

• 综述 •

益生菌对不同病因所致腹泻的防治作用研究进展

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【摘要】 益生菌被认为是对宿主健康有益的活生物体。近年来, 益生菌逐渐成为临床上常用的处方, 被广泛应用于治疗胃肠道疾病和非胃肠道疾病, 然而评估其疗效的相关临床研究结果通常是相互矛盾的。目前仍有大量临床研究探讨益生菌在治疗胃肠道疾病方面的作用, 但对于很多疾病仍无统一论。本文回顾了近年来益生菌在不同病因所致腹泻中的作用, 主要包括感染性腹泻、抗生素相关性腹泻或难辨梭菌相关性腹泻、腹泻型肠易激综合征等, 指出了益生菌对不同疾病、人群中所出现腹泻的临床应用价值及益生菌使用中可能存在的潜在风险, 从而为其今后进一步临床研究及应用提供依据。

【关键词】 腹泻; 有益菌种; 肠易激综合征; 炎症肠疾病; 感染性腹泻; 抗生素相关性腹泻; 难辨梭菌相关性腹泻

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Research Progress on Preventive and Therapeutic Effects of Probiotics on Diarrhea Caused by Different Pathogens

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【Abstract】 Probiotics are considered as a kind of living organisms that are beneficial to the host. In recent years,

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probiotics have gradually become a commonly used clinical prescription to treat gastrointestinal and non-gastrointestinal diseases. However, relevant clinical researches evaluating the efficacy of probiotics are often contradictory. At present, there are still a lot of clinical studies trying to explore the role of probiotics in the treatment of gastrointestinal diseases but without consensus on its effects on many diseases. This paper gives a review on the role of probiotics in diarrhea caused by different pathogens in recent years, including infectious diarrhea, antibiotic-related diarrhea, *Clostridium difficile* infectious diarrhea, and diarrhea-predominant irritable bowel syndrome. This paper points out the clinical application value of probiotics in the treatment of diarrhea caused by different diseases among varied people. Besides, the paper tells clearly about the potential risks in the use of probiotics thus offering a reference for further clinical researches and application in the field.

【Key words】 Diarrhea; Probiotics; Irritable bowel syndrome; Inflammatory bowel diseases; Infectious diarrhea; Antibiotic-associated diarrhea; *Clostridium difficile* associated diarrhea

有胃肠道的动物均有肠道微生物菌群（细菌、古菌、病毒和真核微生物），这些微生物非常丰富，研究表明，成人肠道中细菌细胞数量与人体细胞数量的比例是 10 : 1，其中绝大多数细菌存在于结肠中^[1]。肠道微生物与胃肠道的正常生理有关，其种群相对数量的改变可以破坏微生物与宿主之间的有益相互作用，对人类健康有直接影响^[1]。其作用机制主要有以下几个方面：抑制病原菌黏附、增强肠道屏障功能、调节先天性免疫系统和适应性免疫系统、产生具有抗炎特性的生物活性代谢物并促进其对肠道和中枢神经系统的影响^[2]。

益生菌的最初定义是在 2011 年联合国粮食及农业组织和世界卫生组织专家协商会议上制定的，被定义为“当以适当剂量施用时对宿主健康有益的活生物体”^[3]。许多益生菌最初是从胃肠道中分离出来的，并逐渐用于许多发酵食品、药丸、粉末和液体中，现在这些制剂在社区中被广泛使用，甚至可作为处方用药^[4]。益生元被认为是可发酵的、不可消化的、有选择地促进有益微生物生长和/或活性的代谢底物。尽管人们对益生元的定义进行了讨论和改进，但普遍的共识是益生元不能被人类胃肠道细胞消化，益生元包括低聚糖、菊粉、乳果糖等。合生素为益生菌和益生元的混合物，其使益生元伴随着益生菌到达肠道，从而有助于益生菌的生长和定居^[5-6]。目前已发现人体内外共生着数千种微生物，形成了庞大的微生态系统，主要分布在人体肠道、皮肤、口腔、呼吸道、泌尿生殖道等，其与人类构成存在共生关系，共同参与人体免疫系统的发育和成熟，并决定营养物质的吸收和代谢^[7]。2017 年发表的关于胃肠炎的墨西哥共识建议在下列临床条件下使用益生菌：预防与抗生素有关的腹泻、治疗急性感染性腹泻、预防艰难梭菌感染和坏死性小肠结肠炎、减少根除幽门螺杆菌治疗中的不良反应、缓解肠易激综合征（IBS）症状、治疗成人功能性便秘、诱导和维持溃疡性结肠炎和慢性肠炎缓解以及治疗隐性和显性肝性脑病^[6]。

腹泻是指每天排 3 次或更多的松散、半软的水样大便，其可影响所有人群^[8]。胃肠道系统功能主要是吸收和排泄液体及营养素，其运行机制复杂，在某些因素的影响下肠道微生态系统被破坏，导致肠道正常菌群的种类、数量和比例发生异常变化，出现病理性组合状态，从而引起腹泻^[9-10]。急性腹泻仍然是一个世界性的公共卫生问题，特别在发展中国家，是儿童发病和死亡的重要原因^[11]。腹泻最常见的原因是不同微生物的感染，其最常见的并发症是脱水^[2]。腹泻在本

质上主要分为渗透性腹泻和分泌性腹泻^[12]。

本文主要对近年来益生菌对不同病因所致腹泻防治作用的相关研究进行总结，以期为今后益生菌的临床应用及相关研究提供参考。

1 益生菌对腹泻的防治作用研究进展

研究表明，益生菌菌株可以通过调节内部生态系统直接或间接影响肠道环境，欧洲儿科传染病学会建议益生菌作为治疗腹泻的有效辅助措施，并已证明适当剂量的益生菌是有效的^[13]。益生菌的作用机制是复杂的，可能因物种而异^[14]。其共同机制是创造更有利的肠道环境，支持健康的消化道和免疫系统，主要包括：维持上皮屏障、抑制病原体黏附、竞争性排除致病微生物、产生抗微生物物质、调节肠道转运以及调节免疫系统^[2, 6, 15-16]。具体而言，益生菌菌株可促进肠上皮细胞紧密连接的形成或增强上皮和黏液屏障功能，也可以在信号通路水平发挥作用，导致黏液层增加或防御素及紧密连接的蛋白质的生成而维持肠道屏障功能^[17-18]；可通过物理阻断、增加黏蛋白基因表达和受体的非特异性空间位阻效应而实现抑制病原菌入侵和黏附；也可直接与致病细菌竞争黏膜黏附部位或分泌酶降解黏膜表面受体、产生受体类似物或生物表面活性剂而竞争性排斥致病微生物^[17, 19]；可通过释放各种抗菌因子（包括防御素、抗克罗地亚肽或细菌素、过氧化氢、一氧化氮、短链脂肪酸和各种降低内腔酸碱度的有机酸等）来减缓各种肠道病原体的生长^[12]；以及通过与免疫细胞的直接相互作用或代谢产物、细胞壁成分和 DNA 等，维持并调节胃肠道免疫平衡^[20-22]。

用于人类营养的益生菌大多属于乳酸杆菌属、双歧杆菌属、肠球菌属的某些菌株以及来自丙酸杆菌属和某些酵母如布拉迪链球菌的菌株^[23]。益生菌的作用是具有菌株特异性（不同种类益生菌作用不同）的，每个菌株的临床效果需要分别评估^[24]。

1.1 感染性腹泻 目前益生菌被公认为是中等程度感染性腹泻的安全替代和低成本的治疗方法，且多项临床研究结果表明益生菌在缩短大便持续时间和降低大便频率方面是有效的^[25]。SASAKI 等^[26]针对感染性腹泻患者的回顾性研究表明，经验性抗菌治疗与感染性腹泻患者住院时间延长有关，应谨慎进行抗菌治疗。近年来，学者建议使用益生菌治疗感染性腹泻，SHARIF 等^[27]的一项针对痢疾患者的研究表明，使用益生菌能有效缩短痢疾和腹泻的持续时间。旅游者腹泻（TD）

是一种感染性疾病, 抗生素的使用并没有显著降低TD发生率, 且随着抗生素耐药的增加, 使用益生菌治疗该疾病具有良好前景^[2]。一项纳入11项RCT的系统分析表明, 与安慰剂相比, 益生菌对TD的预防有统计学意义^[28]。另一项系统分析发现, 使用布拉迪酵母菌可以显著降低TD的风险^[29]。但EVANS^[30]所做的系统分析表明, 没有明显证据表明使用益生菌可防治TD。尽管目前越来越多的旅游者考虑使用益生菌作为预防TD的措施, 但是目前高质量的临床研究较少, 结论也较少, 且现有数据之间仍然存在矛盾, 因此不推荐益生菌作为可靠有效防治TD的方法。

1.2 抗生素相关性腹泻(AAD)/难辨梭菌相关性腹泻(CDAD)

抗生素是治疗感染性疾病的基石, 但其也破坏肠道固有的微生物菌群, 并可能导致严重的胃肠功能障碍, 如腹胀、腹泻、黏膜屏障损伤等^[31]。大多数情况下AAD和CDAD是抗生素使用的常见并发症, 特别是氟喹诺酮类、青霉素类、头孢菌素和克林霉素^[2, 32]。AAD通常是一种轻微的自限性疾病, 但15%~39%难辨梭菌感染患者可能发生严重腹泻和死亡^[33]。益生菌是活的微生物, 口服时其可通过使不平衡的胃肠道菌群正常化来预防AAD^[34]。一些益生菌对AAD和CDAD的预防是有效的。目前认为鼠李糖乳杆菌(LGG)预防AAD的有效性和耐受性最好, 回顾性研究提示LGG能有效预防因任何原因使用抗生素治疗的儿童和成人AAD^[24, 35-36]。布拉迪酵母菌在婴幼儿及老年患者中均能有效、安全地预防AAD, 其与LGG效果无明显不同, 可作为AAD的选择性预防药物之一, 且在临床应用中尚未观察到不良事件^[37-41]。但在降低难辨梭菌感染率方面, 干酪乳杆菌被认为具有更好的疗效和中等耐受性, 且在疗效和耐受性方面, 菌株组合没有优于单一菌株。故LGG或布拉迪酵母菌可能是防治ADD的最佳选择。而对于重症难辨梭菌感染患者而言, 干酪乳杆菌似乎是最有效的选择, 其他菌株目前尚缺乏足够的证据^[36, 42]。然而, EHRHARDT等^[43]的一项纳入477例患者的多中心随机对照研究表明, 对于没有其他特殊危险因素成人患者, 没有证据表明布拉迪酵母菌在预防AAD或CDAD方面有作用。同时, 多项系统分析及临床研究显示, 在降低老年患者AAD或CDAD发病率方面, 没有发现益生菌比安慰剂更有效^[33, 44-47]。

综上, 目前针对AAD及CDAD的标准治疗仍为口服甲硝唑或万古霉素治疗, 益生菌疗效仍存在争议, 关于哪些益生菌菌株可以预防难辨梭菌感染尚未达成共识, 未来仍需进一步研究明确。

1.3 腹泻型肠易激综合征(IBS-D) IBS是一种功能性肠病, 按患者主要排便习惯进一步分为IBS-D、便秘型IBS及混合型IBS。部分IBS与肠道微生物菌群的变化、胃肠运动的变化、显微炎症(即显微镜下观察到的肠道结构改变)、胆汁酸吸收不良和肠神经系统的改变有关, 目前尚无标准治疗方案^[48]。在IBS治疗中使用益生菌的基本原理是益生菌具有可纠正肠道菌群紊乱或稳定宿主微生物的潜力^[49]。研究表明双歧杆菌数量与排便急迫性呈负相关^[50]。服用益生菌增加肠腔内双歧杆菌与IBS症状的减少有关, YOON等^[51]的研究

表明, 多菌种益生菌混合物(双歧杆菌、乳酸杆菌、嗜酸杆菌、LGG)显著提高了IBS患者大多数益生菌菌株的粪便浓度, 并改善了腹泻症状评分; 但与之相悖的是, 有研究表明低发酵性低聚糖、二糖、单糖和多元醇(FODMAP)饮食具有改善IBS症状的临床效果, 但其显著降低了腔内双歧杆菌的浓度^[52]。近年来研究提示特定益生菌(包括布拉迪酵母菌、丁酸梭菌、BNR17乳酸菌)可改善IBS-D患者的整体症状、生活质量和排便频率, 被认为是临床治疗IBS-D的有效益生菌^[53-55]。来自美国和加拿大的FORD等^[56]确认了43个涉及3000多名志愿者的RCT, 显示服用益生菌时出现IBS持续症状的相对风险较低, 提示益生菌是治疗IBS的有效药物, 但哪种益生菌菌株对患者最有益尚不清楚^[56]。我国对21个RCT的研究显示, 益生菌有利于IBS症状及生活质量的改善, 且低剂量、短疗程的单一益生菌似乎更有效^[57]。然而, 一项纳入172名女性IBS-D患者的临床研究表明, 服用益生菌对于改善IBS-D患者症状的疗效并没有显著优于安慰剂^[58]。

综上, 对于IBS-D, 益生菌疗效尚无一致性定论, 未来仍需要高质量的临床研究来检测特定益生菌对IBS-D的疗效。

1.4 炎症性肠病(IBD) 有证据表明IBD与肠道微生物菌群的变化有关, 但由于肠道微生物菌群的复杂性, 关于此方面的研究仍处于早期阶段^[59]。2012年欧洲克罗恩病和结肠炎组织(ECCO)指南不建议将益生菌用于维持成人或儿科克罗恩病(CD)患者的缓解, 且多项系统分析显示益生菌在诱导活动性CD的缓解、预防静止期CD的复发或预防手术诱导缓解后CD的复发方面均没有明显益处, 故目前没有强有力的科学证据证明CD患者使用益生菌菌株是有效的^[59-61]。然而, 有数据表明某些益生菌菌株对溃疡性结肠炎(UC)是有效的。ECCO指南建议将大肠杆菌Nissle 1917(EcN)作为5-氨基水杨酸维持溃疡性结肠炎(UC)缓解的有效替代品^[62]。一项Mata分析结果同样表明EcN在预防UC复发方面与美沙拉嗪相当, 从而证实了当前的指导性建议, 而VSL#3(一种多种益生菌混合制剂)有助于缓解慢性UC患者的病情^[63-64]。一项纳入539例活动性UC患者的随机双盲对照研究表明, 治疗8周后, 采用长双歧杆菌BB536组患者在临床缓解率、溃疡性结肠炎活动指数(UCDAI)评分、Rachmilewitz内镜指数及Mayo评分改善方面均显著优于安慰剂组^[65]。另一项针对缓解期UC患者的RCT显示, 益生菌混合制剂(粪链球菌、丁酸梭菌和肠系膜芽孢杆菌)可有效缓解静止期UC患者的病情^[66]。此外, 长期使用益生菌制剂(唾液乳酸杆菌与酸乳杆菌混合制剂)联合美沙拉嗪治疗轻、中度UC是可行的, 可以替代皮质类固醇治疗^[67]。

1.5 治疗相关腹泻 胃肠、腹腔脏器及盆腔肿瘤的化疗和放疗方案可破坏肠道微生物菌群和肠上皮细胞, 引起腹泻、恶心和呕吐等症状^[68]。因治疗引起的腹泻发病率高达50%~80%, 严重的治疗相关腹泻会导致体液、电解质流失和营养不足, 并可能对生活质量产生不利影响^[69]。有随机双盲对照研究表明, 对于接受放疗的盆腔肿瘤患者, 相比安慰剂组, 益生菌组轻、中、重度腹泻明显减少^[70-71]。同时, 多项Mata分析表明, 益生菌在预防和治疗与放疗或化疗有关的

腹泻方面有效,且没有发现明显不良事件^[69, 72-73]。然而,WARDILL等^[74]对既往RCT的分析表明,与安慰剂相比,预防性益生菌并不能预防或降低腹泻的总发病率。

对于益生菌防治化疗相关腹泻的疗效,近年来缺乏大规模高质量前瞻性RCT,且目前系统分析所纳入的研究具有明显异质性,尚不能形成有力的确定性证据,仍需后续进行严谨的临床研究以明确。

1.6 其他 SHIMIZU等^[75]研究显示,在机械通气危重患者中,预防性使用合生元(短双歧杆菌、酪乳杆菌和低聚半乳糖)对肠炎和肺炎有预防作用。心理压力与胃肠道失调相关,一项纳入581名本科生的RCT提示,在应激期间,双歧杆菌R0071可降低腹泻相关症状和应激评分^[76]。腹泻是肠内营养(EN)的常见并发症,而益生菌可预防及缩短EN相关腹泻的病程^[77-78]。

2 不良反应

早期给予益生菌时可能可更有效地影响免疫系统和肠道的微生物群,然而,免疫系统不成熟时给予益生菌的绝对安全性需要证明,特别是在明显免疫系统受损的早产儿中,其安全性和有效性均具有明显的菌株和剂量依赖性^[5]。与益生菌有关的潜在不良事件包括胃肠道不良反应(如腹部绞痛、恶心)、有害代谢活性(如D-乳酸酸中毒)和罕见的局部及系统性感染(如真菌血症、败血症、亚急性细菌性心内膜炎和脑膜炎)^[48]。虽然这些不良反应罕见,但到目前为止,在危重病或老年患者中有许多真菌血症的报道^[79]。MUÑOZ等^[80]对文献进行了系统的回顾,并确定了60例由布拉迪酵母引起的真菌血症,发现与真菌血症相关的因素包括重症监护病房住院、EN或肠外营养的给予以及益生菌的使用,且真菌血症可发生在没有任何明确病因的免疫抑制人群中。SALMINEN等^[81]鉴定了89例乳杆菌菌血症患者,其指出,在社区中使用益生菌并不会导致乳杆菌菌血症的发病率增加,表明益生菌对完全健康的人来说发生不良反应的风险很小。

3 小结及展望

综上所述,益生菌在防治感染性腹泻、AAD/CDAD、IBS-D、IBD等多种引起腹泻的胃肠道疾病中具有良好的应用前景。目前,虽然含2种及以上益生菌的组合产品已成为主流,但在大多数国家,益生菌产品仍不属于药品,而是食品^[16]。在我国,现有益生菌产品主要包括食品、药品、保健品,2012年国家基本药物目录中的地衣芽孢杆菌制剂、枯草杆菌/肠球菌二联活菌制剂、双歧杆菌三联活菌制剂均为乙类口服制剂^[82]。在临床应用中,益生菌菌株的变化、剂量和给药方式,以及患者的健康状况、饮食和日常使用的药物(如抗生素和抗酸剂)使不同益生菌之间疗效的比较变得困难^[83]。因此,需关注益生菌的菌株特性及目标人群,应该明确每一种益生菌菌株的性质,且不能外推到其他菌株,有必要科学地证明该菌株给宿主带来健康益处的功效。此外,使用益生菌过程中仍存在需要监测的潜在风险。目前益生菌临床效果尚存在争议,今后仍需要更多高质量的临床研究来确定益生菌的临床效果、最佳剂量、对脆弱人群的安全性以及特定疾病最有效的益生菌种类和菌株。

作者贡献:张楠进行文章的构思,文献/资料收集、整理,论文撰写,论文、英文的修订;朱华栋进行论文的可行性分析,质量控制及审校,对文章整体负责、监督管理。

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