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儿童肺炎支原体肺炎流行病学及发病机制研究进展

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摘 要

肺炎支原体(*Mycoplasma pneumoniae*, MP)是儿童社区获得性肺炎(Community-acquired pneumonia, CAP)的常见病原体，近年来肺炎支原体肺炎(*Mycoplasma pneumoniae* pneumonia, MPP)发病率在全球呈上升趋势，重症及难治性病例相关报道增多，其免疫机制复杂，目前尚未完全明确。现针对儿童MPP的流行病学特征、发病机制相关研究进展做一综述。

关键词

肺炎支原体，儿童，致病机制，流行病学

Research Progress on Epidemiology and Pathogenesis of Pediatric *Mycoplasma pneumoniae* Pneumonia

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Abstract

***Mycoplasma pneumoniae* (MP) is a common pathogen of community-acquired pneumonia (CAP) in children. In recent years, the incidence of *Mycoplasma pneumoniae* pneumonia (MPP) has been on the**

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rise globally, with an increasing number of reports on severe and refractory cases. Its immune mechanisms are complex and have not yet been fully clarified. This review focuses on the epidemiological characteristics and research progress related to the pathogenesis of MPP in children.

Keywords

***Mycoplasma pneumoniae*, Children, Pathogenic Mechanism, Epidemiology**

1. 引言

肺炎支原体(*Mycoplasma pneumoniae*, MP)是儿童和青少年肺炎支原体肺炎(MPP)的病因，且近年来发病率在全球呈上升趋势[1]，肺炎支原体肺炎(*Mycoplasma pneumoniae* pneumonia, MPP)约占儿童社区获得性肺炎的28%~42% [1]，其临床表现为间歇性刺激性咳嗽，伴有头痛、发热和肌肉疼痛。疾病有发热持续时间长，并发症多，可累计各个脏器的特点。近年来国内外儿童尤其是5岁以下儿童的MPP发病率显著上升[2]，2023~2024年我国多地出现MPP暴发流行，重症MPP (Severe MPP, SMPP)、难治性MPP (Refractory MPP, RMPP)及大环内酯类耐药MPP (Macrolide-resistant MPP, MRMP)病例明显增多，引起广泛关注[3]。国家卫生健康委员会于2025年发布《儿童肺炎支原体肺炎诊疗指南(2025年版)》，对MPP的诊治提出了新的规范和要求[4]。深入理解MPP的流行病学特征、发病机制及并发症对判断患儿预后，制定针对性治疗方案及识别及预防并发症的发生具有重要意义。

2. 流行病学特征

2.1. 流行规律与传播特点

MPP呈世界性分布[5]，全年均可发生。感染普遍在10~12月达流行高峰，11月阳性率最高可达33.56% [6]，MPP主要通过飞沫和直接接触传播，感染后潜伏期为2至3周，潜伏期内至症状缓解数周均具有传染性，在有密切接触的人群中感染率更高，易在人员密集环境中暴发，儿童和青少年发病率最高[7]。

2.2. 全球及我国流行现状与趋势

MP感染后疫情周期约为3至7年出现一次流行峰值，每次疫情持续1至2年[8]，肺炎支原体感染的发病率在多个国家呈现出三至五年的流行周期[9] [10]。

2017年4月至2021年3月间，21个国家不同地点的MP检测全球调查显示，MP病例相较前三年总体下降[11]。

有文章首次报道了武汉地区COVID-19后儿童MP基因型及耐药特征，填补华中地区监测空白，为人型支原体在后疫情时代的监测及感染预防与控制提供了科学数据依据。结果显示MPP占CAP的36.6%，P1-1型占88.98%，P1-2型占11.02% [12]，与北京地区既往数据[13]相似。未发现特定基因型与临床症状严重程度相关。

2023~2024年全球儿童MPP呈现显著再次流行，COVID-19“免疫债”为主要驱动因素[14]。其暴发表现为持续高水平传播，且低龄儿童受累比例明显增加，年龄中位数降至8岁以下。亚洲地区大环内酯耐药率高达90%以上，显著高于欧美，且重症MPP及混合感染问题突出。25%~36%的病例合并腺病毒、

鼻病毒等呼吸道病毒感染，加重病情并延长病程[15]。

但 2023~2024 年 MP 大流行期间儿童疾病严重程度存在争议。西班牙研究显示 14%患儿需 PICU 入住，44%需呼吸支持，高于既往疫情[16]。中国研究报道住院时间延长。但葡萄牙、中国及丹麦等对照研究未发现感染严重性增加[17]，仅丹麦报告 MIRM 等黏膜皮肤表现增多，澳大利亚、美国亦证实此现象[18] [19]。综合来看，这些不同研究报告的疾病严重程度结果不一，但迄今尚无强有力证据表明肺炎分枝杆菌感染总体上比以往流行更严重。

3. 发病机制研究进展

3.1. 粘附定植与上皮细胞损伤机制

目前认为 MPP 发病机制：MP 是缺乏细胞壁的最小原核微生物，可通过顶端黏附结构(黏附细胞器)附着于呼吸道上皮细胞表面，逃避黏膜纤毛清除机制。机械性附导致呼吸道纤毛摆动停止、黏液纤毛运输受抑、细胞凋亡、呼吸道上皮局部损伤及免疫应答过度激活[20]。支原体肺炎支原体与宿主细胞相互粘附作用的主要结构是 P1 黏附素，一种功能性粘附蛋白，质量为 170 kDa 的蛋白质，集中于附着尖端[21] [22]。其与宿主细胞之间的粘附使其免受宿主黏液纤毛清除机制的清除，粘附后导致纤毛功能障碍可持续长达一年，期间能够产生多种局部细胞毒性效应，导致宿主细胞质膜损伤。

3.2. 适应性免疫应答及免疫调控异常

越来越多的证据表明，宿主异常的免疫应答反应在 MPP 发病机制中起关键作用，尤其是在 SMPP、暴发性 MPP (Fulminant MPP, FMPP)及肺外并发症的发生中起重要作用[23]。

感染 MPP 时，肺泡巨噬细胞(AMs)被吸引、激活，进而诱导细胞因子和趋化因子反应[24]。MP 脂蛋白结合 AMs 上的 Toll 样受体(TLRs)，激活核因子(NF)κB，促进促炎细胞因子分泌，增强中性粒细胞聚集和病原体吞噬作用[25]，同时 MP 还通过释放社区获得性呼吸窘迫综合征(Community-acquired respiratory distress syndrome, CARDS)毒素(实验已证实 CARDS 毒素增强了肺炎支原体的毒力)、过氧化氢、超氧阴离子等毒性物质，直接损伤呼吸道上皮细胞，导致纤毛停滞、上皮细胞坏死脱落及气道炎症[26] [27]。

当病原体与宿主细胞相互作用时，会诱导转录基因(MPN372)的加密，该基因编码 CARDS 毒素，并且该蛋白质的水平升高，维持了其与宿主细胞相互作用的作用。在实验动物体内人工引入纯化的重组 CARDS 毒素可复制呼吸道支原体感染临床表现的重要特征，包括细胞因子产生增加、嗜酸性粒细胞增多和气道高反应性，这些特征非常类似于哮喘的临床表现[24] [28]。CARDS 毒素产生与肺炎支原体感染疾病严重程度之间的正相关性。表明该毒素作为疾病决定因素的重要性[29]。此外，肺炎支原体 DNA 检测呈阳性的患者可能出现针对 CARDS 毒素，抗体的阳性反应[26]。重组 CARDS 毒素还可刺激组织培养细胞中 Rab9 相关囊泡的形成(引起支气管上皮细胞的囊泡化或病理改变) [30]。急性 MP 感染可激活先天免疫系统，通过 Toll 样受体 2 (TLR2)识别 MP 脂蛋白，触发下游信号通路，诱导巨噬细胞、中性粒细胞等炎症细胞浸润，释放大量炎症因子[25]。Toll 样受体 2 (TLR2)作为识别病原体相关分子模式的关键模式识别受体，在连接先天免疫与适应性免疫中发挥核心作用。通过三种主要机制 1) 直接机制：TLR2 在 T 细胞上的直接作用[31]；2) 间接机制：TLR2 激活的树突状细胞诱导 Th17 分化[32]；3) NETs 介导的 TLR2 激活机制[33]，通过这些机制共同导致适应性免疫的分化。

最新动物实验研究证实，急性 MPP 动物模型中，肺组织中性粒细胞和巨噬细胞显著浸润，36 种细胞因子/趋化因子在支气管肺泡灌洗液中显著上调，包括 IL-1β、IL-6、IL-17A、TNF-α 等促炎因子，形成“细胞因子风暴”。IL-17 信号通路和细胞因子-细胞因子受体相互作用通路显著富集，提示 Th17 细胞介导的免疫反应在肺组织损伤中发挥核心作用。此外，NLRP3 炎症小体激活、补体系统异常活化及自身免疫反

应(如抗神经节苷脂抗体产生)也参与肺内外组织损伤[34] [35]。CARDS 毒素通过三种关键机制作为 NLRP3 炎症小体激活的上游信号：1) 细胞内 ADP-核糖基化修饰：CARDS 毒素被细胞内化后，其 ADP-核糖基转移酶(ADPRT)活性直接催化 NLRP3 的 ADP-核糖基化修饰；2) 作为第二信号(Signal 2)：炎症小体激活需要两个信号：第一信号(Signal 1)：LPS 等刺激诱导 pro-IL-1β 和 NLRP3 表达；第二信号(Signal 2)：CARDS 毒素作为上游激活信号，触发炎症小体复合物组装和 caspase-1 激活。3) 与 NLRP3 共定位：mCherry 标记的 CARDS 毒素与 NLRP3 在细胞质中共定位，形成特征性的“斑点”(speck)结构，这是炎症小体激活的形态学标志[36]。因此，CARDS 毒素的细胞内 ADP-核糖基转移酶活性确实是激活 NLRP3 炎症小体的关键上游信号事件。

3.3. 气道高反应与慢性气道病变机制

肺炎支原体感染释放促炎细胞因子也被认为可能与导致或加重支气管哮喘等慢性肺部疾病有关。30 多年前，已提出关于肺炎支原体慢性感染可能参与哮喘发病机制的观点[37]。相关问题包括肺炎支原体是否是哮喘的主要原因，还是支原体感染是哮喘发展相关的协同因子。实验对慢性小鼠呼吸道支原体病的发病机制的认识进一步支持支原体病(*Mycoplasma pulmonis*)是一种由肺支原体介导的自然感染，源自肺支原体，病情缓慢进展，受遗传影响显著，且在某些方面与人类哮喘相似，这进一步支持支原体可能导致哮喘等长期肺部疾病的可能性[38]。

有研究证实，伴有急性肺炎支原体感染的喘息儿童，其 IL-5 水平较无症状的肺炎支原体携带者及无喘息的对照组有显著升高。因此，这些作者提出，肺炎支原体可能通过分泌 IL-5 触发易感人群(包括遗传易感或存在其他易感因素者)的喘息过程。因为 IL-5 是已被证实与呼吸道合胞病毒感染相关的气道高反应性发展必不可少的细胞因子[39] [40]。

4. 肺外并发症

研究提示，自身免疫反应可能是与支原体感染相关的许多肺外并发症的原因[20]中枢神经系统(CNS)并发症是 MPP 感染最常见的肺外症状之一[41]，大多数神经系统感染并发症患者的症状出现在呼吸系统症状后 1 至 2 周内，但少数神经系统感染者没有先行或伴随呼吸道感染 MPP 的诊断[42]。由于缺乏支原体实际存在于神经系统组织中的明确证据，有研究提出 MPP 感染后脑部损伤是由交叉反应或自身免疫抗体引起的[42] [43]。

皮肤疾病(包括红斑丘疹性皮疹和水疱性皮疹)也是临床上 MPP 感染最常见的并发症，这些疾病通常具有自限性，MPP 已在某些皮肤病变中比如结膜炎、多形性红斑、疱疹性口炎中被直接检出[44]。

溶血性贫血被认为支原体肺炎的一种罕见但严重的并发症，在儿童中比成人更常见，引起这一并发症的机制被归因于冷凝集素的交叉反应[45]，2004 年病例报道显示与溶血性贫血相关的肺炎支原体感染病例[46]，2015 年病例报道显示高铁血红蛋白可能是 MP 感染的罕见并发症[47]，也有多次报道通过直接检测滑液中的病原体确诊化脓性关节炎，最常见于低丙种球蛋白血症患者[48]。

除了上述并发症外，MP 感染肺外并发症中，可能伴随多种与胃肠道系统相关的非特异性症状。极少数情况下，与胆汁性肝炎和胰腺炎相关[49]。相关心脏并发症，肾脏受累相对少见。肾脏系统感染主要表现为急性间质性肾炎，严重时可造成急性肾衰竭[50]。尽管儿童支原体感染相关的肾脏并发症相对罕见，但若不明原因的肾功能损害持续存在，应考虑进行管间质性肾炎的鉴别诊断并启动检测支原体感染的诊断流程。在某些因支原体感染导致肾功能损害的病例中，可能需要进行肾脏替代治疗或糖皮质激素治疗。尽管儿童 MP 感染引起的肾脏并发症相对罕见，但仍应考虑间质性肾炎，并在不明原因的肾功能损害持续时考虑启动 MP 感染的诊断过程。有效的病因治疗的可能性可以迅速改善病情，避免慢性肾脏病的发

生[48]。

5. 展望

目前证实，肺炎支原体肺炎占儿童呼吸道感染总数的相当一部分比例，目前，儿童 MPP 的发病机制研究已取得显著进展，但临床仍面临许多待解决的问题。MP 毒力因子与宿主免疫应答的分子交互网络尚未完全阐明，特别是 CARDS 毒素诱导“细胞因子风暴”的具体信号通路及关键调控节点仍需深入探索。未来研究方向可从以下几个层面展开：在基础研究层面，需借助单细胞测序等新技术解析肺组织免疫微环境的动态演变；在公共卫生层面，需建立覆盖全国的儿童 MPP 监测网络，实时追踪基因型及耐药谱变迁，为疫苗研发提供流行病学数据支撑。此外，针对“免疫债”现象，未来应如何科学评估后疫情时代呼吸道病原体的流行规律，制定合理的药物及非药物干预策略，也是需要聚焦的问题。

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