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氟喹诺酮和四环素治疗儿童耐大环内酯类肺炎支原体肺炎的研究进展

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摘　要

大环内酯类抗菌药物是治疗肺炎支原体肺炎的一线抗菌药物，对大环内酯类药物耐药是导致难治性肺炎支原体肺炎的主要原因之一。近年来，大环内酯类耐药现象快速增多，尤其在亚洲地区，给临床治疗肺炎支原体肺炎带来困难。有研究表明氟喹诺酮类和四环素类药物在缩短肺炎支原体肺炎症状持续时间方面显示出益处。然而，出于对这两种二线药物在儿童使用中的安全性考虑，临床医生在选择治疗方案时应该权衡风险和益处。本文将对氟喹诺酮和四环素治疗儿童大环内酯类耐药肺炎支原体肺炎的疗效及安全性等方面进行综述。

关键词

肺炎支原体，大环内酯类耐药，耐药机制

Progresses of Fluoroquinolone and Tetracycline in the Treatment of Macrolide-Resistant *Mycoplasma pneumoniae* Pneumonia in Children

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Abstract

Macrolides are the first-line antibiotics for the treatment of *Mycoplasma pneumoniae* pneumonia. Resistance to macrolides is one of the main causes of refractory *Mycoplasma pneumoniae* pneumonia. In recent years, the resistance of macrolides has increased rapidly, especially in Asia, which produces great difficulties for clinical treatment. Fluoroquinolones and tetracyclines have shown benefits in shortening the duration of symptoms of *Mycoplasma pneumoniae* pneumonia. However, for the safety of second-line drugs in children, clinicians should balance the risks and benefits when choosing treatment options. This article will review the efficacy and safety of fluoroquinolone and tetracycline in the treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children.

Keywords

***Mycoplasma pneumoniae*, Macrolide Resistance, Resistant Mechanism**

1. 耐药现状

肺炎支原体(*Mycoplasma pneumoniae*, MP)是引起社区获得性肺炎的常见病原之一，约占儿童和青少年社区获得性肺炎总数的 10%~30%，在 MP 流行季节可增加 3~5 倍[1]。肺炎支原体肺炎(*Mycoplasma pneumoniae* pneumonia, MPP)通常是一种轻度、自限性疾病，但部分可能进展为难治性肺炎支原体肺炎(Refractory *Mycoplasma pneumoniae* pneumonia, RMPP)，造成肺外脏器损害，导致多器官、多系统受累，甚至死亡。近年来，RMPP 的患病率有上升趋势[2]。对大环内酯类抗菌药物耐药是导致难治性肺炎支原体肺炎的主要原因之一[3]。自 1995 年美国首次报告了耐大环内酯类肺炎支原体(Macrolide-refractory *M. pneumoniae*, MRMP)菌株的 A2063G/A2064 位点突变，全世界大环内酯类耐药肺炎支原体的报告增多，尤其是亚洲[4]。中国大陆报道 MP 对大环内酯类抗菌药物的耐药率检出率高达 80%~90% [5] [6]，中国台湾 2017 年报道耐药率约为 10.6%，2018 年约为 47.5%，2019 年升至 62.5% [7]。韩国的一份报告显示，肺炎支原体对大环内酯类的耐药率从 2011 年的 51.1%上升到 2015 年的 87.2% [8]。然而，日本报道 MP 对大环内酯类抗菌药物的耐药率近年来呈下降趋势，从 2011 年的 71.9%降至 2015 年的 53.1% [9]。MP 对大环内酯类抗菌药物的耐药率下降可能与两个因素有关，一是在治疗肺炎支原体感染时适当使用喹诺酮类等二线抗 MP 药物，另一个是 MP 的 P1 型改变。因此，合理使用二线抗 MP 药物和监测抗菌药物耐药性具有重要意义。

2. 耐药机制

肺炎支原体具有重要的区别于其他细菌的微生物学特性。肺炎支原体是能进行自我复制的、能在体外独立存活的最小微生物，拥有极小的基因组[10]。肺炎支原体最初附着在呼吸道上皮细胞表面，由于缺乏细胞壁，支原体膜与宿主膜直接接触，从而使膜成分能够转移或交换。在这个过程中，肺炎支原体利

用有毒分子破坏宿主细胞，诱导纤毛停滞和上皮细胞脱落，以获得生长所需的营养[11]。肺炎支原体对大环内酯类抗菌药物的耐药机制仍未完全清楚，目前国内外对肺炎支原体耐药机制的研究主要有以下五个方面[12] [13]：1) 抗菌药物作用靶位突变；2) 核糖体蛋白氨基酸改变；3) 核糖体 RNA 甲基化修饰；4) 大环内酯类泵或膜通透性改变；5) 抗菌药物失活。

目前肺炎支原体耐药机制中研究最广泛的机制为抗菌药物作用靶位突变。由于肺炎支原体生长缓慢、培养条件要求苛刻，体外培养时间长达 6 周以上[10]，不推荐临床常规做培养进行体外药物敏感性试验了解肺炎支原体耐药性[14]。临床上常通过检测肺炎支原体耐药基因了解耐药性。23rRNA V 区基因位点突变与肺炎支原体对大环内酯类抗菌药物产生耐药性关系密切，其突变导致了此类抗菌药物对核糖体的亲和力降低，阻止细菌蛋白合成的能力下降，从而导致了大环内酯－林可酰胺－链阳菌素 B (MLSB)样耐药发生[15]。14 元环大环内酯类抗菌药物与核糖体的结合位点为 23S rRNA V 区上的第 2063、2064、2607、2611 等位点；而 15 元环、16 元环大环内酯类抗菌药物结合位点为 23S rRNA V 区上的 2062、2063、2064、2616 及 2607 位点[16] [17]。在肺炎支原体临床分离大环内酯类耐药株中，23rRNA V 区 A2063G 突变占主导地位，少数发生 A2064G 突变。A2063G/A2064G 基因位点突变是产生耐药性的主要机制[15] [18]。

3. 有效性及安全性

作用于核糖体抑制细菌蛋白质合成的药物(如大环内酯类、四环素类)或抑制 DNA 复制的药物(如氟喹诺酮类)对肺炎支原体具有抑菌或杀菌活性[19]。A2063G/A2064G 点突变菌株表现出对大环内酯抗菌药物不同程度耐药，但对氟喹诺酮类和四环素类仍敏感[3]。近年来，喹诺酮类和四环素类药物已逐渐用于治疗对大环内酯类抗菌药物耐药的肺炎支原体肺炎患儿。Ahn, J.等[20]纳入三项随机对照试验和五项前瞻性观察研究，比较大环内酯类一线抗菌药物和二线抗菌药物对耐大环内酯类肺炎支原体肺炎的治疗反应，发现四环素类药物可以缩短发热持续时间和住院时间，在开始治疗后 24、48 和 72 小时实现快速退热；而氟喹诺酮类抗菌药物可在治疗 48 小时内实现退热。48 小时内米诺环素可能较妥舒沙星能更有效退热、降低 MP-DNA 拷贝数，但尚无足够的证据确定四环素优于氟喹诺酮[20] [21]。这种差异可能与米诺环素的血药浓度较高，半衰期较长，对肺组织和支气管粘膜的渗透程度更高有关[22]。虽然氟喹诺酮类和四环素类药物通常不推荐用于儿童，但在新的针对大环内酯类抗菌药物耐药菌株的有效药物问世前，它们可能是唯一可行的选择。

3.1. 氟喹诺酮类

氟喹诺酮类是第三代喹诺酮类抗菌药物，主要通过抑制拓扑异构酶Ⅳ和 DNA 回旋酶，导致肺炎支原体无法繁殖及正常合成蛋白质，进而起到杀菌作用[23]。氟喹诺酮类药物具有良好药代动力学特征，口服给药吸收良好，并在体内分布广泛。左氧氟沙星又被称为呼吸氟喹诺酮类药物，对肺炎链球菌和肺炎支原体等呼吸道病原体具有更强抗菌活性。环丙沙星不如其他氟喹诺酮类药物如左氧氟沙星和妥舒沙星有效，但其软骨毒性目前被认为是氟喹诺酮类药物中最低的[24]。在大环内酯类抗菌药物耐药的儿童病例中，将大环内酯类抗菌药物替换为左氧氟沙星后，发热和咳嗽能迅速缓解[25] [26]。左氧氟沙星推荐用法：<5 岁，8~10 mg/kg·d (每天不超过 750 毫克)，q12h；>5 岁，8~10 mg/kg，qd，静脉或口服给药，总疗程 7~10 天[26]。与克拉霉素或阿奇霉素相比，妥舒沙星在 48 小时内退热更有效[22] [27]。

由于存在潜在肌肉骨骼毒性风险，18 岁以下儿童使用氟喹诺酮类抗菌药物相对禁忌，氟喹诺酮类抗菌药物在儿童中的使用通常仅限于特定适应症[28]。基于对幼年动物的一项研究表明，氟喹诺酮类药物会导致承重关节发生侵蚀性关节病[29]。然而，在动物实验中，喹诺酮类药物的软骨毒性与实验动物的类型和喹诺酮类抗菌药物剂量有关，这些药物剂量是儿童正常剂量的 10~30 倍[30]。氟喹诺酮类抗菌药物在

人体内的安全性数据有限，但一些临床试验数据表明，氟喹诺酮类药物在儿童骨骼和关节中引起的不良事件发生率较低，这些不良反应在停药后可以逆转[31] [32] [33]。因此，氟喹诺酮类抗菌药物可能是治疗耐大环内酯类抗菌药物肺炎支原体感染的合适选择。

3.2. 四环素类

四环素类抗菌药物通过与核糖体复合体结合，可逆地抑制细菌蛋白质合成，被认为是抑菌药物，但在高浓度时可能具有杀菌作用[34]。多西环素和米诺环素是第二代四环素类抗菌药物，属于广谱抗菌药物，均表现出良好生物利用度和耐受性。到目前为止，还没有关于肺炎支原体对四环素类抗菌药物自然产生耐药性的报道。出于对有效性与安全性考虑，有学者建议将多西环素作为治疗大环内酯类抗菌药物耐药MPP的首选药物[24]。多西环素的推进剂量为每次4 mg/Kg，bid。多西环素、米诺环素在儿童大环内酯类抗菌药物治疗失败后显示出良好疗效。Kawai等研究表明，米诺环素或多西环素治疗组48小时内的退热率显著高于大环内酯组(90% vs 46.1%) [21]。在一项比较治疗后48小时内退热率和DNA载量下降程度的研究中，米诺环素也优于大环内酯类[35]。

根据接受第一代四环素治疗的儿童出现永久性牙齿变色和牙釉质发育不良的报告，四环素仅推荐用于≥8 岁儿童[36]。但在建议剂量和疗程内，新一代四环素如多西环素和米诺环素并未显示会导致牙齿永久染色[37]。美国儿科学会建议所有年龄段儿童中使用多西环素治疗时间 ≤ 21 天，因为多西环素与钙的结合不像其他四环素那样强烈，与短疗程相关的牙色变的风险很小[20]。因此，新一代四环素可能是治疗≥8 岁儿童耐药肺炎支原体感染的首选药物。

4. 抗菌药物选择时机

肺炎支原体肺炎患儿临床病程主要决定因素是临床症状及肺部病变严重程度，而不是大环内酯类耐药性。在决定使用哪种抗菌药物治疗耐大环内酯类肺炎支原体肺炎时，临床医生必须权衡二线抗肺炎支原体药物的疗效和安全性。在大环内酯类药物耐药率较高的地区，大环内酯类抗菌药物可能不适于经验性治疗，因此，需要四环素类和氟喹诺酮类等抗菌药物作为替代药物。然而，由于四环素和氟喹诺酮类药物的安全性问题，即使在对大环内酯类抗菌药物有很高耐药性的地区，选择二线抗肺炎支原体药物也应充分权衡利弊。日本在大环内酯类抗菌药物耐药率超过80%时，指南仍推荐将大环内酯类抗菌药物作为一线抗肺炎支原体的药物[38]。目前国外学者仍建议将大环内酯类抗菌药物作为肺炎支原体感染患者的一线治疗药物，但治疗48~72小时后若发热仍未消退，建议更换抗肺炎支原体的药物[4] [19]。

到目前为止尚无四环素类或氟喹诺酮类抗菌药物对肺炎支原体的获得性耐药报道。然而，已在体外筛选出对这两类抗菌药物耐药的肺炎支原体菌株，并在突变体中进行了靶向突变[39]。因此，使用不当可能会导致耐药性出现，尤其是氟喹诺酮类药物。

5. 总结

对大环内酯类抗菌药物治疗失败的耐大环内酯类肺炎支原体肺炎患儿，氟喹诺酮类和四环素类药物能迅速退热及改善临床症状，降低MP-DNA载量，可作为治疗儿童MRMP感染的二线药物。然而，现有研究的样本量较少，二线药物在儿童中使用的安全性尚未确定，因此在使用时需进行密切监测。

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