

• 论著 •

大承气汤能够通过调节肠道微生物群抑制轻症急性胰腺炎患者炎症反应并促进胃肠功能恢复

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【摘要】目的 探讨大承气汤对轻症急性胰腺炎(MAP)患者的疗效及其治疗机制。**方法** 采用平行分组随机对照研究方法,选择2018年3月至2021年2月上海市中西医结合医院收治的68例急性胰腺炎(AP)患者。结合患者入院时病情及是否同意使用大承气汤,按照1:1等量随机原则分为常规治疗组和大承气汤组;同时招募20例健康志愿者作为对照。两组患者均予以奥曲肽+禁食、胃肠减压、解热镇痛、抗炎、抑制胃酸和胰液分泌、维持电解质平衡等常规西医治疗;大承气汤组在常规治疗基础上口服大承气汤,每次100mL,每日2次,连续观察7d。记录患者治疗前后炎症指标(白细胞计数(WBC)、C-反应蛋白(CRP)、降钙素原(PCT)、白细胞介素-6(IL-6))和胃肠功能恢复时间(首次排气时间、恢复肠鸣音时间、首次排便时间),并对粪便样本进行16S rRNA基因测序,对经质量控制等相关处理后获得的归一化数据进行多样性分析(Alpha多样性和Beta多样性)及线性判别分析效应量分析(LFSe分析),观察MAP患者肠道微生物区系变化;采用Spearman等级相关系数分析炎症指标与肠道属水平微生物的相关性。治疗期间监测MAP患者血、尿、粪三大常规及肾功能和心电图,以评估安全性。**结果** 68例AP患者中,排除中重症AP患者16例、未收集到标本或自动放弃治疗患者4例,最终48例MAP患者纳入分析,常规治疗组和大承气汤组各24例。两组治疗7d炎症指标均较治疗前明显降低,其中大承气汤组CRP、PCT、IL-6水平显著低于常规治疗组[CRP(mg/L):8.50(3.50, 13.00)比16.00(9.25, 29.75), PCT(μg/L):0.06(0.03, 0.08)比0.09(0.05, 0.11), IL-6(ng/L):6.36(3.96, 10.79)比13.24(6.69, 18.87),均P<0.05];且大承气汤组胃肠功能恢复时间也较常规治疗组明显缩短(首次排气时间(d):1.62±0.65比2.80±0.65,恢复肠鸣音时间(d):1.13±0.58比2.31±0.76,首次排便时间(d):3.12±0.75比4.39±0.76,均P<0.05)。肠道菌群多样性分析显示,无论是微生物群落的多样性还是丰富度,健康对照组均最高,常规治疗组均最低;且健康对照者微生物群落与MAP患者的重合度均较小,而不同治疗方法间MAP患者的重合度相对较大。LFSe分析显示,大承气汤降低了大肠埃希菌-志贺菌属和丹毒梭状芽孢杆菌属的相对丰度,同时提高了乳杆菌属、罗姆布茨菌属、布劳特菌属3个有益菌属的相对丰度;在MAP患者肠道中,黏液乳杆菌属和联合乳杆菌属均明显富集。相关性分析显示,大肠埃希菌-志贺菌属与WBC、CRP、PCT、IL-6这4个炎症指标均呈显著正相关(r值分别为0.31、0.41、0.57、0.43,均P<0.05);其他菌属与炎症指标无明显相关性。治疗过程中,MAP患者血、尿、粪三大常规及肾功能和心电图指标均未见明显异常。**结论** 大承气汤可通过调节MAP患者肠道微生物区系的组成,抑制炎症反应,促进肠道微生态平衡和胃肠功能恢复,改善肠道屏障功能;治疗期间未出现明显的不良反应。

【关键词】 大承气汤; 急性胰腺炎; 肠道菌群; 炎症指标; 胃肠功能

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Dachengqi decoction reduces inflammatory response and promotes recovery of gastrointestinal function in patients with mild acute pancreatitis by regulating the intestinal microbiota

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【Abstract】Objective To explore the therapeutic effect and mechanism of Dachengqi decoction on patients with mild acute pancreatitis (MAP). **Methods** A parallel randomized controlled trial was conducted. Sixty-eight patients with acute pancreatitis (AP) admitted to Shanghai Traditional Chinese Medicine (TCM)-Integrated Hospital from March 2018 to February 2021 were enrolled. Referring to the condition on admission of the patients and whether they agreed to receive the Dachengqi decoction or not, they were divided into conventional treatment group and Dachengqi decoction group according to the principle of 1:1 equal randomness. Meanwhile, 20 healthy volunteers were recruited as controls. Both groups of patients were treated with octreotide, fasting, gastrointestinal decompression, antipyretic

and analgesic, anti-inflammatory, inhibition of gastric acid and pancreatic juice secretion, maintenance of electrolyte balance and other western conventional medicine. The patients in the Dachengqi decoction group received Dachengqi decoction orally on the basis of routine treatment, 100 mL each time, twice a day, for seven consecutive days. The inflammation parameters [white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6)] before and after treatment and the recovery time of gastrointestinal function (first exhaust time, time to recover bowel sounds, first defecation time) of patients were recorded. 16S rRNA gene sequencing of stool samples was recorded, and normalized data were obtained after quality control and other related processing. The data were subjected to diversity analysis (Alpha diversity and Beta diversity) and linear discriminant analysis effect size analysis (LEfSe analysis) to observe changes in the gut microbiota of MAP patients. Spearman rank correlation coefficient was used to analyze the correlation between inflammatory indexes and microorganisms at the intestinal genus level. Blood, urine, stool samples, renal function, and electrocardiogram (ECG) during treatment of MAP patients were detected to assess the safety of the treatment.

Results Of the 68 patients with AP, 16 were excluded from moderate-severe AP, 4 were not collected or voluntarily abandoned treatment. Finally, 48 patients with MAP were enrolled, 24 in the conventional treatment group and 24 in the Dachengqi decoction group. The inflammation parameters levels at 7 days of treatment in both groups were significantly lower than those before treatment. CRP, PCT and IL-6 levels in the Dachengqi decoction group were significantly lower than those in the conventional treatment group [CRP (mg/L): 8.50 (3.50, 13.00) vs. 16.00 (9.25, 29.75), PCT (μ g/L): 0.06 (0.03, 0.08) vs. 0.09 (0.05, 0.11), IL-6 (ng/L): 6.36 (3.96, 10.79) vs. 13.24 (6.69, 18.87), all $P < 0.05$]. The first exhaust time, time to recover bowel sounds and first defecation time in the Dachengqi decoction group were significantly shorter than those in the conventional treatment group [first exhaust time (days): 1.62 ± 0.65 vs. 2.80 ± 0.65 , time to recover bowel sounds (days): 1.13 ± 0.58 vs. 2.31 ± 0.76 , first defecation time (days): 3.12 ± 0.75 vs. 4.39 ± 0.76 , all $P < 0.05$]. The analysis of intestinal microflora diversity showed that both the diversity and abundance of microbial communities were the highest in the healthy control group and the lowest in the conventional treatment group. In addition, the coincidence degree of microbial communities in healthy controls and MAP patients was small, while the coincidence degree of MAP patients among different treatment methods was relatively large. LEfSe analysis showed that Dachengqi decoction reduced the relative abundance of *Escherichia coli*-*Shigella* and *Clostridium erysipelae*, and increased the relative abundance of three beneficial bacteria, namely *Lactobacillus*, *Rombutzia* and *Brutella*. In the intestines of MAP patients, *Lactobacillus mucilaginus* and *Lactobacillus conjunctus* were significantly enriched. Correlation analysis showed that positive correlations between *Escherichia coli*-*Shigella* and the four inflammatory indicators including WBC, CRP, PCT, IL-6 were statistically significant (r value was 0.31, 0.41, 0.57, 0.43, respectively, all $P < 0.05$). There was no significant correlation between other bacteria and inflammatory indicators. During the treatment, there was no obvious abnormality in blood, urine and feces, renal function and ECG of MAP patients.

Conclusions Dachengqi decoction could reduce inflammatory responses and promote recovery of intestinal microecological balance and gastrointestinal function in patients with MAP by regulating the composition of intestinal flora. No significant adverse effects were observed during the treatment period.

【Key words】 Dachengqi decoction; Acute pancreatitis; Intestinal flora; Inflammatory indicator; Gastrointestinal function

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急性胰腺炎(acute pancreatitis, AP)是一种急性炎症性胰腺疾病,由多种病因导致自身胰酶活化出现的胰腺损伤,可引发局部损伤或全身炎症反应综合征(systemic inflammatory response syndrome, SIRS),甚至会出现多器官功能障碍综合征(multiple organ dysfunction syndrome, MODS)^[1]。AP具有发病率高、严重程度不同、重症患者病死率高、医疗费用高的特点^[2]。许多疾病的发生发展或预后过程中均伴有肠道微生物的参与^[3-5]。AP时肠道微生态被打破后出现肠道屏障损伤,过多的肠道菌群(革兰阴性菌)引起胰腺组织坏死和感染^[6]。进一步探究AP患者肠道菌属信息,并予以针对性治疗,可以提前抑制菌群移位,降低炎症反应,减轻肠道损伤,从而维持AP患者肠道微生态平衡。因此,明确AP患者肠道微生物区系组成对于临床治疗具有重要的参考价值。

大承气汤是《伤寒论》的著名方剂之一,也是治疗AP的经典方剂,由大黄、厚朴、枳实、芒硝组成,已在临床治疗中得到广泛认可^[7]。研究证实,大承气汤具有很强的抗炎作用,能够减轻胰腺病理损害,减少肠道毛细血管渗漏,有效缓解肠损伤^[8-9]。引起肠道损伤的重要参与者是肠道菌群和炎症介质,由此我们推测,大承气汤通过调节肠道菌群来抑制炎症介质,改善AP患者的肠道损伤,促进胃肠功能恢复。本研究旨在采用16S rRNA基因测序技术分析轻症急性胰腺炎(mild acute pancreatitis, MAP)患者肠道微生物多样性,并观察大承气汤对肠道微生物的影响;通过分析患者治疗前后炎症水平变化、炎症指标与肠道微生物的相关性,以及胃肠功能恢复情况,探讨大承气汤减轻炎症反应、改善肠道微生态、促进胃肠功能恢复的治疗机制。

1 资料和方法

1.1 研究对象:选择 2018 年 3 月至 2021 年 2 月上海中医药大学附属上海市中西医结合医院收治的 68 例 AP 患者。结合患者入院时病情及是否同意使用大承气汤,按照 1:1 等量随机原则分为常规治疗组和大承气汤组;同时招募 20 例健康志愿者作为对照。本研究是一项单中心平行分组随机对照研究,符合医学伦理学标准,并通过上海市中西医结合医院伦理委员会批准(审批号:2016-015-1),所有患者和健康志愿者均自愿签订知情同意书。

1.1.1 MAP 患者纳入标准:①符合 2012 年亚特兰大 MAP 诊断标准^[10];②符合《急性胰腺炎中医诊疗专家共识意见(2017)》中 AP 脓实热结证的诊断标准^[11];③年龄 18~75 岁;④患者自愿签订知情同意书。

1.1.2 健康对照者纳入标准:①体格检查无异常;②三大常规、血糖、肝肾功能、胸部 CT、腹部 B 超、心电图等无明显异常;③年龄 18~70 岁;④无消化道、心脑血管疾病或其他慢性病史;⑤30 d 内无便秘、腹泻等胃肠病史,也未使用过调节肠道菌群的药物和抗菌药物。

1.1.3 排除标准:①已参与其他研究者;②有手术指征或诊断为中重症或重症 AP 者;③存在严重的基础疾病、慢性病者;④孕妇、精神病患者或对本次试验的药物过敏者。

1.1.4 剔除标准:①依从性差者;②主动放弃治疗者;③治疗期间发生不良事件且无法继续者。

1.2 治疗方法:两组患者均予以常规西医治疗,包括奥曲肽+禁食、胃肠减压、解热镇痛、抗炎、抑制胃酸和胰液分泌、维持电解质平衡等对症治疗,连续观察 7 d;大承气汤组在常规治疗基础上口服大承气汤[由上海市中西医结合医院煎制;药物组成:厚朴 24 g,枳实 12 g,大黄 12 g(后下),芒硝 9 g(溶服)],每次 100 mL,每日 2 次,连续观察 7 d。

1.3 观察指标:MAP 患者于入院当天进行急性生理学与慢性健康状况评分Ⅱ(acute physiology and chronic health evaluation Ⅱ, APACHE Ⅱ);MAP 患者取治疗前和治疗 7 d 空腹静脉血,健康对照者取清晨空腹静脉血,于本院检验科检测炎症指标[包括白细胞计数(white blood cell count, WBC)、C-反应蛋白(C-reactive protein, CRP)、降钙素原(procalcitonin, PCT)、白细胞介素-6(interleukin-6, IL-6)];记录胃肠道功能恢复时间(首次排气时间、恢复肠鸣音时

间、首次排便时间);收集受试者粪便,分析 Alpha 多样性和 Beta 多样性,并进行肠道微生物群的组成分析和相关性分析。

1.4 16S rRNA 基因测序和生物信息学分析:采用 16S rRNA 基因测序检测人类肠道菌群构成。提取粪便标本中的微生物基因组 DNA,以稀释的 DNA 作为模板进行聚合酶链反应(polymerase chain reaction, PCR),用特异性引物(342F-806R)在 16S rRNA 基因 V3+V4 区扩增;构建文库后进行基因测序,使用 vSearch(2.14.1 版)和 Usearch10 软件对原始测序数据进行分析^[12-13]。在切除嵌合序列和质量控制后,使用 UNOISE3 软件对干净的序列进行解析,并将其合并为扩增序列变体(amplicon sequence variant, ASV),将相似度≥97% 的序列聚为一个操作分类单位(operational taxonomic unit, OTU)。采用分类法进行物种注释,最终归一化数据用于下游的数据分析。

通过组间比较分析各单个样本中菌群的 Alpha 多样性(Shannon 指数和 Richness 指数),同时通过主坐标分析(principal co-ordinates analysis, PCoA)进行 Beta 多样性分析(未加权 Unifrac 距离);采用稀释曲线评价样本测序深度;上述结果均采用 R 软件(3.6.3 版本)进行计算并实现可视化。采用线性判别分析效应量(linear discriminant analysis effect size, LEfSe)寻找各组肠道菌群丰富度存在差异的物种,首先采用 Kruskal-Wallis 检验得到差异有统计学意义的物种(即生物标志物),然后采用 Wilcoxon 秩和检验分析各亚种是否处于同一分类水平,最后用线性判别分析(linear discriminant analysis, LDA)分值($\lg \text{LDA} > 2$)筛选生物标志物^[14]。

1.5 不良事件监测:在研究过程中需严格监测不良事件的发生情况。分别于治疗前后检测三大常规、肾功能和心电图,以评估治疗的安全性。

1.6 统计学分析:临床相关数据使用 SPSS 21.0 软件进行统计学分析。符合正态分布的连续变量以均数±标准差($\bar{x} \pm s$)表示,采用 t 检验;不符合正态分布的连续变量以中位数(四分位数)[$M(Q_L, Q_U)$]表示,采用 Wilcoxon 秩和检验及 Kruskal-Wallis 秩和检验。分类变量以频数(百分比)表示,采用 χ^2 检验。MAP 患者的炎症指标、胃肠功能恢复情况均应用 GraphPad Prism 8.3.0 软件进行数据可视化;使用 Spearman 等级相关系数分析炎症指标与 MAP 肠道菌属的相关性,并采用 R 软件(3.6.3 版本)计算后实现可视化。 $P < 0.05$ 被认为差异有统计学意义。

2 结 果

2.1 肠道微生物区系分析:68例AP患者中,排除中重症AP患者16例,未收集到标本或自动放弃治疗患者4例,最终48例MAP患者纳入分析,常规治疗组和大承气汤组各24例。治疗前收集所有MAP患者粪便,治疗后每组随机收集9例患者粪便。最终共收集粪便样本86份,其中MAP患者治疗前粪便样本48份,治疗后粪便样本18份;健康对照组粪便样本20份。

2.1.1 多样性分析

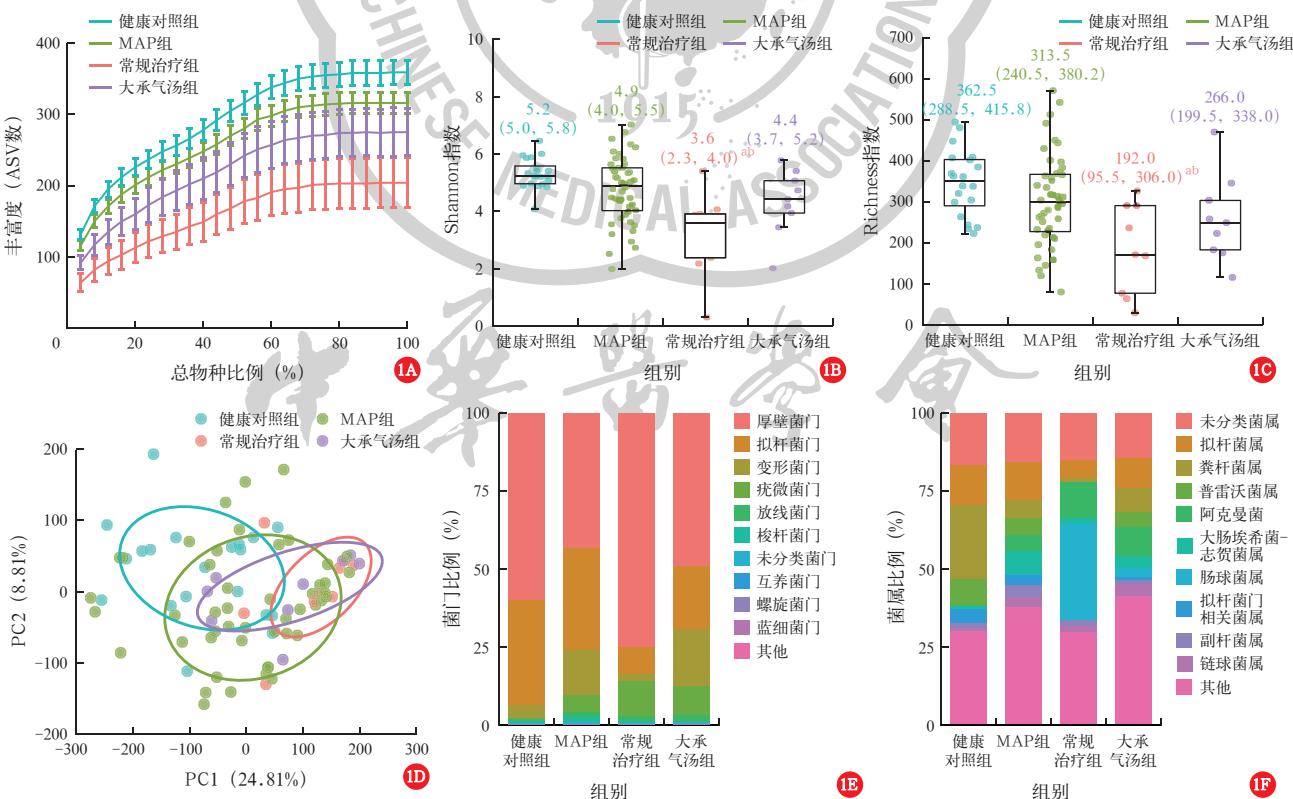
2.1.1.1 Alpha多样性分析:待测肠道菌群稀释曲线(图1A)显示,4条稀释曲线的走势均为先陡峭,随后趋于平缓,表明各组测序深度合理,并已经观察到绝大部分ASV。Shannon指数(图1B)和Richness指数(图1C)分析显示,在群落多样性和丰富度上,健康对照组均最高,常规治疗组均最低;无论是菌群的多样性还是丰富度,健康对照组与常规治疗组患者差异均有统计学意义(均 $P<0.05$)。

2.1.1.2 Beta多样性分析:根据特征丰度表计算样本间的距离,使用未加权Unifrac距离的PCoA分析来

评估肠道微生物群落的相似度。结果显示(图1D),第一组成分解释各组间存在24.81%的差异,第二组成分解释各组间存在8.81%的差异;健康对照组与大承气汤组和常规治疗组的重合度较小,说明组间差异相对较大;MAP组与大承气汤组和常规治疗组的重合度相对较大,说明组间差异相对较小。

2.1.2 肠道菌群组成分析:在门水平上(图1E),各组占比最大的微生物均为厚壁菌门;而在属水平上(图1F),各组占比最大的微生物不同,健康对照组为粪杆菌属,常规治疗组为肠球菌属,MAP组和大承气汤组均为未分类菌属。

使用LEFSe分析进一步得出各组丰富度差异较显著的物种。结果显示(图2),在门水平上,拟杆菌门在健康对照组显著富集;变形菌门在大承气汤组显著富集;厚壁菌门在常规治疗组显著富集。在属水平上,在健康对照组显著富集且影响较大的显著差异物种包括粪杆菌属、普雷沃菌属、拟杆菌属和罗氏菌属;在MAP组显著富集且影响较大的显著差异物种包括大肠埃希菌-志贺菌属和未分类菌属;在大承气汤组显著富集且影响较大的显著差异物种



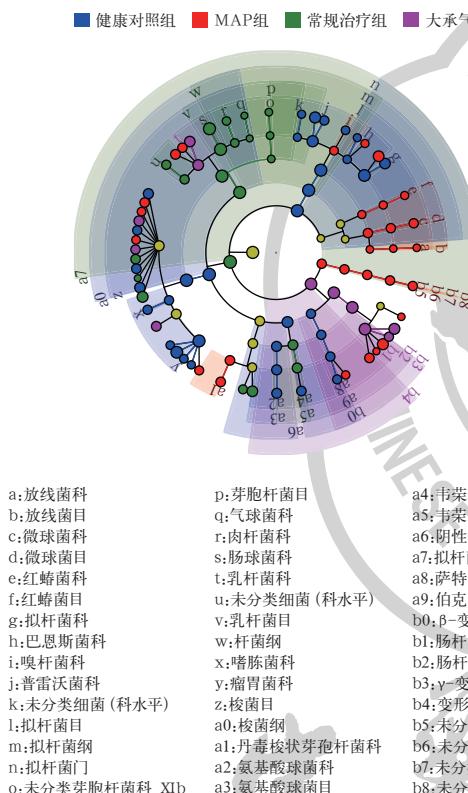
注:A为待测肠道微生物的稀释曲线,提示各组测序深度合理;MAP为轻症急性胰腺炎,ASV为扩增序列变体。B和C分别为肠道微生物Alpha多样性分析[包括多样性(Shannon指数)和丰富度(Richness指数)];与健康对照组比较,^a $P<0.05$;与MAP组比较,^b $P<0.05$ 。D为肠道微生物Beta多样性分析[即主坐标分析(PCoA)],每个点代表一个样本;第一组成分(PC1)解释各组间存在24.81%的差异,第二组成分(PC2)解释各组间存在8.81%的差异。E和F分别为门水平及属水平的肠道微生物区系组成直方图

图1 各组受试者肠道微生物区系多样性及群落组成分析

包括未分类菌属、乳杆菌属、罗姆布茨菌属和布劳特菌属；在常规治疗组显著富集且影响较大的显著差异物种包括肠球菌属和未分类菌属。

2.2 大承气汤疗效分析：常规治疗组与大承气汤组MAP患者性别、年龄、病因及入院时APACHE II评分差异均无统计学意义(均 $P>0.05$ ；表1)。

2.2.1 大承气汤可减轻MAP患者炎症反应(图3)：治疗前两组MAP患者炎症指标差异均无统计学意义(均 $P>0.05$)。治疗7d两组炎症标志物均较治疗前明显降低，且大承气汤组CRP、PCT和IL-6水平降低更为显著(均 $P<0.05$)。



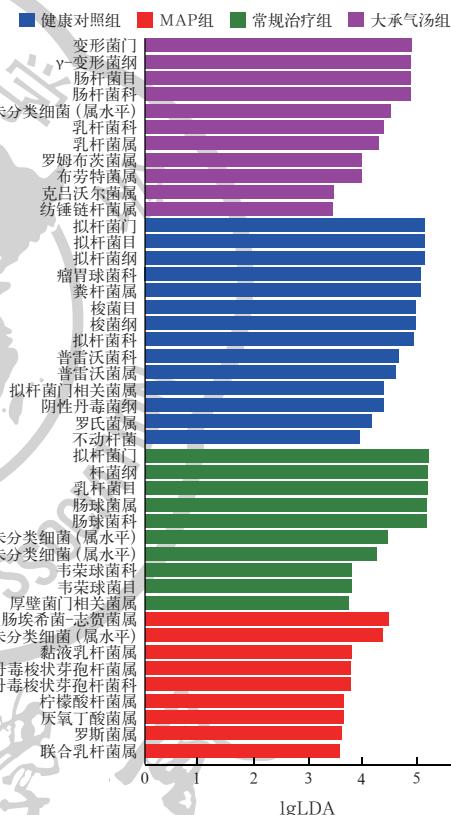
a:放线菌科
b:放线菌目
c:微球菌科
d:微球菌目
e:红蝽菌科
f:红蝽目
g:拟杆菌科
h:巴恩斯菌科
i:拟杆菌科
j:普雷沃菌科
k:未分类细菌(科水平)
l:拟杆菌目
m:拟杆菌纲
n:拟杆菌门
o:未分类芽孢杆菌科_XIb

p:芽孢杆菌目
q:气球菌科
r:肉杆菌科
s:肠球菌科
t:乳杆菌科
u:未分类细菌(科水平)
v:乳杆菌目
w:杆菌纲
x:嗜陈菌科
y:瘤胃菌科
z:梭菌目
a4:韦荣球菌科
a5:韦荣球菌目
a6:阴性丹毒菌纲
a7:拟杆菌门
a8:萨特菌科
a9:伯克菌目
b0: β -变形菌纲
b1:肠杆菌科
b2:肠杆菌目
b3: γ -变形菌纲
b4:变形菌门
b5:未分类细菌(科水平)
b6:未分类细菌(目水平)
b7:未分类细菌(纲水平)
b8:未分类细菌(门水平)

表1 不同治疗方案两组MAP患者一般资料比较

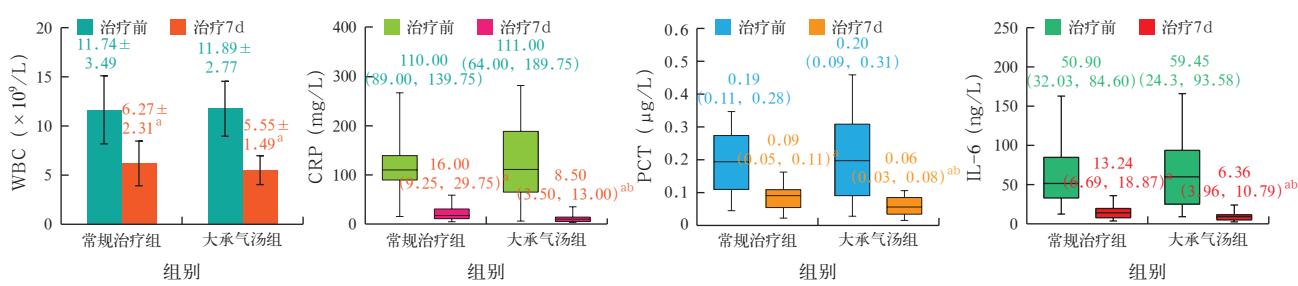
组别	例数(例)		年龄(岁, $\bar{x} \pm s$)	APACHE II评分(分, $\bar{x} \pm s$)
	男性	女性		
常规治疗组	24	13	11	53.13 \pm 14.94
大承气汤组	24	17	7	50.63 \pm 13.50
组别	病因[例(%)]			
	(例)	胆源性	脂源性	酒精性
常规治疗组	24	10(41.7)	6(25.0)	5(20.8)
大承气汤组	24	9(37.5)	6(25.0)	3(12.5)
		4(16.7)	4(16.7)	2(8.3)

注：两组患者均予以常规西医治疗，大承气汤组在常规治疗基础上口服大承气汤；MAP为轻症急性胰腺炎，APACHE II为急性生理学与慢性健康状况评分II



注：MAP为轻症急性胰腺炎，LEFSe为线性判别分析效应量，LDA为线性判别分析

图2 各组受试者肠道菌群特征LEFSe分析的进化分支图(A)及LDA分值柱形图(B)



注：两组患者均予以常规西医治疗，大承气汤组在常规治疗基础上口服大承气汤；MAP为轻症急性胰腺炎，WBC为白细胞计数，CRP为C-反应蛋白，PCT为降钙素原，IL-6为白细胞介素-6；

与本组治疗前比较，^a $P < 0.05$ ；与常规治疗组比较，^b $P < 0.05$

图3 不同治疗方案两组MAP患者治疗前后炎症指标变化比较

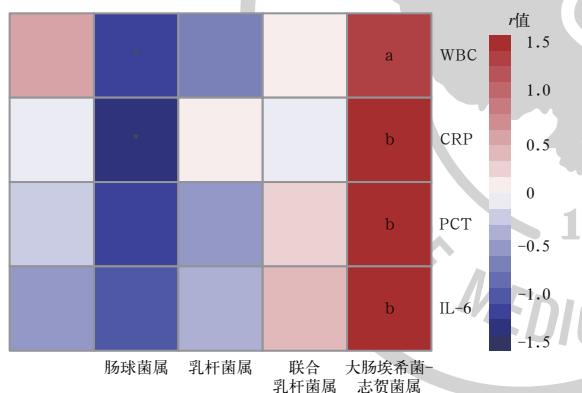
2.2.2 大承气汤能够促进 MAP 患者胃肠功能恢复(表2):大承气汤组胃肠功能恢复时间均较常规治疗组明显缩短(均 $P<0.05$)。

表2 不同治疗方案两组MAP患者
胃肠功能恢复时间比较($\bar{x}\pm s$)

组别	例数 (例)	首次排气 时间(d)	恢复肠鸣音 时间(d)	首次排便 时间(d)
常规治疗组	24	2.80±0.65	2.31±0.76	4.39±0.76
大承气汤组	24	1.62±0.65 ^a	1.13±0.58 ^a	3.12±0.75 ^a

注:两组患者均予以常规西医治疗,大承气汤组在常规治疗基础上口服大承气汤;MAP为轻症急性胰腺炎;与常规治疗组比较, $^aP<0.05$

2.3 炎症指标与肠道微生物的相关性分析(图4):大肠埃希菌-志贺菌属与WBC、CRP、PCT、IL-6这4个炎症指标均呈显著正相关(r 值分别为0.31、0.41、0.57、0.43,均 $P<0.05$);而联合乳杆菌属、乳杆菌属、肠球菌属、双歧杆菌属则与炎症指标均无明显相关性。



注:MAP为轻症急性胰腺炎,WBC为白细胞计数,CRP为C-反应蛋白,PCT为降钙素原,IL-6为白细胞介素-6; $^aP<0.05$, $^bP<0.01$

图4 MAP患者属水平肠道微生物与炎症指标的相关性

2.4 安全性:治疗期间未观察到与大承气汤和奥曲肽有关的严重不良事件,临床指标也无明显异常。

3 讨论

AP的病因多样、病机复杂,是消化系统常见的急腹症之一。本研究MAP患者的病因中胆源性、脂源性和酒精性因素占81.3%,饮食和其他因素占18.7%。AP发生时,胰腺腺泡细胞内溶酶体提前激活酶原,大量活化的胰酶消耗了胰腺自身,受损的胰腺释放大量炎症介质、细胞因子等,引发炎症反应,造成肠道屏障损伤。炎症反应是贯穿AP发生发展的重要病理反应。AP发病后,白细胞在炎症部位聚集,发挥防御和保护作用,WBC是常用炎症指标之一,但不能精确反映AP炎症程度。CRP是一种非

特异性炎症标志物,美国消化学会指南指出,AP患者发病72 h CRP水平更准确^[15],故选用CRP预测AP患者病情严重程度需要对发病时间有严格要求。PCT是一种细菌感染时释放的反应产物,用于观测AP早期全身炎症反应^[16],能可靠、快速评估AP患者感染和预后^[17]。IL-6是一种促炎细胞因子,能区分AP严重分级^[18],提高预测重症AP的准确性^[19]。本研究中大部分MAP患者上述4种炎症指标均明显升高。

人体肠道微生物区系是由多种微生物和多种细胞构成的复杂群落。生理状态下,宿主与肠道菌群共生共存;但AP时,局部炎症损伤释放大量炎症介质导致肠道屏障功能障碍,使肠黏膜通透性增加,肠道细菌移位,出现菌群失调,加重肠道损伤,继发严重并发症^[20]。对于未并发严重并发症和器官功能衰竭的MAP患者,其肠道菌群情况容易被忽略。本研究收集了MAP患者治疗前后的粪便,发现其肠道菌群失调,条件致病菌大肠埃希菌-志贺菌属和肠球菌属过度生长,与前期研究结果一致^[21-23];同时,致病菌丹毒梭状芽孢杆菌属也过度生长。但有趣的是,MAP患者治疗前肠道内黏液乳杆菌属和联合乳杆菌属显著富集,肠道内有益菌可修复肠道屏障损伤,减少细菌移位。对于本研究中有益菌的存在,我们推测可能是因为MAP患者症状较轻,也可能是MAP不会出现全身并发症和器官功能衰竭的关键机制所在。也有研究显示,AP患者肠道微生物群发生变化,其中,致病菌增加,但益生菌乳杆菌相对未受到影响^[24]。

目前针对AP的治疗仍缺乏特异性,仅限于支持治疗。近年对于AP的治疗推荐中西医结合疗法,目的在于控制感染、改善胃肠动力和促进内环境稳定等^[25]。大承气汤可以通过调节肠道菌群来增强肠蠕动,缓解腹胀,降低腹压,改善患者免疫功能^[26-28]。本研究中观察了大承气汤联合奥曲肽对MAP患者肠道微生物区系的影响。结果显示,在炎症指标方面,两组治疗均显效,且大承气汤组CRP、PCT、IL-6和胃肠功能恢复时间均明显优于常规治疗组。提示大承气汤能有效减少炎症因子,降低炎症反应,促进胃肠功能恢复。在肠道菌群调节方面,经大承气汤治疗后,MAP患者肠道内乳杆菌属、罗姆布茨菌属、布劳特菌属3种有益菌显著富集;经常规治疗后,患者肠道内致病菌肠球菌属相对丰度较高。罗姆布茨菌属源自消化链球菌科,在健康肠道内更丰富,

在肠息肉、大肠癌及营养不良患者中的丰度较低或消失,且罗姆布茨菌缺失是肠道黏膜改变的首个指标^[29-30]。布劳特菌属是一种厌氧细菌,具备有益菌特性,可调节人体健康,参与生物转化及缓解代谢综合征^[31]。此外,本研究中还分析了炎症指标与肠道微生物的相关性,提示大肠埃希菌-志贺菌属与炎症指标均呈显著正相关。上述结果说明,大承气汤在治疗AP时是通过调节肠道菌群来降低炎症反应,改善胃肠功能。这一结论可能与大黄中的大黄素具有抗炎、抗菌、抑制胰蛋白酶原分泌、免疫调节、改善微环境有关^[32];与大黄中的大黄酸具有降低促炎介质表达、减轻肠炎症的作用有关^[33];与厚朴中的厚朴酚具有抗炎、抗菌、调节代谢等生物活性有关^[34]。

综上所述,大承气汤能够降低MAP患者炎症因子水平,抑制炎症反应,促进胃肠功能恢复,改善肠道屏障功能,其机制可能是通过调节肠道微生物群、抑制致病菌生长和减少肠道菌群移位实现的。

利益冲突 所有作者均声明不存在利益冲突

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