的生物量和细胞密度[36]。此外，一些病例报告(包括一些涉及儿童的病例报告)表明，囊性纤维化患者通过雾化器或静脉途径使用噬菌体可降低痰中细菌密度，改善患者健康状况并延长后续再次感染时间[37] [38]。其他药物如阿奇霉素可以干扰群体感应分子并阻止藻酸盐产生[39]，乙酰半胱氨酸被发现既能抑制生物膜形成，又能破坏预先形成的生物膜[40]，已被广泛应用于临床实践中。

除上述药物外，左氧氟沙星的抗生物膜作用在此前已被证实[41] [42]。该类药物具备诸多优势，如半衰期较长，能够在体内维持相对稳定的血药浓度；抗菌谱广泛，可有效覆盖多种病原菌；尤为突出的是，在肺组织中能够达到较高的浓度，且组织穿透能力强[43]，对细菌生物膜具有良好的通透性，为常规疗效不佳的 PBB 患者提供了新的治疗策略。既往研究评估了左氧氟沙星、莫西沙星、环丙沙星、阿莫西林克拉维酸和头孢曲松对铜绿假单胞菌、流感嗜血杆菌和肺炎链球菌产生的生物膜的干扰能力，发现肺炎链球菌的生物膜对抗生素的敏感性明显更高，氟喹诺酮类药物在减少铜绿假单胞菌、肺炎链球菌和流感嗜血杆菌的生物膜生成方面最为有效[44]。临床试验发现，左氧氟沙星吸入溶液或混悬液具有优异的生物膜渗透性和快速对抗铜绿假单胞菌的活性，同时可减少痰液的产生并改善患者的肺功能[45]。欧盟和美国食品药品监督管理局(FDA)的药品说明书中，已将左氧氟沙星纳入多种儿科疾病的适应症范围，但是该类药物在儿童中应用仍然有限。长远来看，抗细菌生物膜治疗有望为 PBB 的诊治提供一定的启示与潜在的治疗方向。

3.3. 调节免疫功能及纤毛－黏液清除功能

大环内酯类药物中 14、15 元内酯结构具有免疫调节作用，其临床作用机制主要是抗炎和免疫调节作用。小剂量阿奇霉素目前广泛用于儿童呼吸系统疾病，其免疫调节机制包括增强巨噬细胞的功能、诱导中性粒细胞凋亡等[46] [47]。既往研究数据表明，阿奇霉素可减少慢性气道疾病急性加重的发生率，可降低慢性化脓性肺疾病或支气管扩张患儿的肺部恶化率[48] [49] [50]。此外，阿奇霉素还直接作用于呼吸道上皮细胞，对 MUC5AC 的分泌产生抑制作用。阿奇霉素可通过多条信号传导通路抑制黏液的生成过程[46] [51]，从本质上改善慢性气道疾病中黏液的高分泌状态。Simon 等研究发现季节性使用阿奇霉素治疗

PBB 不会导致抗菌药物的耐药性增加[52]，表明该药用于 PBB 治疗的安全性。

另外，使用长效抗胆碱药物(LAMA)可改善中度至重度慢性阻塞性肺疾病(COPD)患者的痰液产生状况和咳嗽症状[53]，其作用机制可能是通过限制气道杯状细胞的增殖或抑制黏膜下腺体的分泌功能，进而减少黏液的分泌量。

4. 总结与展望

PBB 患儿的发病机制尚未完全明晰，临床医生应根据患者病情采取个体化的治疗方案，未来的研究可进一步探索细菌生物膜形成的分子机制和气道微生物组与宿主免疫系统的相互作用机制，以及开发针对细菌生物膜的有效治疗方法和基于微生物组特征的个体化治疗策略，以应对日益严重的抗生素耐药性问题，改善 PBB 患儿的生活质量。

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