·临床研究·

老年肺炎继发抗生素相关性腹泻患者临床特征及营养序贯治疗的效果

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【摘 要】 **目的** 探讨老年肺炎继发抗生素相关性腹泻(AAD)患者临床特征并分析营养序贯治疗的效果。**方法** 选取2022年5月至2023年12月北大荒集团建三江医院收治的132例老年肺炎继发AAD患者为AAD组,同期老年肺炎未继发AAD的132例患者为非AAD组,分析继发AAD患者的临床特征及继发AAD的影响因素。将AAD组患者以随机数表法分为观察组(66例)和对照组(66例),对照组接受常规干预,观察组在对照组基础上给予营养序贯治疗,比较两组患者腹泻停止时间及治疗前后外周血T淋巴细胞亚群水平。采用SPSS 22.0统计软件进行数据分析。根据数据类型,分别采用t检验或χ^2检验进行比较。采用多因素logistic回归模型分析影响老年肺炎患者继发AAD的相关因素。**结果** AAD组患者腹泻症状出现于抗生素应用后3~17(7.72±2.21)d。AAD组患者年龄≥80岁、重症肺炎、侵袭性操作、使用抗生素种类≥3种、抗生素使用时间≥7 d、禁食占比高于非AAD组,差异有统计学意义(P<0.05)。观察组腹泻停止时间短于对照组,两组治疗后白细胞分化抗原(CD)3$^+$、CD4$^+$水平较治疗前升高,且观察组高于对照组;CD8$^+$均较治疗前降低,且观察组低于对照组,差异有统计学意义(P<0.05)。多因素logistic回归分析显示,年龄≥80岁(OR=2.643,95%CI 1.486~4.703)、重症肺炎(OR=2.147,95%CI 1.238~3.724)、侵袭性操作(OR=1.931,95%CI 1.056~3.531)、抗生素使用时间≥7 d(OR=2.210,95%CI 1.269~3.848)及禁食(OR=1.804,95%CI 1.034~3.148)均为AAD发生的独立危险因素(P<0.05)。**结论** 年龄≥80岁、重症肺炎、侵袭性操作、抗生素使用时间≥7 d及禁食均为AAD发生的高危因素,营养序贯治疗可改善患者免疫功能,促进病情恢复。

【关键词】 老年人;肺炎;抗生素相关性腹泻;营养序贯
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Clinical characteristics of antibiotic-associated diarrhea secondary to pneumonia in elderly patients and efficacy of nutritional sequential therapy

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【**Abstract**】 **Objective** To explore the characteristics of elderly patients with antibiotic-associated diarrhea (AAD) secondary to pneumonia and analyze the efficacy of nutritional sequential therapy. **Methods** A total of 132 elderly patients with AAD secondary to pneumonia admitted in our hospital from May 2022 to December 2023 were enrolled as AAD group, and another 132 pneumonia patients without secondary AAD were included and served as non-AAD group. Clinical characteristics of secondary AAD and its influencing factors were analyzed. The patients in the AAD group were randomly divided into observation subgroup (66 cases) and control subgroup (66 cases). The control subgroup received routine intervention, while the observation subgroup was given nutritional sequential therapy on the basis of routine intervention. The diarrhea stopping time and levels of peripheral blood T lymphocyte subsets before and after treatment were compared between the two subgroups. SPSS statistics 22.0 was used for data analysis. Depending on data type, t test or *Chi*-square test was performed for comparison. Multivariate logistic regression analysis was employed to identify the related factors affecting secondary AAD in elderly patients with pneumonia. **Results** The diarrhea symptom of the AAD group appeared 3-17 (7.72±2.21) d after the application of antibiotics. The AAD group had significantly larger proportions of age ≥80 years, severe pneumonia, invasive procedures, use of antibiotics ≥3 types, time of antibiotics ≥7 d, and fasting than the non-AAD group (P<0.05). The diarrhea stopping time was obviously shorter in the observation subgroup than the control subgroup (P<0.05). After treatment, the percentages of cluster of differentiation (CD)3$^+$and CD4$^+$ cells were notably risen while that of CD8$^+$ cells was reduced in both subgroups, and the percentages of former cells were higher and that of the latter cells was lower in the observation subgroup than the control subgroup (P<0.05). Multivariate logistic regression analysis showed that age ≥80 years (OR=2.643, 95%CI 1.486-4.703), severe pneumonia (OR=2.147, 95%CI 1.238-3.724), invasive procedure (OR=1.931, 95%CI 1.056-3.531), time of antibiotic use ≥7 d (OR=2.210, 95%CI

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1.269-3.848) and fasting (*OR* = 1.804, 95% *CI* 1.034-3.148) were independent risk factors for secondary AAD occurrence ($P<0.05$). **Conclusion** Age ≥80 years, severe pneumonia, invasive procedure, time of antibiotic use ≥7 d and fasting are high risk factors for secondary AAD. Nutritional sequential therapy can improve the immune function and promote the recovery in the patients.

【Key words】 aged; pneumonia; antibiotic-associated diarrhea; sequential nutrition

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抗生素相关性腹泻(antibiotic-associated diarrhea, AAD)是指在使用抗生素治疗过程中或治疗结束后发生的、其他原因无法解释的腹泻,AAD 的发生不仅影响抗生素治疗的有效性,还可能延长康复进程,严重者甚至可能引发败血症或死亡[1]。随着抗生素的广泛使用,AAD 的发生率呈上升趋势,老年患者由于胃肠道屏障功能下降,在接受抗生素治疗时更易发生肠道菌群失衡,从而更容易发生 AAD[2]。目前,已有研究针对 AAD 的临床特征及危险因素进行探讨,但目前尚无统一结论[3]。部分 AAD 患者症状较轻,可通过停用抗生素、服用微生态制剂改善,但对于肺炎继发的 AAD 患者,通常不允许停用抗生素,因此需在调节抗生素剂量、种类的基础上予以营养干预,改善肠道微环境,增强免疫功能。营养序贯治疗通过提供循序渐进式营养支持,在改善机体营养状态、免疫功能的同时,逐步恢复肠道屏障功能[4]。本研究旨在分析老年肺炎继发 AAD 患者的临床特征、危险因素,并评估营养序贯治疗的效果。

1 对象与方法

1.1 研究对象

选取 2022 年 5 月至 2023 年 12 月北大荒集团建三江医院收治的 132 例老年肺炎继发 AAD 患者为 AAD 组。纳入标准:(1)年龄≥60 岁;(2)符合肺炎诊断标准[5]并接受抗生素治疗;(3)符合 AAD 诊断标准[6],即使用抗生素后首次出现腹泻症状,急性腹泻≥3 次/d,持续时间≥48 h,或伴大便性状改变、发热、腹痛或腹部压痛、血白细胞升高,大便涂片检查显示菌群失调或培养发现优势菌(排除急性肠炎、饮食不当等其他因素引起的腹泻);(4)依从性良好,自愿配合相关治疗。排除标准:(1)合并严重基础疾病(如晚期肿瘤、严重心肝肾功能不全等);(2)慢性腹泻或患有肠炎等其他胃肠道疾病;(3)腹泻症状出现前 3 d 内有不当饮食或服用过泻药;(4)长期使用免疫抑制剂或糖皮质激素;(5)未配合完成治疗、检查及随访,临床资料不完整。另选取同期老年肺炎未继发 AAD 的 132 例患者,纳入非 AAD 组。除未发生 AAD 外,其余纳入与排除标准同 AAD 组。本研究获得北大荒集团建三江医院医学伦理委员会批准(批号:2024110209Z),研究对象及家属对研究内容知情并签署知情同意书。

1.2 方法

1.2.1 资料收集 收集患者年龄、性别、肺炎严重程度(是否重症肺炎)、医疗干预措施(是否接受机械通气、中心静脉导管置入等侵袭性操作)、抗生素使用情况(抗生素种类、使用时间)、禁食情况(治疗期间是否曾禁食),记录 AAD 临床表现。

1.2.2 AAD 组患者治疗方法 根据随机数表法将 AAD 组患者分为观察组(66 例)和对照组(66 例)。观察组中男性 33 例,女性 33 例;年龄(75.05±8.43)岁;高血压 43 例,糖尿病 32 例,吸烟史 32 例。对照组中男性 39 例,女性 27 例;年龄(74.29±7.79)岁;高血压 42 例,糖尿病 28 例,吸烟史 24 例,两组患者基线资料比较,差异均无统计学意义($P>0.05$)。对照组予以对症支持治疗,如退热、止泻、纠正水电解质紊乱和酸碱平衡失调等,视患者病情及病原学检查结果调整抗生素种类和剂量,优先选择窄谱抗生素,另予以复方嗜酸乳杆菌片(通化金马药业,H10940114)口服,1 g/次,3 次/d。观察组在对照组基础上予以肠内营养序贯治疗:起始阶段予以百普素(德国 Milupa GmbH,H20170170),起始泵注速率为 20 ml/h,观察患者耐受情况,若无明显不适,逐步增加泵注速率至 100 ml/h,初始营养密度为 2.5 kJ/ml,可根据患者耐受性调整至 3.2 kJ/ml,持续 3 d;3 d 后改为能全素(德国 Milupa GmbH,H20170172),起始剂量为每日总能量需求的 40%,如无不良反应,逐步增加至 100% 能量供给,营养液密度同样为 3.2 kJ/ml,泵注速率维持在 100 ml/h。持续治疗 2 周。

1.2.3 观察指标 (1)腹泻停止时间;(2)治疗前后采用流式细胞仪检测外周血 T 淋巴细胞亚群中白细胞分化抗原(cluster of differentiation, CD)3^+、$CD4^+$、$CD8^+$水平。

1.3 统计学处理

采用 SPSS 22.0 统计软件进行数据处理。计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验。计数资料以例数(百分率)表示,组间比较采用 χ^2 检验。采用多因素 logistic 回归模型分析影响老年肺炎患者继发 AAD 的相关因素。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 AAD组与非AAD组患者临床资料

AAD组患者腹泻症状出现于抗生素应用后3~17(7.72±2.21)d,主要临床表现为每日3次以上稀便或水样便,其中13例(9.85%)伴有黏液便或血便,87例(65.91%)伴有腹痛,92例(69.70%)出现发热,40例(30.30%)出现恶心呕吐。AAD组患者年龄≥80岁、重症肺炎、侵袭性操作、使用抗生素种类≥3种、抗生素使用时间≥7 d、禁食占比高于非AAD组,差异有统计学意义(P<0.05;表1)。

表1 AAD组与非AAD组患者临床资料比较

Table 1 Comparison of general data between AAD group and Non-AAD group [n=132, n(%)]

Item	AAD group	Non-AAD group	χ^2/t	P value
Age			20.772	<0.001
≥80 years	82(62.12)	45(34.09)		
<80 years	50(37.88)	87(65.91)		
Gender			0.061	0.805
Male	72(54.55)	70(53.03)		
Female	60(45.45)	62(46.97)		
Hypertension	85(64.39)	79(59.85)	0.580	0.447
Diabetes mellitus	60(45.45)	55(41.67)	1.558	0.212
Smoking	56(42.42)	49(37.12)	0.775	0.379
Severe pneumonia	57(43.18)	34(25.76)	8.871	0.003
Invasive procedures	39(29.55)	22(16.67)	6.161	0.013
Number of antibiotics used			4.991	0.025
≥3 types	31(23.48)	17(12.88)		
<3 types	101(76.52)	115(87.12)		
Duration of antibiotic use			10.800	0.001
≥7 d	94(71.21)	68(51.52)		
<7 d	38(28.79)	64(48.48)		
Fasting	42(31.82)	22(16.67)	8.250	0.004

AAD: antibiotic-associated diarrhea.

2.2 老年肺炎患者继发AAD的多因素logistic回归分析

以单因素分析中差异有统计学意义的因素为自变量,是否继发AAD为因变量(是=1,否=0),进行多因素logistic回归分析,结果显示年龄≥80岁、重症肺炎、侵袭性操作、抗生素使用时间≥7 d及禁食均为继发AAD的独立危险因素(P<0.05;表2)。

2.3 观察组与对照组干预效果

观察组腹泻停止时间为(4.28±1.15)d,对照组为(5.12±1.09)d,观察组短于对照组;两组治疗后$CD3^+$、$CD4^+$水平较治疗前升高,且观察组高于对照组;$CD8^+$均较治疗前降低,且观察组低于对照组,差异均有统计学意义(P<0.05;表3)。

3 讨 论

老年患者因免疫功能减退、合并多种基础疾病、长期住院及频繁使用广谱抗生素,是AAD的高发人群[7]。AAD不仅增加了治疗难度,还可引发伪膜性肠炎、肠穿孔及败血症等严重并发症,威胁患者的生命安全[8]。因此,探讨老年肺炎继发AAD的临床特征、危险因素及其有效治疗手段具有重要意义。

本研究中,AAD疾病谱从轻度的稀便、水样便到伴有黏液或血便的严重肠黏膜损伤不等,且发生时间长短不一。长时间使用抗生素(≥7 d)是继发AAD的独立危险因素,分析原因为AAD的发生与抗生素对肠道菌群的破坏密切相关,广谱抗生素如头孢菌素类、喹诺酮类和大环内酯类可破坏肠道菌群平衡,使有益菌减少,致病菌大量繁殖,破坏肠道黏膜屏障,使细菌毒素更容易进入血液,引发免疫反应[9]。此外,本研究结果显示年龄≥80岁、重症肺炎、

表2 老年肺炎患者继发AAD的多因素logistic回归分析

Table 2 Multivariate logistic regression analysis of AAD in elderly pneumonia patients

Factor	β	SE	$Wald\ \chi^2$	OR	P value	95%CI
Age≥80 years	0.972	0.294	10.930	2.643	0.001	1.486-4.703
Severe pneumonia	0.764	0.281	7.392	2.147	0.007	1.238-3.724
Invasive procedures	0.658	0.308	4.564	1.931	0.033	1.056-3.531
Number of antibiotics used ≥3 types	0.811	0.416	3.801	2.250	0.052	0.996-5.085
Duration of antibiotic use ≥7 d	0.793	0.283	7.852	2.210	0.005	1.269-3.848
Fasting	0.590	0.284	4.316	1.804	0.038	1.034-3.148

AAD: antibiotic-associated diarrhea.

表3 两组患者治疗前后外周血T淋巴细胞亚群水平比较

Table 3 Comparison of peripheral blood T lymphocyte subsets levels before and after treatment between two groups

(n=66, %, $\bar{x}\pm s$)

Group	$CD3^+$		$CD4^+$		$CD8^+$	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation	48.29±7.73	65.22±10.07*	30.35±4.17	46.22±5.17*	29.56±4.68	22.09±3.84*
Control	48.01±6.04	54.09±9.27*	30.02±5.82	39.23±4.46*	30.07±4.06	25.80±3.97*
t	1.241	6.606	0.374	8.317	0.669	5.457
P value	0.217	<0.001	0.709	<0.001	0.505	<0.001

Compared with before treatment, * P<0.05.

侵袭性操作及禁食也是继发 AAD 的独立危险因素。年龄≥80 岁的患者继发 AAD 风险增加,可能原因是老年患者免疫功能衰退,对抗生素治疗的耐受性较差,肠道屏障更容易受到破坏,故 AAD 风险增加[10]。重症肺炎患者因病情较为严重,使用抗生素种类多、剂量大、时间久,且常需要进行机械通气、中心静脉置管等侵袭性操作,增加了肠道菌群紊乱和细菌转移的风险[11]。此外,禁食状态下肠道蠕动减慢,肠道菌群的多样性和稳定性受到影响,易导致致病菌增殖,还容易引起肠道黏膜萎缩,削弱黏膜屏障功能,因此禁食不仅影响患者的营养状况,还可能通过改变肠道环境增加 AAD 的发生风险[12]。由此可见,AAD 的发生是多种因素共同作用的结果,对于高龄和重症患者,应视患者病情及病原学检查结果合理选择抗生素,尽量缩短抗生素的使用时间,优先选择窄谱抗生素,并在可能的情况下减少侵袭性操作的频率并及时进行营养支持,避免不必要的禁食,以维护肠道功能和菌群平衡,预防 AAD 发生。

对于已发生 AAD 者,其治疗关键是修复患者肠道屏障及肠道黏膜免疫功能。营养序贯治疗是一种循序渐进的营养支持策略,其基本理念是通过逐步恢复肠道对营养物质的吸收和利用功能,促进肠道屏障功能的修复,从而改善患者的整体营养状况和免疫功能[13]。初期使用易于吸收的短肽型肠内营养剂能够减轻肠道炎症反应,保护肠道黏膜,促进肠黏膜修复;随着患者耐受性提高,逐步提高肠内营养剂浓度和泵注速率,后期过渡到整蛋白型营养剂,提供更全面的营养支持,同时稳定肠道微生态,确保机体功能恢复至最佳状态,在此过程中逐步恢复肠道功能,改善患者的营养状况和免疫功能[14,15]。本研究中,观察组腹泻停止时间短于对照组,且 T 细胞亚群 $CD3^+$、$CD4^+$水平较对照组升高更显著,$CD8^+$水平较对照组下降更显著,证实营养序贯治疗可有效控制腹泻、恢复免疫功能。

综上,高龄、重症肺炎、侵袭性操作、抗生素使用时间长及禁食均为老年肺炎患者继发 AAD 的危险因素,营养序贯治疗有助于缓解腹泻症状,增强免疫功能,为有效治疗措施。本研究的不足之处为样本量有限,缺乏长期随访,未来可开展多中心、大样本、前瞻性研究并延长随访时间,以验证研究结论。

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