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# 阿奇霉素与甘草锌联合治疗对支原体肺炎患儿炎症反应程度及免疫应答功能的影响

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**[摘要]** **目的:**探讨阿奇霉素与甘草锌联合治疗方案对支原体肺炎患儿炎症反应程度及免疫应答功能的影响。**方法:**收集2014年1月~2017年1月间在本院接受治疗的肺炎支原体患儿150例,按照随机数表法分为对照组、观察组,各75例。对照组患儿接受阿奇霉素治疗,观察组患儿接受阿奇霉素与甘草锌联合治疗,均持续14 d,对比两组患儿治疗前后血清中炎症因子、Th17/Treg细胞因子、免疫球蛋白含量的差异。**结果:**治疗前,两组患儿血清中炎症因子、Th17/Treg细胞因子、免疫球蛋白含量的差异无统计学意义( $P>0.05$ )。治疗后,观察组患儿血清中炎症因子白介素(IL)-6、IL-12、IL-13、单核细胞趋化蛋白-4(MCP-4)的含量低于对照组患儿( $P<0.05$ );血清中Th17/Treg细胞因子IL-17、IL-25的含量低于对照组患者,IL-10、IL-35的含量高于对照组患者( $P<0.05$ );血清中免疫球蛋白免疫球蛋白(Ig)A、IgG、IgM的含量高于对照组患儿( $P<0.05$ )。**结论:**阿奇霉素与甘草锌联合治疗可有效降低支原体肺炎患儿的全身炎症反应,优化免疫功能。

**[关键词]** 支原体肺炎;阿奇霉素;甘草锌;炎症反应;免疫应答

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## Effect of azithromycin combined with licorzinc therapy on inflammatory response and immune response in children with mycoplasma pneumonia

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**View from specialist: It is creative, and of certain scientific and educational value.**

**[ABSTRACT]** **Objective:** To study the effect of azithromycin combined with licorzinc therapy on inflammatory response and immune response in children with mycoplasma pneumonia. **Methods:** A total of 150 children with mycoplasma pneumonia who were treated in our hospital between January 2014 and January 2017 were collected and divided into control group and observation group according to the random number table, with 75 cases in each group. Control group received azithromycin therapy while observation group received azithromycin combined with licorzinc therapy, and both therapies lasted for 14 days. The differences in serum levels of inflammatory factors, Th17/Treg cytokines and immunoglobulin were compared between the two groups before and after treatment. **Results:** Before treatment, differences in serum levels of inflammatory factors, Th17/Treg cytokines and immunoglobulin were not statistically significant between two groups of patients ( $P>0.05$ ). After treatment, serum inflammatory factors IL-6, IL-12, IL-13 and MCP-4 levels of observation group were significantly lower than those of control group ( $P<0.05$ ); serum Th17/Treg cytokines IL-17 and IL-25 levels were significantly lower than those of control group ( $P<0.05$ ) while IL-10 and IL-35 levels were significantly higher than those of control group ( $P<0.05$ ); serum immunoglobulin IgA, IgG and IgM levels were significantly higher than those of control group ( $P<0.05$ ). **Conclusions:** Azithromy-

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cin combined with licorzinc therapy can effectively reduce systemic inflammatory response and optimize immune function in children with mycoplasma pneumonia.

[KEY WORDS] Mycoplasma pneumonia; Azithromycin; licorzinc; Inflammatory response; Immune response

支原体肺炎是小儿最常见的肺部感染性疾病,呈间质性肺炎及毛细支气管炎样改变,临床表现以顽固性剧烈咳嗽为主,若不及时治疗可导致心血管系统、神经系统、消化系统等重要脏器并发症<sup>[1,2]</sup>。阿奇霉素是支原体肺炎治疗的首选抗生素,属于第二代大环内酯类药物,较多实验证实有助于支原体肺炎患儿病情的控制,但是部分患者仍出现病情进展,可能与机体微量元素锌等缺乏相关<sup>[3,4]</sup>。甘草锌可促进黏液分泌及上皮细胞更新,在溃疡及创伤性疾病的治疗中获得成功应用<sup>[5]</sup>,有学者推荐将其用于支原体肺炎患儿的辅助治疗,但目前相关研究开展不多。本次研究将阿奇霉素联合甘草锌用于支原体肺炎患儿的治疗,从全身炎症反应及免疫功能等方面进行对其作用进行探讨。

## 1 资料与方法

### 1.1 病例资料

选取2014年1月~2017年1月间在本院接受治疗的肺炎支原体患儿150例作为研究对象,患儿家属签署知情同意书。按照随机数表法将入组患儿分为对照组、观察组,各75例,对照组中男性40例、女性35例,年龄1~7岁;观察组中男性38例、女性37例,年龄1~9岁。两组患儿的性别、年龄分布无显著差异( $P>0.05$ ),具有可比性,研究获医院伦理委员会批准。

### 1.2 入组及排除标准

入组标准:(1)根据临床表现、实验室检查结果及影像学结果,确诊支原体肺炎;(2)入院前6个月内无肺炎病史;(3)全程完成治疗及相关检查。排除标准:(1)合并严重先天性疾患;(2)入院前自主应用抗生素或其他治疗;(3)阿奇霉素、甘草锌过敏。

### 1.3 治疗方案

对照组患儿接受常规阿奇霉素治疗,具体如下:乳糖酸阿奇霉素针(浙江震元制药有限公司,国药准字H20020257)  $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ,连续治疗3~5 d,其后停药4 d,再治疗3 d,持续治疗14 d。观察组患儿接受阿奇霉素联合甘草锌治疗,具体如下:甘草锌颗粒(山东达因海洋生物制药股份有限公司,国药准字H19993277)口服,  $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ,分两次服用,单次最大剂量20 mg,持续治疗14 d。阿奇霉素用法用量同对照组患儿。

### 1.4 观察指标

治疗前、治疗14 d后,均抽取两组患儿的外周静脉血3~5 mL,抗凝后室温静置分层,3 500 r/min离心取上层血清,冻存于 $-70^\circ\text{C}$ 冰箱中备用。采用酶联免疫吸附法(ELISA)检测血清中炎症因子白介素-6(IL-6)、白介素-12(IL-12)、白介素-13(IL-13)、单核细胞趋化蛋白-4(MCP-4)的含量。采用ELISA检测血清中Th17/Treg细胞因子的含量,包括Th17细胞因子白介素-17(IL-17)、白介素-25(IL-25),Treg细胞因子白介素-10(IL-10)、白介素-35(IL-35)。

采用放射免疫法检测血清中免疫球蛋白A(IgA)、免疫球蛋白G(IgG)、免疫球蛋白M(IgM)的含量。

### 1.5 统计学处理

统计数据由专业人员进行记录、计算,软件选择SPSS20.0。炎症因子、Th17/Treg细胞因子、免疫球蛋白等计量资料以均数±标准差表示,比较采用 $t$ 检验。 $P<0.05$ 作为差异有统计学意义的标准。

## 2 结果

### 2.1 炎症因子

治疗前及治疗14 d后,两组患儿血清中炎症因子IL-6、IL-12、IL-13、MCP-4含量的比较如下:两组患儿治疗前血清中IL-6、IL-12、IL-13、MCP-4的含量无显著性差异( $P>0.05$ );与治疗前比较,两组患儿治疗后血清中IL-6、IL-12、IL-13、MCP-4的含量均显著降低,且观察组患儿治疗后血清中IL-6、IL-12、IL-13、MCP-4的含量低于对照组患儿,差异有统计学意义( $P<0.05$ )。见表1。

表1 两组患儿治疗前后血清中炎症因子含量的比较( $n=75$ ,pg/mL, $\bar{x}\pm s$ )

| 组别  | 时间     | IL-6          | IL-12         | IL-13        | MCP-4         |
|-----|--------|---------------|---------------|--------------|---------------|
| 对照组 | 治疗前    | 84.29±9.17    | 73.17±8.94    | 27.38±4.11   | 79.27±9.61    |
|     | 治疗14 d | 52.76±6.34*   | 40.85±5.12*   | 15.19±2.32*  | 43.28±5.62*   |
| 观察组 | 治疗前    | 83.76±9.42    | 72.53±8.61    | 27.19±4.07   | 79.64±9.53    |
|     | 治疗14 d | 29.51±4.38* # | 23.64±4.28* # | 6.38±0.79* # | 17.28±2.17* # |

注:与组内治疗前比较,\* $P<0.05$ ;与对照组治疗14 d比较,# $P<0.05$ 。

### 2.2 Th17/Treg细胞因子

治疗前及治疗14 d后,两组患儿血清中Th17/Treg细胞因子IL-17、IL-25、IL-10、IL-35含量的比较如下:两组患儿治疗前血清中IL-17、IL-25、IL-10、IL-35的含量无显著性差异( $P>0.05$ );与治疗前比较,两组患儿治疗后血清中IL-17、IL-25的含量均显著降低,IL-10、IL-35的含量显著升高,且观察组患儿治疗后血清中IL-17、IL-25的含量低于对照组患者,IL-10、IL-35的含量高于对照组患者,差异有统计学意义( $P<0.05$ )。见表2。

表2 两组患儿治疗前后血清中Th17/Treg细胞因子含量的比较( $n=75$ , $\bar{x}\pm s$ )

| 组别  | 时间     | IL-17         | IL-25         | IL-10         | IL-35         |
|-----|--------|---------------|---------------|---------------|---------------|
| 对照组 | 治疗前    | 62.18±7.95    | 46.74±5.09    | 17.29±2.71    | 11.27±1.83    |
|     | 治疗14 d | 40.26±5.34*   | 29.65±3.41*   | 24.18±3.25*   | 17.64±2.29*   |
| 观察组 | 治疗前    | 62.62±7.89    | 45.62±5.16    | 17.34±2.61    | 11.31±1.95    |
|     | 治疗14 d | 23.18±4.56* # | 17.34±2.19* # | 35.67±4.59* # | 31.55±4.68* # |

注:与组内治疗前比较,\* $P<0.05$ ;与对照组治疗14 d比较,# $P<0.05$ 。

### 2.3 免疫球蛋白

治疗前及治疗14 d后,两组患儿血清中免疫球蛋白IgA、IgG、IgM含量的比较如下:两组患儿治疗前血清中IgA、IgG、IgM的含量无显著性差异( $P>0.05$ );与治疗前比较,两组患儿治疗后血清中IgA、IgG、IgM的含量均显著升高,且观察组患儿治疗后血清中IgA、IgG、IgM的含量高于对照组患儿,差异有统计学意义( $P<0.05$ )。见表3。

表3 两组患儿治疗前后血清中免疫球蛋白含量的比较( $n=75$ , g/L,  $\bar{x}\pm s$ )

| 组别  | 时间      | IgA          | IgG           | IgM          |
|-----|---------|--------------|---------------|--------------|
| 对照组 | 治疗前     | 1.42±0.17    | 13.28±1.79    | 1.41±0.17    |
|     | 治疗 14 d | 1.89±0.25*   | 19.76±2.48*   | 1.65±0.21*   |
| 观察组 | 治疗前     | 1.43±0.18    | 13.31±1.85    | 1.42±0.16    |
|     | 治疗 14 d | 2.27±0.34* # | 24.15±3.07* # | 2.27±0.28* # |

注:与组内治疗前比较,\* $P<0.05$ ;与对照组治疗 14 d 比较,# $P<0.05$ 。

### 3 讨论

小儿支原体肺炎的发病率极高,阿奇霉素作为抗支原体的敏感抗生素,目前已经在支原体肺炎治疗中获得成功应用,但单独应用阿奇霉素后部分患者病情仍未得到有效控制,故较多学者推荐联合应用其他作用机制的药物以扩大疗效。最新研究显示,小儿肺炎患儿体内微量元素缺乏概率较高,其中以锌缺乏最常见,锌具有免疫调节剂的作用,明显的锌缺乏可能导致患儿免疫功能下降,并进一步加重支原体感染后的脏器功能损伤<sup>[6,7]</sup>。甘草锌是复方锌制剂,对急性慢性胃溃疡具有一定保护作用,可促进上皮细胞增生及创面愈合,但其在肺炎支原体患儿中的应用效果及作用机制研究目前开展较少。本次研究在肺炎支原体患儿的治疗中联合应用阿奇霉素及甘草锌,探讨联合用药与单独阿奇霉素治疗的效果差异。

肺内局部及全身炎症反应是支原体肺炎的最主要病理改变,炎症反应程度也与患儿病情程度高度一致<sup>[8,9]</sup>。IL-6、IL-12、IL-13 是典型的促炎因子,在支原体感染后早期即可释放增加,并进一步诱导中性粒细胞聚集于感染局部,加重肺内局部炎症<sup>[10,11]</sup>。MCP-4 是来源于单核上皮细胞的促炎因子,可选择性募集 Th2 细胞至炎症部位并引发炎症损伤<sup>[12]</sup>。本次研究首先对比两组患者的治疗前后全身炎症反应程度,发现:与治疗前比较,两组患者治疗后血清中 IL-6、IL-12、IL-13、MCP-4 的含量均较低;进一步与对照组比较,观察组患者治疗后血清中 IL-6、IL-12、IL-13、MCP-4 的含量较低,证实阿奇霉素治疗的基础上加入甘草锌联合治疗,可进一步减轻患儿的全身炎症反应,宏观优化治疗效果。

甘草锌应用后可增加患儿体内微量元素锌含量,较多学者认为可能与其增强患儿体质有关,但具体免疫功能的变化趋势未明。Th17、Treg 细胞是新发现的 T 细胞亚群,Th17 细胞可释放效应性细胞因子 IL-17、IL-25,促进并放大炎症反应<sup>[13,14]</sup>。Treg 细胞具有负性免疫调节作用,通过分泌细胞因子 IL-10、IL-35 而抑制 T 淋巴细胞活化、增殖。支原体肺炎患儿存在 Th17/Treg 失衡,具体表现为 Th17 细胞分泌旺盛及 Treg 细胞合成抑制<sup>[15,16]</sup>。本次研究对比两组患儿治疗前后血清中 Th17/

Treg 细胞因子含量的差异,发现:与治疗前比较,两组患儿治疗后血清中 IL-17、IL-25 的含量较低,IL-10、IL-35 的含量较高;进一步与对照组比较,观察组患者治疗后血清中 IL-17、IL-25 的含量较低,IL-10、IL-35 的含量较高,证实阿奇霉素联合甘草锌治疗可更为有效的抑制 Th17 细胞功能并增加 Treg 细胞合成。

体液免疫功能异常也是导致支原体肺炎发生及病情进展的重要原因,IgA 在机体免疫调节中具有抗菌抗病毒作用;IgM 具有溶菌及较高的抗原结合作用;IgG 在抗感染中发挥主要作用,具有调理吞噬细胞、中和毒素等免疫作用<sup>[17,18]</sup>。支原体肺炎患儿存在不同程度的免疫球蛋白表达减少,且上述免疫球蛋白含量与患儿病情严重程度高度一致。本次研究对比两组患儿血清中免疫球蛋白含量的差异,发现:与治疗前比较,两组患儿治疗后血清中 IgA、IgG、IgM 的含量均增加;进一步与对照组比较,观察组患儿治疗后血清中 IgA、IgG、IgM 的含量较高,证实阿奇霉素联合甘草锌治疗可有效增强患儿的体液免疫功能。

阿奇霉素联合甘草锌治疗可有效减轻支原体肺炎患儿的全身炎症反应,均衡 Th17/Treg 细胞功能,增强体液免疫功能,是临床支原体肺炎患儿治疗的可靠方法,值得在日后临床实践中推广应用。

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