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益生菌、益生元、合生元在肠易激综合征中的应用与最新进展

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Progress in application of probiotics, prebiotics, and synbiotics in irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a common functional bowel disorder characterized by recurrent abdominal pain accompanied by changes in defecation frequency and/or stool characteristics. The global incidence of IBS is increasing year by year. Intestinal symptoms caused by IBS (such as constipation, diarrhea, abdominal pain, and abdominal distension) and accompanying changes in general nervous system function can significantly reduce patients' quality of life and work efficiency, and lead to high medical costs. Therefore, finding safe, effective, and economical treatments has become a hot research topic in recent years. Studies have shown that the intestinal flora of patients with IBS is different from that of healthy subjects, and regulating the intestinal flora can treat IBS. The purpose of this review is to summarize the application and recent progress of probiotics, prebiotics, and synbiotics in the treatment of IBS by regulating the intestinal flora.

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Key Words: Irritable bowel syndrome; Intestinal flora; Treatment; Probiotics; Synbiotics

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摘要

肠易激综合征(irritable bowel syndrome, IBS)是一种常见的功能性肠病, 主要表现为反复发作的腹痛伴排便频率和(或)粪便性状改变, 腹痛常在排便后缓解, 全球发病率呈逐年上升趋势. IBS引起的肠道症状(如便秘、腹泻、腹痛、腹胀等)及其伴随的一般神经系统功能的改变会显著降低患者的生活质量和工作效率, 并造成一系列高额的医疗费用. 因此, 寻找安全、有效、经济的治疗方案成为近年的研究热点. 研究表明IBS患者和健康受试者的肠道菌群有所不同, 调节IBS患者的肠道菌群可治疗IBS. 本综述的目的是总结益生菌、益生元、合生元通过调节肠道菌群治疗IBS的应用与最新进展.

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关键词: 肠易激综合征; 肠道菌群; 治疗; 益生菌; 益生元; 合生元

核心提要: 肠易激综合征(irritable bowel syndrome, IBS)处于反复发作与缓解的过程中, 带来的经济损失和精神压力日益增加. 肠道菌群失调是肠易激综合征的病因之一, 益生菌能改善肠道菌群并治疗肠易激综合征, 该方法经济、有效、安全, 越来越受到临床医生的重视.

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0 引言

肠易激综合征(irritable bowel syndrome, IBS)的全球平均发病率约为11%, 范围约在9%到43%, 是一种十分常见的疾病^[1]. IBS引起的如便秘、腹泻、腹痛、腹胀等的肠道症状及其伴随的一般神经系统功能的改变会造成患者的生活质量和工作效率降低. 不仅如此, IBS总是处于循环往复的复发和缓解的过程, 因此IBS对个人和社会都造成了重大的影响, 由此导致的社会经济负担与日俱增. 研究表明, 每年与IBS相关的直接或间接的经济开销在欧洲高达80亿欧元, 在中国高达20亿美元, 在美国已超过100亿美元^[2]. 另一方面, IBS发病机制复杂, 至今尚无定论. 目前发现的机制有遗传因素、肠道的急慢性感染、肠道菌群的紊乱、肠道黏膜屏障功能异常、胆汁盐代谢紊乱、5-羟色胺代谢异常、肠神经系统调控功

能和形态学改变等^[3]. 其中肠道菌群的紊乱是近年的研究热点之一, 研究表明益生菌等可通过调节肠道菌群来治疗IBS. 本综述的目的是总结益生菌、益生元、合生元通过调节肠道菌群治疗IBS的应用与最新进展.

1 IBS的诊断、分型和治疗

国际上诊断IBS主要采用罗马IV标准^[4], 即排除器质性疾病后, 患者出现反复发作的腹痛, 至少1日/周(最近3个月内发作), 并有下列症状中的2个或以上: (1)与排便有关; (2)排便频率发生改变; (3)粪便性状改变. 症状至少在诊断前6个月出现, 且最近3个月符合上述诊断标准即可诊断. 根据粪便性状, 目前将IBS分为腹泻型(irritable bowel syndrome-diarrhoea, IBS-D)、便秘型(irritable bowel syndrome-constipation, IBS-C)、混合型(irritable bowel syndrome-mixed stool pattern, IBS-M)及不定型(irritable bowel syndrome-unclassified, IBS-U). IBS的治疗方法包括非药物治疗和药物治疗, 其中非药物治疗包括了调节生活方式、饮食结构和心理疗法等, 非药物治疗效果缓慢, 疗效不确切. 一线药物治疗包括泻药、止泻药和解痉药, 用于腹泻、便秘、腹痛等症状的对症支持治疗, 但无法改善其他伴随症状, 例如乏力、抑郁等. 二线药物治疗包括抗抑郁药物和针对中枢神经系统或中枢神经调节器的药物, 二线用药不良反应较多, 且目前的相关临床试验质量欠佳, 疗效难以明确. 此外, 针灸、按摩及中药治疗也可用于治疗IBS, 中药治疗包括藿香正气软胶囊、固肠止泻丸、疏肝汤、四肾丸等. 中药的疗效不甚确切, 但其多为天然植物性原料组成, 因此副作用较少.

2 IBS患者肠道菌群的变化

人类肠道大约生存着多达 10^{14} 种微生物, 它们来源于约1000个物种, 其中原核生物(细菌和单细胞微生物)占主导地位, 真菌、古生菌、寄生虫和病毒也是肠道的居住者^[5,6]. 肠道菌群中的细菌主要有四门, 即厚壁菌门、拟杆菌门、变形菌门和放线菌门^[7]. 不同个体的肠道菌群存在差异, 这种差异可归因于个体婴儿时期的分娩和喂养类型、年龄、性别、饮食、卫生和生活条件、健康问题、饮酒情况以及生活的地理区域等^[8]. 肠道菌群的失调可能与某些微生物的过度生长或缺乏以及遗传异常有关, 菌群的失调可触发免疫系统反应, 导致肠道炎症和肠脑轴的破坏, 并导致多种心血管、神经系统或肠道疾病, 其中包括IBS^[7,9].

IBS分为IBS-D、IBS-C、IBS-M及IBS-U, IBS患者肠道菌群与健康个体肠道菌群不同, 不同亚型中的肠道菌群的变化也不尽相同, 这提示不同亚型的IBS患者可能需要不同的治疗方法. 总的来说, 变形菌门、肠杆菌

科(大肠杆菌、志贺氏菌、弯曲杆菌、沙门氏菌)、铜绿假单胞菌、革兰阴性杆菌、梭菌属、瘤胃球菌属、拟杆菌属在各种亚型中的数量均有增加^[10-14]。其中变形菌门、拟杆菌属、革兰氏阴性菌在IBS-D患者肠道显著增多^[11,12]。另外, 韦永氏球菌、节段丝状菌、普雷沃菌在IBS-D患者中也明显升高^[12,15]。此外, IBS患者肠道中*Blautia*属的细菌占比较高,*Blautia*属被认为是微生物群失衡的标志^[14]。双歧杆菌属在各亚型IBS患者肠道中均明显减少^[10,12]。一项针对中国IBS-D患者的研究中提示厚壁菌门、梭杆菌门、放线菌门均有所减少, 异普雷沃菌和梭杆菌在IBS-D患者中显著降低^[11]。目前研究发现乳酸杆菌、节段丝状菌、产甲烷菌在IBS患者中的数量变化仍有争议。乳酸杆菌主要在IBS-C患者中增加, 而IBS-D中减少。节段丝状菌在IBS-D中的数量较健康个体高, 在IBS-C中较健康个体低^[12]。另外, 大多数产甲烷菌在IBS-C中的数量较IBS-D高, 甲烷与便秘的发生呈正相关, 这也与其分型相对应^[16]。

IBS患者的临床症状与肠道菌群的变化相关。研究发现IBS患者腹胀的发生可能与乳酸杆菌、拟杆菌、拟球梭菌、铜绿假单胞菌、节段丝状菌和革兰氏阴性菌的数量增加相关。其中乳酸杆菌可以从葡萄糖或果糖中产生包括乳酸和(或)乙酸在内的有机酸, 可能与患者的腹痛、腹胀相关^[12]。另外, 产毒素的拟杆菌可以释放毒素, 溶解粘膜糖蛋白, 影响肠道微环境、结肠黏膜生成和肠道蠕动, 引起腹痛、腹泻等。韦永氏球菌属可以导致丁酸升高, 可诱导内脏超敏反应, 加重了IBS的症状^[10]。双歧杆菌属则能通过发酵使得肠腔内环境酸化, 抑制细菌的入侵, 减少致病菌定植。双歧杆菌还可以降低患者的抑郁评分, 改善患者的生活质量^[10,12]。IBS患者肠道菌群的变化为通过益生菌、益生元、合生元治疗IBS提供了理论依据。

尽管研究人员努力寻找IBS患者的菌群失调模式, 但获得的结果仍有许多争议。部分研究者甚至发现IBS患者和健康人群的粪便样本没有发现明显的微生物群异常^[17,18]。这可能与研究对象的IBS分型相关, 也可能与受试者样本量不足, 采集样本的肠道位置不同, 分析方法不同, 甚至与人口差异相关。

3 单种益生菌制剂在IBS中的应用

越来越多的研究表明肠道菌群紊乱是IBS的发病机制之一, 通过调节IBS患者的肠道菌群能改善相关临床症状。益生菌被定义为对宿主健康有益的活微生物, 它的效应归因于菌株, 即使是同一种类的两株不同菌株也可能对患者有不同的影响。益生菌在不同人群、不同阶段和不同类型的疾病中具有不同的作用^[19]。

大多数研究证实益生菌可用于治疗IBS。少部分研究没有观察到益生菌对治疗IBS具有统计学意义。不仅如此, 研究者观察到植物乳杆菌*MF1298*胶囊制剂甚至对IBS受试者造成了不利影响^[20]。研究人员发现由益生菌发酵而来的酸奶能改善IBS患者的症状, 这使得许多研究者对益生菌在IBS中的应用产生了兴趣。有学者对两种独立的益生菌, 即*Lb.acidophilus DDS-1*(一种乳酸杆菌菌株制剂)和*B.lactis UABla-12*(一种双歧杆菌菌株制剂)进行了分析。他们发现了这两种益生菌菌株不仅能缓解IBS患者的腹痛, 还减轻了腹泻、便秘的严重程度, 改善了IBS患者的总体症状。此外, 研究者发现*Lb.acidophilus DDS-1*(有助于降低IBS患者的应激水平^[21])。另一项基于*B.langum ESI*(一种双歧杆菌菌株)菌株的研究提示该菌株对于IBS患者总体症状有改善作用, 它增强了IBS-D患者的肠道屏障完整性及肠道免疫力^[22]。此外, 一项基于*B.longum HA-196*(一种双歧杆菌活菌制剂)和*Lb.paracasei R0175*(一种乳酸杆菌活菌制剂)的研究表明这两种益生菌都改善了参与者的社会生活质量。该研究观察到*B.longum HA-196*可以使受试者的双歧杆菌属的丰度增加, 而*Lb.paracasei R0175*则对于粪便样本中的乳酸杆菌的丰度增加没有明显作用^[23]。*Lb.gasseri BNR17*、*Lb.casei*、*Lb.rhamnosus*等都属于乳酸杆菌, 它们均被发现可以用于改善IBS患者的临床症状^[24-28]。其他能有效改善IBS症状的益生菌是凝结芽孢杆菌(*Bacillus coagulans*)菌株^[29-31]。研究者观察到*B.coagulans MTCC 5856*(一种凝结芽孢杆菌活菌)可减少IBS-D患者的失眠和抑郁^[30]。*B.coagulans LBSC*(一种凝结芽孢杆菌活菌)也被证实能改善IBS患者的肠道菌群的失衡^[31]。此外, 酵母菌属(*Saccharomyces spp.*)^[32]、大肠杆菌(*Escherichia coli*)^[33]、布拉氏酵母菌(*Saccharomyces boulardii*)^[34]也被观察到能够改善IBS的疾病症状。

受限于临床试验的各种因素, 例如研究方案、受试者样本量、取样部位等, 临床试验的结论可能存在局限性。因此, 部分研究人员开展了动物实验和体外实验以此进行分析。研究人员对来源于PI-IBS-D(感染后肠易激综合征腹泻型)患者的回肠和结肠黏膜培养组织模型进行了体外分析, 证实*Lb.casei DG*(一种乳酸杆菌制剂)能够减少黏膜炎症^[26]。相似的, Seong等人^[27]制造了慢性约束应激诱导的大鼠IBS模型, 他们同样发现*Lb.casei DKGF7*(一种乳酸杆菌制剂)能降低结肠组织中的炎症细胞因子和血清皮质酮水平, 增加紧密连接蛋白的表达率, 最终改善IBS的症状。另一项通过制造2,4,6-三硝基苯磺酸诱导的小鼠PI-IBS模型的研究同样表明*C.butyricum*(一种丁酸梭状芽菌)可降低小鼠的肠道内脏超敏反应, 并减轻小鼠的结肠黏膜炎症^[35]。

4 多菌株益生菌制剂在IBS中的应用

上述研究均针对单种益生菌制剂, 没有分析多菌株益生菌制剂对于IBS的作用. 事实上, 多菌株益生菌制剂作为IBS的治疗方法被更广泛地研究, 它们可以有效地减轻IBS的症状. 研究者通过PI-IBS小鼠模型, 观察到由*S.bouardii*(布拉氏酵母菌)、*Lb.acidophilus LA-5*(一种乳酸杆菌)和*B.lactis BB-12*(一种双歧杆菌)组成的复合益生菌制剂有助于降低小鼠血清促炎细胞因子水平和内脏超敏反应^[36]. 除了在动物疾病模型中有相关多种益生菌制剂对于IBS的治疗的研究外, 也有不少研究观察了多益生菌制剂在人体中的治疗作用. 研究发现由*S.bouardii*、*B.lactis BB-12*、*Lb.acidophilus LA-5*和*Lb.plantarum*构成的多菌株益生菌制剂*Lactolevure*可有效减轻腹胀和腹痛的严重程度, 特别是在IBS合并小肠细菌过度生长(small intestinal bacterial overgrowth, SIBO)患者中^[37]. 另外, 益力多(*Yakult*)作为一种含有多种乳酸杆菌的乳制饮品同样可以降低SIBO并减轻腹痛, 并已投入生产使用.

5 整体的粪菌移植在IBS中的应用

粪菌移植(fecal microbiota transplantation, FMT)通常指将健康供体的粪便微生物群落整体转移到受体体内, 快速改变受体的肠道菌群组成. 研究发现FMT可治疗多种慢性疾病, 如代谢综合征、恶性肿瘤、自身免疫性疾病、神经系统疾病和肠道疾病^[38]. 最新的研究提示^[39]FMT可以改变IBS患者的肠道菌群, 主要观察到乳酸杆菌属、拟杆菌属、双歧杆菌属等益生菌的增多. 研究表明^[39,40]FMT能改善IBS患者的临床症状, 尤其在改善腹泻上有明显作用. 同时, FMT可以有效减轻患者的乏力, 显著提升IBS患者的生活质量和工作效率. 但FMT的作用可能在1年后减轻^[40], 且可能产生轻度的、自限性的胃肠道症状^[39]. 另外, 由于移植的菌群来自于供体, 这增加了各种传染性疾病的传播风险, 因此FMT的流程需要更加严格^[41].

6 益生元、合生元在IBS中的应用

益生元是寄生在宿主肠道中的有利于微生物的底物, 目前关于益生元对IBS患者健康改善作用的研究很少. 目前被研究的益生元主要有低聚果糖、短链低聚果糖、反式-低聚半乳糖、部分水解瓜尔胶等.

1999年, 低聚果糖作为益生元被首次用于治疗IBS, 研究者认为低聚果糖的作用是具有边缘性的, 仅在IBS-C患者中起作用^[42]. 对于低聚果糖能否改善IBS患者的症状是有争议的, 有研究者认为低聚果糖对于IBS的治疗没有明显的有利影响^[43]. 另一项研究提示短链低聚

果糖可以改善IBS患者的焦虑水平并影响粪便中双歧杆菌的数量^[44]. 而后, 另一种在乳糖中添加*Bifidobacterium bifidum NCIMB 41171*(一种双歧杆菌)发酵产生的反式-低聚半乳糖混合物被发现可以缓解肠胃胀气、腹痛和不适等症状, 以及粪便形状, 而且还增加了粪便样本中双歧杆菌的数量^[45]. 此外, 部分水解瓜尔胶也被证实可以缓解IBS患者的腹胀^[46]. 这些研究提示益生元能改善IBS患者的症状, 这一作用可能与其能增加肠道菌群中的某些有益细菌相关.

合生元将益生菌和益生元结合起来以改善宿主的健康状况, 近年来, 不少研究者观察并分析了合生元对于IBS患者的影响, 它可以发挥益生菌的生理活性, 也可以增加益生菌的数量, 使其作用更加显著、持久. 尽管也有部分研究者没有观察到合生元(例如*Probinul*和*Balance*)对于IBS患者的治疗效果^[47,48], 但更多的研究数据表明合生元可明显改善IBS的临床症状. 在合生元*Probinul*治疗IBS的临床试验中, 研究者发现受试者持续使用*Probinul*治疗4周后, 腹胀得到明显缓解^[49]. 在使用合生元*Lactol*进行的临床试验中, *Lactol*也被证实可以有效改善IBS患者的腹痛和腹泻等症状, 适用于IBS-D患者. 然而, 这项临床试验发现*Lactol*制剂可能存在一定的副作用^[50]. 关于*Lactol*制剂的生物安全性尚有争议, 另一项使用*Lactol*治疗儿童功能性腹痛的研究不仅验证了其有效性, 并且没有发现该制剂的任何副作用^[51].

7 小结

由于IBS患者长期处于复发和缓解的过程中, 因而某些药物可能需要长期使用, 例如泻药、止泻药、改善精神类药物等, 这会给IBS患者带来许多副作用及不良反应. 近二十年来, 有关益生菌、益生元、合生元治疗IBS的研究取得了令人满意的结果, 益生菌等在IBS的治疗中被公认为是相对有效和安全的. 益生菌、益生元、合生元的安全性和有效性使得其可以作为这些药物的替代品. 另外, FMT成为了近年的研究热点, 不仅因为其能明显改善IBS患者的临床症状, 也因为FMT被发现可用于治疗多种慢性疾病, 如代谢综合征、恶性肿瘤、自身免疫性疾病、神经系统疾病和肠道疾病等. 但因FMT潜在的传播传染性疾病的风险, 治疗流程需要更加严格化、规范化. 总的来说, 在以微生物为基础的治疗领域中, 益生菌、益生元、合生元是改善IBS患者症状的一个有前途的方向.

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