

• 专家共识 •

中国微生态调节剂临床应用专家共识(2025 版)

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人体肠道微生态是指肠道内大量微生物及其相互作用的生态系统。这些微生物种类丰富、数量庞大, 与人体共栖共生, 构成了人体最重要的微生态系统之一。人体肠道内含有 $10^{13} \sim 10^{14}$ 个微生物细胞, 是人体细胞总数的 10 倍, 总重量可达 1.5 kg^[1]。肠道微生物种类丰富, 包括细菌、真菌和病毒等, 以细菌为主。这些微生物为人体提供了约 60 万个基因, 对宿主的健康和疾病状态具有深远影响^[2]。肠道微生态在多种生理功能中扮演关键角色, 包括消化和营养吸收、维生素合成、肠道屏障保护、免疫调节以及代谢调控, 与人体健康密切相关^[3]。肠道微生态失衡可能诱发或加剧多种疾病, 如感染性疾病、肝病、消化道疾病、糖尿病、肥胖症、孤独症、阿尔茨海默病和高血压等。更重要的是, 肠道微生态在复杂疾病的发生发展中扮演着桥梁角色。如肠道菌群失衡与肿瘤的发生和对免疫治疗的响应相关, 菌群组成可能显著影响肿瘤免疫治疗的效果。在 COVID-19 等新发传染病中, 肠道菌群的组成可能与病程进展和预后相关, 为疾病的精准诊断和治疗提供了新思路。肠道微生态研究不仅推动了多种疾病的基础和临床研究, 也为个性化治疗策略的开发提供了重要启示。

肠道微生态失衡(dysbiosis)是指肠道菌群的种类、数量、比例或分布发生异常, 导致其功能受损的状态。其临床表现根据失衡程度分为 3 类^[4]: 1. 一度失衡: 也称潜伏型, 仅在细菌定量检测中发现异常, 无明显症状, 去除病因后可恢复; 2. 二度失衡: 即局限型, 可能伴有慢性疾病, 如慢性肠炎, 表现不可逆; 3. 三度失衡: 又称菌群交替症, 原籍菌被抑制, 少数菌过度繁殖, 临床症状严重, 多见于长期使用抗菌药物、免疫抑制剂或患有糖尿病、肿瘤

等患者。肠道微生态失衡的诊断依据主要包括: 1. 病史中具有能引起肠道微生态失衡的原发性疾病; 2. 有肠道微生态失衡的临床表现, 如腹泻、腹胀、腹痛、腹部不适等症状; 3. 有肠道微生态失衡的实验室依据: (1)粪便镜检球/杆菌比值。健康成人参考值为 1:3, 也有人建议采用康白标准 3:7; (2)粪便双歧杆菌与肠杆菌 DNA 拷贝数对数比值(B/E 值)小于 1^[5]; (3)粪便菌群涂片或培养中, 非正常细菌明显增多, 甚至占绝对优势; (4)利用细菌指纹图谱或宏基因组测序技术明确菌群变化; (5)李兰娟院士团队开发的十联检技术通过对人体肠道内 10 大优势细菌采用实时荧光定量 PCR 绝对定量, 快速、准确地反映肠道菌群的健康状态^[6]。

肠道微生态失衡的防治原则包括: (1)治疗原发病和减少诱因。积极治疗导致微生态失衡的基础疾病, 避免滥用抗菌药物、免疫抑制剂等对肠道菌群有害的药物, 减少环境和饮食不良因素的影响。(2)调整免疫和营养状态。改善机体免疫功能, 提供均衡的营养支持, 尤其是肠内营养对维护肠道屏障功能至关重要。(3)合理使用微生态调节剂。针对不同失衡类型, 可使用益生菌、益生元或合生元调节肠道菌群, 同时探索后生元(如短链脂肪酸)和肠菌移植(fecal microbiota transplantation, FMT)等新兴疗法。微生态调节剂的使用可单独使用活菌制剂或益生元制剂, 也可两种联合使用。补充益生菌应注重发挥优势菌株的作用, 选择能够降低肠腔氧分压、恢复肠上皮细胞能量供应的菌株^[7-8]。(4)促进健康的生活方式。通过高纤维、低加工食品的饮食习惯, 配合规律运动和压力管理, 促进肠道微生态平衡。(5)监测和个性化干预。利用宏基因组测序和肠道十联菌检测^[6]等新技术, 精准评估肠道菌群状态, 并实施

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个性化治疗策略,改善健康状况。

微生态调节剂在调节肠道微生态失衡方面具有显著作用。随着微生态学研究的不断深入,其种类和应用范围不断扩大。国际上对微生态调节剂的研究起步较早,并制定了规范化使用指南。但由于益生菌菌株、剂型以及研究对象的差异,直接采用国外标准并不完全适用于我国患者的实际情况。中华预防医学会微生态学分会联合中国医师学会感染科医师分会联合组织基础研究、微生态制剂和临床研究领域的专家,于 2016 年编写了第一版《中国消化道微生态调节剂临床应用专家共识(2016 年版)》,2020 年进行补充修订。该共识为微生态调节剂的规范化应用提供了科学指导。近年来,微生态学研究发展迅猛,新技术和理念不断更新传统医学认知。在此背景下,为了更好地指导临床医师在不同场景下科学合理地选择和应用微生态调节剂,于 2025 年再次修订专家共识。

1 幽门螺杆菌相关性胃炎

幽门螺杆菌(*Helicobacter pylori*, Hp)感染是慢性胃炎的主要病因。随着 Hp 耐药率的增加和根除率的下降,以及胃内微生态组成的逐渐明确,益生菌的应用为改善胃肠道微生态、辅助根除 Hp、减少治疗期间副作用提供了新的思路^[9]。

在 Hp 根除方案中添加益生菌作为辅助治疗,能够有效减少根除治疗后肠道微生物群的波动,促进菌群迅速恢复至基线水平,并提高肠道菌群的多样性^[10-12]。益生菌还可通过调节胃内菌群、产生抗 Hp 物质、调节免疫系统、抑制炎症通路、竞争黏膜粘附、增强胃黏膜屏障等机制抑制 Hp 的生长。某些益生菌单独使用可以使少数 Hp 感染患者得到根治,如大剂量罗伊氏乳杆菌(*Lactobacillus reuteri*)联合质子泵抑制剂对 Hp 的根除率可高达 12.5%^[12]。整体来讲,单用益生菌抗 Hp 治疗根除率较低,目前益生菌仍主要推荐用于 Hp 根除的辅助治疗。三联或四联方案联合益生菌,推荐使用枯草芽孢杆菌、屎肠球菌^[13-14]、双歧杆菌^[15-18]、布拉氏酵母菌^[15, 19-21]、嗜酸乳杆菌(*Lactobacillus acidophilus*)^[22]、罗伊氏乳杆菌^[12, 23]等益生菌提高根除率。此外,推荐使用鼠李糖乳酪杆菌(*Lactocaseibacillus rhamnosus*)^[24]和卷曲乳杆菌(*Lactobacillus crispatus*)^[25]用于减缓 Hp 辅助治疗的不良反应。目前尚缺乏益生菌联合三联疗法根除 Hp 的研究。不同疗程和剂量的益生菌亚组在 Hp 根除率和不良反应发生率上的差异均具有统计学意义;其中,服用益生菌 14 d 的方案为最佳选择。肠道微生态不稳定

或难治性 Hp 感染患者在根除治疗之前和期间服用含有乳杆菌的复合益生菌制剂至少 14 d,可适当延长疗程^[17-18, 20, 26]。综上,益生菌在 Hp 感染的辅助治疗中显示出潜在益处,包括调节肠道菌群变化、提高根除率和减少治疗相关副作用。选择适当的益生菌种类和组合,并合理安排疗程,可以显著提高治疗效果。

2 代谢相关性脂肪性肝病

代谢相关性脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)旧称非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD),是遗传易感个体由于营养过剩和胰岛素抵抗(insulin resistance, IR)引起的慢性进展性肝病,以弥漫性肝细胞大泡性脂肪变为主要病理特征,疾病谱包括代谢相关性脂肪肝(metabolic-dysfunction-associated fatty liver, MAFL)、代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)及其相关纤维化和肝硬化^[27]。肠道微生态影响 MAFLD 的发生发展。研究表明^[28],益生菌制剂辅助治疗 MAFLD 可改善肝脏酶谱和血脂,减轻 IR 和炎症水平。临床数据较多的益生菌制剂包括双歧杆菌、枯草芽孢杆菌、屎肠球菌、乳酸杆菌及其组合制剂。例如,长双歧杆菌联合低聚果糖可以降低 MAFLD 患者的肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、C-反应蛋白(C-reactive protein, CRP)、天冬氨酸转氨酶(aspartate aminotransferase, AST)和血清内毒素水平。保加利亚乳杆菌(*Lactobacillus bulgaricus*)和嗜热链球菌联合使用可以显著改善 MAFLD 患者丙氨酸转氨酶(alanine aminotransferase, ALT)、AST 和 γ -谷氨酰转肽酶(γ -glutamyl transpeptidase, γ -GT)水平。益生菌组合嗜酸乳杆菌、鼠李糖乳酪杆菌、副干酪乳酪杆菌(*Lactocaseibacillus paracasei*)、戊糖片球菌(*Pediococcus pentosaceus*)、乳双歧杆菌(*Bifidobacterium lactis*)和短双歧杆菌可改善 MAFLD 患者的总体脂、肝内脂肪、甘油三酯(triglyceride, TG)及总胆固醇(total cholesterol, TC)的水平^[29]。临床研究证实^[30-31],MAFLD 患者口服 3 个月的 VSL#3 微生态调节剂后,不仅血清转氨酶水平显著下降,而且血清 TNF- α 和脂质过氧化终产物亦有降低。MAFLD 患者口服含有干酪乳酪杆菌、鼠李糖乳酪杆菌、嗜热链球菌、短双歧杆菌、嗜酸乳杆菌、长双歧杆菌、保加利亚乳杆菌的复合胶囊 28 周后,空腹血糖(fasting plasma glucose, FBG)和炎症指标明显改善^[32]。国内的一些研究也表明,MAFLD 患者口服双歧杆菌三联活菌胶囊(长双歧杆菌、嗜酸乳杆菌和粪肠球菌)3 个月或枯草杆菌

二联活菌肠溶胶囊(枯草芽孢杆菌、屎肠球菌)4周后,肝功能指标、内毒素和二胺氧化酶水平明显下降,肝脏脂肪含量明显减少。机制上,可能与益生菌上调脂肪分解和脂肪酸氧化相关基因的表达、下调脂肪从头合成以及上调参与肝脏胆固醇代谢的相关基因 *Cyp7a1* 有关,从而降低血清 TG、TC、游离脂肪酸和肝脏脂肪水平;降低肠道通透性、血清内毒素水平,下调肝脏炎症因子(如 TNF- α)、抑制促炎性 M1 型 Kupffer 细胞的应答以及促进抗炎性 M2 型反应;并通过其代谢产物(如丁酸盐)维持肠道微生态平衡、降低肠道通透性,进而影响宿主代谢相关基因的表达。在 MAFLD 患儿肠道菌群中,厚壁菌门(Firmicutes)数量明显减少,而拟杆菌属、变形杆菌属、肠杆菌属和埃希菌属等显著增加,尤其是产乙醇菌增加,当内生的过量乙醇超出肝脏代谢能力,可产生类似于酒精性脂肪肝病的表现。

除上述传统益生菌外,近年来新一代益生菌(next generation probiotics, NGP)在治疗 MAFLD 和其他代谢性疾病中也受到了越来越多的关注^[33]。NGP 包括嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*)、普拉梭菌(*Faecalibacterium prausnitzii*)、单形拟杆菌(*Bacteroides uniformis*)、解木聚糖拟杆菌(*Bacteroides xylanisolvens*)和霍氏真杆菌(*Eubacterium hallii*)等。其中,嗜黏蛋白阿克曼菌(也称 Akk 菌)被寄予厚望。多项研究表明^[34-36]Akk 菌在调节宿主代谢方面发挥重要作用,如改善 IR、降低血脂,有助于减少脂肪堆积并改善肥胖,这可能与它能够调节肠道屏障功能、减轻内毒素血症以及促进肠道短链脂肪酸的生成有关。普拉梭菌、拟杆菌属等 NGP 在 MAFLD 和肥胖等代谢性疾病中亦有较多研究报道,其机制主要与短链脂肪酸(尤其是丁酸盐)对脂代谢、IR 及天然免疫等通路的调控有关。普拉梭菌、拟杆菌属等 NGP 在 MAFLD 和肥胖等代谢性疾病中亦有较多研究,已报道的机制主要与短链脂肪酸尤其是丁酸盐在脂代谢、IR、天然免疫调控等通路的调控作用有关。

总体上,益生菌能通过调节肠道菌群的平衡,改善 MAFLD 及代谢相关指标,缓解全身慢性炎症反应。但现阶段不同益生菌菌株的有效性和安全性仍有待进一步的研究与验证。

3 肝硬化

肝硬化是我国常见的消化系统疾病,主要病因为乙型肝炎病毒(hepatitis B, HBV)感染、丙型肝炎病毒(hepatitis C, HCV)感染、酗酒等,药物性肝炎、自身免疫性肝病和脂肪肝也可以进展为肝硬化。肝

硬化有诸多并发症,如内毒素血症、自发性细菌性腹膜炎、上消化道大出血、肝性脑病、肝肾综合征和肝癌等。这些并发症可独立于病因出现,并可能加重病情。肝硬化患者常伴有肠道微生态失衡和肠道细菌代谢改变。通过“肠-肝-脑”轴,肝硬化并发症的发生发展与肠道微生态失衡,肠道定植抗力下降,肠道细菌易位等密切相关。肠道微生态失衡在肝病重型化中发挥加速器的作用。

3.1 微生态制剂在肝硬化肠源性内毒素血症中的应用 肝硬化患者常伴有肠源性内毒血症,内毒素除对肝细胞具有直接毒性外,还可激活 Kupffer 细胞、中性粒细胞和单核细胞等免疫细胞,促使其释放炎症因子(如 TNF- α 、IL-6 等),从而加重肝脏损伤。源于肠道的有益原籍菌(如双歧杆菌、乳酸杆菌、肠球菌等)的微生态制剂的使用^[37],可促进肠道内乳酸等代谢产物的产生,抑制潜在致病菌的过度生长定植,提供维持肠道微生态平衡的厌氧条件,从而减少细菌易位和内毒素的生成。

对肝硬化肠源性内毒素血症患者,推荐使用双歧杆菌四联活菌、双歧杆菌三联活菌、乳酸杆菌(包括鼠李糖乳酪杆菌 GG 株)、枯草杆菌二联活菌、地衣芽孢杆菌等制剂作为辅助治疗^[38-42]。此外,乳果糖和拉克替醇可促进双歧杆菌和乳酸杆菌增殖,改善肠道营养环境,降低炎症因子,改善肝功能,亦推荐使用^[43]。

3.2 微生态制剂在肝硬化自发性细菌性腹膜炎中的应用 自发性细菌性腹膜炎是肝硬化失代偿期的严重并发症和导致患者死亡的重要并发症之一。肠道细菌易位在自发性细菌性腹膜炎中起重要作用,大肠埃希菌(*Escherichia coli*)、肺炎克雷伯菌(*Klebsiella pneumoniae*)、唾液链球菌(*Streptococcus salivarius*)、肠球菌等肠道潜在致病菌过度生长,并且上移定植成为优势菌,释放内毒素等,通过细菌易位导致感染。革兰阴性菌(如大肠埃希菌)可优先易位,某些大肠埃希菌菌株(如生化表型 C1、C2、C3、C4、C25 等)在宿主代谢紊乱及炎症条件下,其肠黏膜易位发生率更高,肝硬化自发性细菌性腹膜炎腹水分离到的大肠埃希菌呈现基因多样性。

对肝硬化自发性细菌性腹膜炎的预防和治疗,推荐使用枯草芽孢杆菌二联活菌、地衣芽孢杆菌、双歧杆菌四联活菌、双歧杆菌三联活菌、酪酸梭菌等作为辅助治疗^[44-46],推荐使用乳果糖或拉克替醇联合益生菌治疗^[47-48]。含有枯草芽孢杆菌的微生态制剂,一方面通过消耗氧气制造厌氧环境,促进双歧杆菌、乳酸杆菌等肠道有益厌氧菌的生长,减少

肠道毒素的吸收；另一方面可以通过脂肽、泛素素阻碍致病菌，如金黄色葡萄球菌的信号转导作用可清除细菌定植^[49]。乳酸杆菌和双歧杆菌可促进免疫组织器官的成熟，提高机体体液免疫和细胞免疫水平。酪酸梭菌产生的丁酸盐不仅具有抗氧化、抗炎作用，还能为肠道上皮细胞代谢提供能量，具有修复上皮细胞屏障的作用。此外，这些微生态制剂还可促进机体对营养物质的吸收，降低血氨，改善肝功能。

3.3 微生态制剂在肝硬化肝性脑病中的应用 肝硬化肝性脑病与肠道菌群失衡及其代谢产物(如氨、假性神经递质、吲哚和内毒素)导致的炎症有关。肝硬化微生物产胺模块、锰相关的转运系统模块及 γ -氨基丁酸(gama-aminobutyric acid, GABA)生物合成模块富集。在高血氨情况下，内毒素引起的炎症反应可加剧神经炎性损伤、脑水肿和最终的神经元功能障碍。基底神经节锰的积累和 GABA 在肝性脑病中发挥作用。

推荐使用乳果糖和拉克替醇，他们能促进双歧杆菌和乳酸杆菌生长，减少吲哚等胺类物质，降低血氨水平，显著改善肝性脑病的临床症状，预防肝性脑病复发。

酪酸梭菌、乳酸杆菌和双歧杆菌等为主要成分的微生态制剂，能促进肠道有益菌增殖，抑制腐败菌的生长，通过减少氨类和吲哚物质的产生降低血氨和假性神经递质水平，改善肝性脑病患者症状^[50-51]。针对肝硬化肝性脑病的益生菌辅助治疗，推荐使用枯草芽孢杆菌二联活菌、双歧杆菌四联活菌、双歧杆菌三联活菌、VSL#3、地衣芽孢杆菌、粪肠球菌等^[52-56]。

在肝硬化微生态治疗的前沿研究中，新菌株的研究为未来的肝硬化微生态治疗方案提供了重要方向。狄氏副拟杆菌(*Parabacteroides distasonis*)在改善肝纤维化方面展现出显著潜力。该菌株通过增加胆汁酸水解酶活性、抑制肠道 FXR 信号通路、降低肝脏牛磺鹅脱氧胆酸(taurochenodeoxycholic acid, TCDCA)水平等，减少了 MPT-Caspase-11 介导的肝细胞焦亡，从而改善肝星状细胞的活化和肝纤维化^[57]。研究发现^[58-59]，嗜黏蛋白阿克曼菌可通过改善肠道屏障功能和调节免疫反应改善肝纤维化和高氨血症，为酒精性肝病的治疗提供了新思路。此外，普拉梭菌被认为是关键的丁酸盐产生菌，在调节全身炎症和改善肝硬化相关病症方面具有潜力^[60-61]。这些菌株不仅为肝硬化的微生态治疗提供了创新视角，也为未来个性化治疗方案奠定了基础。

4 肝衰竭与肝移植

4.1 肝衰竭 肝衰竭作为临床上最为严重的肝病之一，其特征性临床表现包括凝血酶原时间的显著延长(凝血酶原活动度 $<40\%$)、胆红素水平持续上升、不同程度肝性脑病发作以及腹水的形成。根据病程的不同，肝衰竭可分为急性、亚急性、慢加急性和慢性四种类型。肝脏通过分泌胆汁和免疫调节等机制，维护肠道环境和微生物群的平衡。肝衰竭存在肠道微生态失衡、肠道屏障功能受损，通过肠道细菌易位，加剧肝脏损伤。“肠漏”可能是肝衰竭患者病情加重的关键因素之一。

20 世纪 90 年代，发现慢加急性肝衰竭(acute on chronic liver failure, ACLF)患者肠道微生态出现了严重的失衡现象，表现为肠道双歧杆菌、类杆菌、毛螺菌科、拟杆菌科和瘤胃球菌科等潜在益生菌数量显著减少，肠球菌科、链球菌科、巴斯德菌科、肠杆菌科、葡萄球菌科、酵母菌等潜在有害菌数量显著增加。肠道微生态失衡可能通过释放更多的内毒素、微生物代谢物和炎症因子，进一步激发全身性的炎症反应，从而加剧肝脏的慢性炎症状态。肠道微生态失衡与终末期肝病模型(model for end-stage liver disease, MELD)评分、Child-Pugh 评分和器官衰竭相关，并与肝性脑病和感染等并发症显著相关，肠道菌群失衡的程度可以预测其 28 d 和 3 个月的生存率^[62-65]。补充双歧杆菌和乳杆菌等益生菌有助于改善机体炎症状况及肝衰竭。然而，这些益生菌的干预对肝衰竭的作用效果仍需进一步验证。

4.2 肝移植 肝移植是肝衰竭等终末期肝病的有效治疗方法。在肝移植临床研究发现采用厌氧培养和分子生物学方法均证明肝移植受者存在肠道菌群失调，主要表现为有益的双歧杆菌、乳酸杆菌和柔嫩梭菌等显著减少，潜在致病的肠球菌属、肠杆菌科细菌显著增加^[66-67]。肝移植后感染并发症是肝移植受者移植肝失去功能、住院时间延长和死亡的主要原因之一。恢复良好且生存期较长的肝移植受者肠道微生态状况更接近健康人群^[67-68]。肝移植受者术前服用益生菌和益生元可以减少肠道菌群异位，显著降低移植术后感染的发生率，特别是尿路感染的发生率，缩短抗菌药物应用和住院时间^[69-70]。临床研究证实^[71-72]微生态制剂可以改善肝移植术后早期的肝功能，但目前无证据提示其可以提高肝移植的 5 年生存率。尽管肝移植受者处于免疫抑制状态，但未发现微生态制剂的应用会诱发感染，其具有较好的安全性^[73]。因此，肝移植围手术期应用微生态

制剂对减少肝移植术后感染等并发症、促进肝功能恢复有益,但肝移植微生态仍需要深入研究,积累更多数据应用于临床。

5 胆囊切除术后综合征

胆囊切除术后综合征(postcholecystectomy syndrome, PCS)是指胆囊切除术后,术前相似症状再发,通常表现为伴随或不伴黄疸的上腹疼痛和消化不良^[74]。胆囊切除后患者肠道细菌种群数量明显低于对照组,切除后患者肠道中有更多的卵形布劳特菌(*Blautia obeum*)和小韦荣球菌(*Veillonella paroula*)^[75]。与健康人相比,胆囊切除术后患者粪便中双歧杆菌、*Anaerostipes* 和 *Dorea* 的丰度增加^[76]。也有文献报道胆囊切除术后患者大肠埃希菌和肠球菌计数均明显增加,双歧杆菌和乳酸杆菌计数则明显减少,双歧杆菌/大肠埃希菌比值倒置显著。

在确诊为 PCS 的患者肠道中,发现厚壁菌门和拟杆菌门与消化不良、放线菌门与腹痛有显著相关性,提示肠道微生物的改变可能与 PCS 相关^[77-78]。对于胆囊切除术后腹泻的患者,推荐使用双歧杆菌三联活菌或四联活菌,能有效调节肠道菌群,调节胃肠激素分泌和分泌型免疫球蛋白(secretory immunoglobulin A, sIgA)水平,改善肠道功能^[79]。

6 抗生素相关性腹泻

抗生素相关性腹泻(antibiotic-associated diarrhea, AAD)是指伴随抗生素使用而发生的无法用其他原因解释的腹泻,目前主要认为与抗生素使用引发的肠道微生态失衡有关。其发病率因不同人群和抗生素种类而异,一般为 5%~39%^[80],腹泻可在抗生素处理结束后持续长达两个月。AAD 发生在各年龄人群中,但与成人相比,儿童通常发作更快,症状持续时间更短。25%~30% 的 AAD 是由艰难梭菌感染(*Clostridium difficile* infection, CDI)引起的,其通过分泌毒素 A、毒素 B 和/或二元毒素引起肠道黏膜损伤和炎症,导致艰难梭菌相关性腹泻。如不及时医治,可导致严重的伪膜性肠炎和脓毒血症,病死率为 15%~24%。几乎所有抗生素都会增加 CDI 的易感性,使用克林霉素,第三代和第四代头孢或青霉素,氟喹诺酮类药物的 CDI 风险更高^[81-82]。

目前治疗 AAD 的益生菌主要包括双歧杆菌、乳酸杆菌、酵母菌、芽孢杆菌、链球菌和肠球菌等。鼠李糖乳酪杆菌和布拉氏酵母菌是目前预防儿童 AAD 有确定疗效和安全性的益生菌^[83]。在儿童、成人和老年人中,益生菌用于预防 AAD 具有中等效

果^[84-86]。对于具有 AAD 风险因素(如抗生素类别、治疗持续时间、年龄、住院需求、合并症或既往 AAD 发作)的患者考虑使用益生菌预防 AAD,推荐给予高剂量($\geq 5.0 \times 10^9$ CFU/d)鼠李糖乳酪杆菌或布拉氏酵母菌与抗生素同时使用^[84],或给予枯草芽孢杆菌二联活菌^[87-88]。抗生素首次使用 2 d 内给予布拉氏酵母菌;或合并使用嗜酸乳杆菌和干酪乳酪杆菌;或合并使用嗜酸乳杆菌、德氏乳杆菌保加利亚亚种和两歧双歧杆菌;或合并使用嗜酸乳杆菌、干酪乳酪杆菌和鼠李糖乳酪杆菌;或合并使用嗜酸乳杆菌、德氏链球菌保加利亚亚种、两歧链球菌和嗜热链球菌,用于 CDI 的一级预防^[80, 89-92]。

益生菌的作用具有菌株特异性和剂量依赖性。高剂量益生菌($\geq 5.0 \times 10^9$ CFU/d)可使儿童 AAD 发病率降低 63%^[84]。儿童 AAD 患者使用鼠李糖乳酪杆菌 $1 \times 10^{10} \sim 2 \times 10^{10}$ CFU 可获得最佳效果, AAD 风险降低 71%,但成人的最佳剂量尚未明确^[93]。益生菌的补充剂量通常限制在 $1.0 \times 10^8 \sim 1.0 \times 10^{11}$ CFU,但最佳使用剂量应根据不同菌株、剂型做进一步研究。

7 肠易激综合征

肠易激综合征(irritable bowel syndrome, IBS)是以腹痛、腹胀或腹部不适为主要症状,与排便相关或伴随排便习惯,如频率和(或)粪便性状改变,通过临床常规检查,尚无法发现能解释这些症状的器质性疾病^[94]。IBS 包括腹泻型(IBS with diarrhea, IBS-D)、便秘型(IBS with constipation, IBS-C)、混合型(IBS with mixed, IBS-M)和未定型(unclassified IBS, IBS-U)4 种亚型,其可能与内脏高敏感性、胃肠道动力异常、肠道菌群失调、小肠细菌过度生长、肠道感染、食物不耐受、免疫异常、社会心理因素以及菌群-肠-脑轴失调等有关。肠道微生态失衡可能与 IBS 症状和持续有关,主要表现为肠道微生物定植抗力受损、微生物多样性降低、黏膜相关菌群组成、肠道菌群构成和代谢产物活性改变,如肠道中大肠埃希菌、肠球菌和厚壁菌门比例增加,拟杆菌门、梭状芽孢杆菌和双歧杆菌比例减少,短链脂肪酸代谢紊乱。此外,IBS-D 患者还存在肠道真菌失调^[95]。

微生态调节剂为临床治疗 IBS 提供了新思路,具有一定疗效,但目前不同研究对微生态调节剂治疗 IBS 的疗效评价存在差异,可能与不同研究采用的微生态调节剂的种类、剂量、剂型、使用方法和疗效评价标准不同有关。根据《WGO 全球指南:益生菌和益生元》^[96],微生态调节剂治疗 IBS 可以改

善患者腹胀、肠胀气、腹泻、便秘，一些特定菌株还可以缓解疼痛，缩短患者症状持续时间、降低抑郁评分，提高生活质量。所以根据患者的病情、症状，选取有针对性的微生态调节剂就显得尤为重要。微生态调节剂改善 IBS 主要通过以下四个方面起作用：(1)调节肠道菌群；(2)改善肠黏膜屏障功能；(3)调节肠道免疫功能；(4)降低内脏高敏感性；(5)改善肠道蠕动功能。

IBS-D 患者治疗常使用如枯草芽孢杆菌、屎肠球菌、酪酸梭菌、鼠李糖乳酪杆菌、植物乳植杆菌、婴儿双歧杆菌、长双歧杆菌、布拉氏酵母菌、地衣芽孢杆菌、凝固芽孢杆菌中的一种或几种菌组成的微生态调节剂，以改善患者腹痛、腹泻症状，还可降低症状持续时间；IBS-C 患者治疗常使用如双歧杆菌、酪酸梭菌、鼠李糖乳酪杆菌、植物乳植杆菌、嗜酸乳杆菌、枯草芽孢杆菌、屎肠球菌、动物双歧杆菌(*Bifidobacterium animalis*)、嗜热链球菌或保加利亚乳杆菌中的一种或几种菌组成微生态调节剂，以改善患者腹胀、腹痛、便秘、肠胀气等症状，并可提高排便频率；IBS-M 和 IBS-U 患者的治疗可使用具有双向调节作用的微生态调节剂，常见菌株包括双歧杆菌、鼠李糖乳酪杆菌、植物乳植杆菌、嗜酸乳杆菌、屎肠球菌、酪酸梭菌等，不仅可以改善患者腹胀、腹痛，还可以降低患者肠道敏感性、抑郁评分、减轻肠道炎症反应^[97-100]。微生态调节剂推荐使用剂量为 $10^7 \sim 10^{10}$ CFU，可联合短链低聚果糖、低聚半乳糖等益生元、合生素、后生元等才能达到改善 IBS 的目的^[96]。还需注意的是，应根据患者病情适当调整微生态调节剂的使用剂量。综上，微生态调节剂可作为 IBS 综合治疗的手段之一，但应根据患者的具体病情，选择合适的微生态调节剂，并需要多中心临床试验进一步验证。

8 炎症性肠病

炎症性肠病(inflammatory bowel disease, IBD)包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD)。IBD 患者肠道微生物种类与健康人有明显差异，其肠道菌群的多样性和丰富度降低。益生菌可通过改变肠道菌群，增加抗菌物质产生，加强肠屏障功能和黏膜免疫调节而发挥作用^[101]。

益生菌可以在轻中度 UC 患者疾病活动期诱导临床缓解并预防复发^[102]，尤以双歧杆菌属和乳酸杆菌属为基础的配方在 UC 患者中最为有效^[103]。长双歧杆菌 536、德氏乳杆菌、发酵乳杆菌、鼠李糖乳酪

杆菌 NCIMB30、鼠李糖乳酪杆菌 NCIMB174 等均可显著降低 UC 疾病活动指数，达到临床缓解。另外，非致病大肠埃希菌 Nissle1917 对 UC 的疗效也与美沙拉嗪相当。混合益生菌 VSL#3 在轻中度 UC 诱导缓解、维持治疗、预防和治疗术后贮袋炎方面有效，维持治疗的效果与 5-ASA 相当^[104]。对于 CD 的治疗，仅有双歧杆菌显示出有益效果^[103]。双歧三联活菌制剂可改善 CD 患者症状和肠道屏障功能^[105]。益生菌作为辅助治疗与 IBD 治疗药物联用较单用 IBD 治疗药物疗效更佳。双歧杆菌三联活菌、双歧杆菌乳杆菌三联活菌、布拉氏酵母菌、地衣芽孢杆菌、复方嗜酸乳杆菌、枯草芽孢杆菌二联活菌等与美沙拉嗪联合使用可提高美沙拉嗪的治疗效果^[106-110]。长双歧杆菌或双歧杆菌三联活菌与英夫利昔单抗联用优于单用英夫利昔单抗。以上益生菌耐受性良好，没有明显的副作用，在推荐剂量下是安全的。

益生元低聚果糖和菊粉可改善 CD 疾病活动指数，低聚半乳糖可改善 UC 活动性^[111]，菊粉可减轻 UC 术后贮袋炎^[112]。低聚果糖、菊粉和包括长双歧杆菌、短双歧杆菌、嗜酸乳杆菌、鼠李糖乳酪杆菌、保加利亚乳杆菌、嗜热链球菌等多种益生菌组成的合生元可改善 IBD 疾病活动度^[113-115]。

微生态制剂用于 IBD 治疗的菌种选择、配伍，给药时机、剂量和疗程等仍需进一步临床证据支持。

9 益生菌治疗乳糖不耐受

乳糖不耐受(lactose intolerance, LI)是指摄入乳糖后因乳糖酶缺乏(lactase deficiency, LD)导致乳糖消化吸收不良，引发腹胀、腹痛、腹泻、恶心等一系列消化道症状的临床综合征^[116]。根据病因可将其分为先天性乳糖酶缺乏、原发性(成人型)乳糖酶缺乏、继发性乳糖酶缺乏、发育性乳糖酶缺乏四类。

益生菌可以缓解 LI 相关症状，尤其是腹痛和胀气，但个别报道认为疗效不确切。不同研究对益生菌治疗 LI 的疗效评价存在差异，可能与不同研究采用的益生菌种类、剂量、剂型、使用方法和疗效评价标准不同有关^[117-122]。研究显示^[117, 123]，嗜酸乳杆菌 DDS-1 可以显著改善腹泻、腹痛、呕吐等消化道症状，而嗜酸乳杆菌 BG2FO4 对 LI 的症状无明显改善。

对继发性乳糖不耐受的婴幼儿，推荐使用枯草芽孢杆菌二联活菌^[124-125]，双歧杆菌、酪酸梭菌二联活菌^[126]，以及长双歧杆菌、保加利亚乳杆菌、嗜热链球菌三联活菌^[127]等制剂作为辅助治疗。对于成人型乳糖不耐受，推荐使用双歧杆菌^[118, 120]，乳酸杆菌(包括 DDS-1^[117, 120]和鼠李糖乳酪杆菌^[118, 122])等制剂作

为辅助治疗。但服用过多的益生菌对改善 LI 无较大帮助,单菌株益生菌给药对减轻腹痛更有效,多菌株益生菌联用对缓解腹泻更有效^[120]。

10 胃肠道黏膜微生态屏障功能障碍及衰竭的微生态综合治疗

胃肠道功能障碍(gastrointestinal dysfunction, GID)及衰竭,同时也存在胃肠道黏膜微生态屏障功能障碍(gastrointestinal mucosal microecological barrier dysfunction)及衰竭。此现象普遍存在于重症监护病房(intensive care unit, ICU)患者,是被低估的严重并发症之一^[128]。欧洲医学会把危重症患者的 GID 的临床症状进行了等级评分(GIDS)。该体系把 GID 分成五个等级:0 级:无风险;1 级:风险升高;2 级:功能障碍;3 级:功能衰竭;4 级:有死亡风险^[129]。

对于胃肠道黏膜微生态屏障功能障碍及衰竭的营养及微生态治疗,分阶段、个性化综合营养及微生态治疗对胃肠道微生态黏膜屏障功能的修复至关重要。其治疗建议,尽可能采用肠内营养(enteral nutrition, EN)和/或经口营养补充(oral nutritional supplement, ONS)。早期补充含有活菌制剂、膳食纤维成分的肠内营养的患者比其他患者表现更好。肠道通透性较低,感染较少^[130-131]。初期的肠内营养推荐补充双歧杆菌和乳酸杆菌、枯草芽孢杆菌二联活菌为主的适量肠内营养,不足部分由肠外营养补充^[132-133]。

乳酸菌作为一类重要的益生菌,被广泛应用于维持肠道微生态平衡,修复肠黏膜损伤,维持肠上皮细胞屏障功能和作用,具有保护肠道黏膜微生态屏障,提高宿主免疫功能^[134]。在促进胃肠道黏膜微生态屏障功能障碍及衰竭患者胃肠道微生态恢复方面,推荐大剂量微生态调节剂冲击治疗,微生态调节剂口服剂量应 $\geq 10^{10} \sim 10^{12}$ CFU/mL,新鲜发酵形成凝固的乳酸菌菌落、未经冻干处理的微生态调节剂,可以使用 400~1 200 mL/d;也可以与其他益生菌的干粉制剂或肠内营养粉剂联合使用,如将酪酸梭菌活菌胶囊(0.2 g, 5×10^7 CFU)与含双歧杆菌、鼠李糖乳酪杆菌等活菌的酸奶和短肽类营养制剂联合应用于术后早期危重症患者,可延缓患者营养状况恶化,改善患者胃肠道功能,防止肠道黏膜屏障损害,提高患者免疫力,减少感染性并发症发生,其疗效明显优于单纯的早期肠内营养治疗。必要时配合微生态调节剂灌肠,如禁食状态下更需使用微生态调节剂灌肠治疗^[135-136]。肠内营养配方中添加适量的谷氨酰胺 0.3~0.5(kg·d)可促进肠黏膜结构和功能的恢复^[137]。

11 肝癌

原发性肝癌是我国第 4 位常见恶性肿瘤,肝细胞癌(hepatocellular carcinoma, HCC)是最常见的病理学类型,占 75%~85%。肝癌的常见病因包括:病毒性肝炎、肝硬化、脂肪性肝病、酒精摄入、黄曲霉毒素暴露和马兜铃酸暴露等^[138]。肠-肝轴在肝癌的发生和发展中发挥了重要作用。

肝癌患者存在明显的肠道菌群失调,疣微菌门(Verrucomicrobia)、另枝菌属(*Alistipes*)、考拉杆菌属(*Phascolarctobacterium*)和瘤胃球菌属(*Ruminococcus*)的丰度显著降低,克雷伯菌属(*Klebsiella*)和嗜血杆菌属(*Haemophilus*)明显富集^[139]。还有研究发现^[140],肝癌患者肠道中拟杆菌属和疣微菌科增加,双歧杆菌属减少。

肠道共生菌长双歧杆菌与 HCC 患者手术预后相关,粪便中富含长双歧杆菌的患者术后肝功能恢复较快。HCC 患者口服包含长双歧杆菌、嗜酸乳杆菌和粪肠球菌的益生菌混合物,可以明显加速术后肝功能恢复。其可能通过增加 5-羟色胺、次级胆汁酸和短链脂肪酸来减轻肝脏炎症和纤维化并促进肝细胞增殖从而加速肝功能恢复^[141]。此外,有研究报道^[142-144]口服枯草芽孢杆菌二联活菌、双歧杆菌、乳酸杆菌和低聚半乳糖等可以促进围手术期肝癌患者的恢复,减少术后并发症,但结果并不稳定,仍需要大样本临床循证证据。

总之,微生态调节剂在肝癌治疗中前景广阔,但仍需更多的大样本、多中心、前瞻性的研究和深入探索。

12 结直肠癌

结直肠癌(colorectal cancer, CRC)是常见的发生于结直肠部位的消化道恶性肿瘤。多数 CRC 起源于腺瘤性息肉,部分随时间进展为腺癌。CRC 通常从息肉开始,并继续发展为肿瘤。其早期没有任何症状,到其进展期出现腹痛、便血、腹泻、体重减轻等症状,后期出现转移灶症状,如转移至肺或肝脏等部位,严重威胁人类生命健康。肠道菌群失调与 CRC 发生发展密切相关,大多数 CRC 患者都有明显的肠道菌群失调现象。鉴于肠道微生物在肠癌的发生发展中的作用,对肠道菌群进行干预是预防和治疗 CRC 的潜在措施。

目前,结直肠癌的治疗以化疗(如奥沙利铂、5-氟尿嘧啶、卡培他滨等)、放疗和外科手术为主,化疗药物往往会引起不同程度的消化道反应,如恶

心、呕吐等。此外,术后还可能出现肠道黏膜屏障功能降低,全身炎症增加,免疫功能降低等。因此生态调节剂(包含双歧杆菌、乳酸杆菌、肠球菌等)的使用,可以促进肠道内短链脂肪酸的产生,重建肠道菌群平衡,防止肠道细菌易位,恢复肠道屏障功能,提高机体免疫功能。

12.1 微生态制剂在结直肠癌围手术期中的应用 对结直肠癌围手术期患者,推荐使用长双歧杆菌活菌、酪酸梭菌二联活菌等制剂作为术前辅助治疗^[145-146],为术前做好充分的肠道准备,有利于术后肠道功能恢复。推荐使用双歧杆菌二联活菌、双歧杆菌三联活菌、双歧杆菌四联活菌等制剂作为围手术期辅助治疗^[147-151],可以有效改善肠道微生态,减少感染等并发症的发生,促进肠道屏障功能恢复,提高化疗和免疫治疗的效率。益生元可以促进肠道益生菌生长,改善肠道营养环境,减轻患者应激反应,提高免疫功能,亦推荐使用复合益生元[低聚果糖(25%)、低聚木糖(25%)、聚葡萄糖(25%)和抗性糊精(25%)]^[152]。

12.2 微生态制剂在结直肠癌根治术后的应用 术后禁食、禁饮及预防性使用抗生素均可改变肠道微环境,引起肠道菌群失调,表现为益生菌减少并被致病菌逐渐取代。致病菌的大量繁殖破坏双歧杆菌、肠杆菌和肠球菌构成的肠菌群屏障,诱发肠道菌群、内毒素易位,产生肠源性感染与内毒素血症。术后及时的微生态制剂介入策略和加强治疗策略对患者的术后并发症具有缓解作用。益生元是益生菌和肠道常驻菌群发酵的底物,其发酵产物可为宿主提供营养支持并发挥生理调节作用。微生态制剂给药可作为 CRC 患者基于膳食补充剂的调节策略之一。

对行结直肠癌根治术的患者,推荐术后使用乳双歧杆菌四联活菌(嗜酸乳杆菌 LA-5、植物乳植杆菌、乳双歧杆菌 BB-12、布拉氏酵母菌)、鼠李糖乳酪杆菌、双歧杆菌三联活菌、戊糖片球菌、植物乳植杆菌 2362、副干酪乳酪杆菌、肠膜明串珠菌(*Leuconostoc mesenteroides*)等作为辅助治疗^[148, 153]。此外,亦推荐使用低聚果糖和抗性淀粉(resistant starch)。低聚果糖和抗性淀粉均可促进益生菌增殖,低聚果糖还可改善肠道营养环境,抗性淀粉可诱导肠细胞中谷胱甘肽 S-转移酶的活性,该酶与化学预防作用相关^[154-155]。

12.3 微生态制剂在结直肠癌化疗中的应用 由于化疗药物在抗癌治疗期间会引起各种副作用,如破坏免疫系统、诱发胃肠道黏膜炎症、肠道微生物失调和损伤生理功能等。这些化疗引起的并发症会影响化疗的抗癌效果,导致治疗中断甚至治疗失败。微

生态制剂辅助治疗可通过直接补充或促进肠道益生菌增殖并调节肠道微生态,减轻化疗相关的肠道副作用。

对结直肠癌化疗患者,推荐使用双歧杆菌四联活菌^[156]制剂作为辅助治疗。乳果糖、低聚果糖可促进双歧杆菌和乳酸杆菌增殖,改善肠道营养环境,抗性淀粉可促进肠道益生菌增殖,并诱导肠细胞中谷胱甘肽 S-转移酶的活性,亦推荐使用。

12.4 结直肠癌免疫治疗的 FMT 应用 由于肠道微生物的组成能够影响免疫检查点阻断治疗的效果和毒性,因此可以通过使用 FMT 改变肠道微生物的组成增强疗效并减弱毒性。抗 PD-1 与 FMT 联合治疗可克服实体肿瘤对抗 PD-1 治疗的耐药性,增强免疫治疗的效果。

对行结直肠癌免疫治疗的患者,推荐在抗 PD-1 治疗时联合使用 FMT 以增强抗 PD-1 治疗效果,改善肠道微环境^[157]。FMT 在临床应用中仍存在一些局限性,如“有益”菌群组成的定义尚不明确,其可能带来潜在不良反应,如严重全身性炎症反应和传播耐药菌等^[158]。未来需进一步明确肠道菌群与肿瘤免疫治疗的关系,并优化 FMT 的临床应用。在结肠癌免疫治疗中,推荐在必要时对个体患者的肠道菌群组成进行评估。

13 肿瘤的微生态免疫治疗

基于免疫的抗癌疗法主要通过增强患者的自身免疫功能或用免疫物质攻击显示外来抗原的癌细胞来抑制癌症。微生物的存在可以增加或减少肿瘤免疫原性,并促进或抑制抗肿瘤免疫。

患者的肠道微生物特征与免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)治疗反应有关。与晚期黑色素瘤患者的 ICIs 反应相关的物种,包括假小链双歧杆菌(*Bifidobacterium pseudocatenulatum*)、罗氏菌属和嗜黏蛋白阿克曼菌^[159]。瘤胃球菌科与结直肠癌患者对 ICIs 的更好反应有关,而微球菌科(*Micrococcaceae*)在无反应者中更为常见。另外,基于菌株水平的肠道微生物特征可以作为预测 ICIs 反应的指标。微生物群特征在不同 ICIs 治疗方案间存在特异性差异,因此微生物学诊断或反应预测应优先依据具体 ICIs 方案,而非癌症类型^[160]。调节肠道菌群和使用益生菌能够增强癌症患者对 ICIs 治疗的响应和临床结果。接受 ICIs 联合益生菌治疗的非小细胞肺癌(non-small cell lung cancer, NSCLC)患者将获得更长的总生存期和无进展生存期^[161],推荐 NSCLC 患者使用酪酸梭菌、双歧杆菌、粪肠球菌、嗜酸乳

杆菌作为接受 ICIs 的辅助治疗^[162-163]。接受纳武利尤单抗-伊匹木单抗的转移性肾细胞癌患者,推荐使用酪酸梭菌^[164]。不可切除的肝癌患者推荐应用鼠李糖乳酪杆菌 Probio-M9 延长患者的总生存期。黑色素瘤患者,推荐使用罗伊氏乳杆菌。

14 肥胖与糖尿病

14.1 肥胖与肠道微生态 肥胖是糖尿病、心血管疾病、肿瘤等慢性疾病的重要危险因素,已成为我国的重大公共卫生问题。肥胖患者 FMT 促进小鼠体重增长证实肠道菌群在肥胖发生中的重要作用,随后大量流行病学研究^[165-166]揭示了肥胖人群存在显著的肠道微生态改变,表现为菌群多样性降低、厚壁菌门/拟杆菌门比例增加,以及一系列特定菌种的丰度变化,如阿克曼菌属和多形拟杆菌(*Bacteroides thetaiotaomicron*)。目前认为菌群失调与肥胖互为因果,肥胖可以调控菌群组成,而菌群也通过短链脂肪酸、胆汁酸、支链氨基酸代谢和脂多糖(lipopolysaccharides, LPS)等菌体成分作用于脑、肝、脂肪、肠道等器官,调控宿主代谢,影响肥胖进程^[166]。调节肠道微生态在肥胖干预中的作用表现出巨大潜力。

益生菌具有改善超重肥胖人群体重和 BMI 的作用^[167-169],如口服短双歧杆菌、嗜酸乳杆菌、干酪乳酪杆菌、植物乳植杆菌复合益生菌(5×10^9 CFU/d)可以一定程度降低超重肥胖人群的体重和 BMI。此外,益生元可通过改变肠道菌群的组成,促进其产生短链脂肪酸等有益代谢物,从而改善宿主代谢。目前益生元主要与益生菌联合补充用于减重,例如低聚果糖、菊粉联合益生菌使用可以改善超重肥胖人群 BMI。此外,菊粉、抗性淀粉等益生元单独使用也可以通过调节肠道菌群的组成来改善超重肥胖人群的 BMI^[170-180]。然而值得注意的是,可能受限于样本量、干预时间等因素,这些临床研究的减重幅度都十分有限,并且结果具有不稳定性,仍然需要大样本临床循证证据的支持。

14.2 糖尿病与肠道微生态 研究发现^[181-182],2 型糖尿病患者不仅存在代谢紊乱,还伴随有肠道菌群失衡。肠道菌群失调破坏肠道屏障功能,增加肠道通透性,导致慢性低度炎症,促进 IR 的发生;某些细菌产生的短链脂肪酸等代谢产物能影响葡萄糖代谢,加重 IR,进一步干扰胰岛素作用。因此,应用微生物生态调节剂(如益生菌和益生元)改善肠道微生物群失调,可能为糖尿病的防治开辟新途径。

双歧杆菌属和乳杆菌属对糖尿病患者血糖水平有一定改善作用^[183-185],如两歧双歧杆菌(*Bifidobac-*

terium bifidum)、长双歧杆菌长亚种(*Bifidobacterium longum subsp. longum*)、嗜酸乳杆菌、干酪乳酪杆菌、鼠李糖乳酪杆菌等。接受益生菌干预的糖尿病患者的 FBG、空腹胰岛素水平(fasting insulin, FINS)、糖化血红蛋白(glycosylated hemoglobin, HbA1c)、胰岛素抵抗指数(homeostatic model assessment of insulin resistance, HOMA-IR)等血糖相关指标有一定改善。妊娠糖尿病(gestational diabetes mellitus, GDM)作为一种特殊类型的糖尿病,在糖尿病管理中也具有重要地位。接受益生菌干预的 GDM 患者的血糖、IR 等指标有明显改善^[186-188]。布拉氏酵母菌、乳酸乳球菌、嗜热链球菌和凝结芽孢杆菌等益生菌也对糖尿病患者的血糖有干预作用^[188-190]。补充菊粉或低聚果糖等益生元可显著降低受试者的 FBG、HbA1c、FINS 和 HOMA-IR^[191]。益生元如菊粉和低聚果糖等亦可联合益生菌使用,发挥改善血糖代谢的作用^[184, 187, 190]。

目前研究中益生菌补充剂量多在 5×10^9 CFU,最佳剂量尚不明确,仍需进一步的大样本临床数据支持。在小鼠实验均中表现出良好的减重降糖、改善肠道屏障的作用,是可以开发的新一代益生菌,未来需进一步开展临床试验验证其在人体内的效应^[165, 192-193]。

15 呼吸系统疾病

在健康成人中,肺部微生物群落对于维持肺功能和免疫防御具有重要作用。这些微生物可能起源于口腔或上呼吸道,并通过微量误吸或吸入等方式进入肺部。在健康的肺部环境中,厚壁菌门、拟杆菌门和变形菌门是最常见的菌门,而普氏菌属、韦荣氏球菌属(*Veillonella*)、链球菌属和假单胞菌属是常见的微生物细菌属^[194]。在肺部感染时,如肺炎、COVID-19、结核和过敏性疾病中,肺部微生物群落的组成会发生变化。

肠道微生物通过产生代谢产物调节免疫反应,经肠-肺轴影响肺部疾病。对呼吸道感染,如新冠、流感、结核的肠道微生物组宏基因组测序分析发现,感染及抗生素应用易导致患者肠道微生态失衡,且肠道微生态与疾病的严重程度以及预后相关。

肠道微生态失衡,肠道屏障受损,肠道有害物质可进入血液循环,激活免疫系统,加重肺部炎症和氧化应激反应。FMT 在恢复肠道微生态的同时可减轻肺部氧化应激反应,从而达到治疗肺部疾病的效果^[195]。补充枯草芽孢杆菌及屎肠球菌可以降低 H7N9 患者继发细菌感染的风险^[196-197]。研究发现^[198-200],目前很多的微生态制剂,可以通过增强免疫反应、改善肠道屏障功能、调节炎症过程和增强抗感染能力

来对呼吸道感染产生积极影响。

李兰娟院士提出的包括“微生态平衡”在内的 H7N9 高致病性禽流感病毒感染防治的“四抗二平衡”方案，在武汉的实践中显示了其有效性。国家卫生健康委员会和国家中医药管理局发布的《新型冠状病毒肺炎诊疗方案（试行第七版）》提及 COVID-19 患者可使用肠道微生态调节剂，维持肠道微生态平衡，预防继发细菌感染。

进一步探索肠道微生物群、呼吸道微生态与呼吸道感染之间的相互作用，为通过调节肠道-呼吸道微生态，维护肺部健康，提供预防和治疗策略。

16 精神类疾病

精神疾病是指在各种生物、心理、社会等因素影响下，出现不同程度的认知、情感、意志和行为等精神活动异常为临床表现的一类疾病。微生物-肠-脑轴的研究为探索精神疾病的发病机制、创新诊治策略提供了新契机。肠道微生态改变不仅与抑郁障碍、双相情感障碍、精神分裂症、孤独症谱系障碍（autism spectrum disorder, ASD）等常见精神疾病的发生发展相关，而且与共病代谢性疾病、胃肠道疾病、神经退行性疾病（如阿尔茨海默病）等也存在关联。基于肠道微生态的干预疗法，正逐步展现出其独特的优势与潜力，有望为精神疾病患者带来更加安全、有效的治疗选择。

16.1 抑郁障碍 抑郁障碍是一种常见的以心境低落、兴趣减退、快感缺失为主要表现的情感障碍。有研究表明^[201-202]，瑞士乳杆菌 R0052 与长双歧杆菌 R0175 的组合（ 3×10^9 CFU/d，连续 8 周）能显著改善抑郁症状，可能通过提升大脑中脑源性神经营养因子（brain-derived neurotrophic factor, BDNF）水平来改善大脑功能^[203]。这两种益生菌与抗抑郁药物联用，可增强抗抑郁疗效并改善肝功能^[204]。使用 2'-岩藻糖基乳糖^[205]或 S-腺苷甲硫氨酸与干酪乳杆菌、长双歧杆菌（ 3×10^9 CFU/d，连续 6 周）的联合干预，有助于缓解亚临床抑郁障碍个体的情绪症状^[206]。此外，4G- β -D-半乳糖基蔗糖可提高患者的自我效能感，但在缓解抑郁症状方面效果不显著^[207]。使用短双歧杆菌 CCFM1025、长双歧杆菌 CCFM687 和乳酸片球菌 CCFM6432（ 4×10^9 CFU/d，连续 4 周）的联合干预作为辅助治疗，有助于改善抑郁障碍患者伴有的胃肠道功能失调症状^[208]。

16.2 双相情感障碍 双相情感障碍是一种以情绪高低交替为主要临床特征的重性情感障碍，根据临床表现常分为双相 I 型和双相 II 型。有研究表明^[209]，动

物双歧杆菌亚种 BAMA-B06/BAu-B0111（ 1×10^9 CFU/d，连续 1 月）作为双相 I 型患者的辅助治疗，可以有效改善抑郁症状，并抑制空腹血糖的升高速度。首发未用药双相情感障碍患者在接受益生菌补充剂（双歧杆菌、乳杆菌和肠球菌复合胶囊）治疗 8 周后，躁狂症状明显减轻，氧化应激指标同步改善^[210]。鼠李糖乳酪杆菌 GG 株和动物双歧杆菌乳亚种 Bb12 株的辅助治疗（ $> 10^8$ CFU/d，连续 24 周）可以降低躁狂患者再住院率，并减少再住院天数^[211]。9 种益生菌合剂（双歧杆菌 W23、乳双歧杆菌 W51、乳双歧杆菌 W52、嗜酸乳杆菌 W22、干酪乳杆菌 W56、副干酪乳杆菌 W20、植物乳植杆菌 W62、唾液乳杆菌 W24 和乳酸乳球菌 W19， $> 2.5 \times 10^9$ CFU/d，连续 3 月）可以改善双相障碍患者胃肠道功能相关的生活质量、认知功能和免疫反应^[212]。此外，该制剂也可能有助于改善稳定期双相障碍患者的认知功能^[213]。

16.3 精神分裂症 精神分裂症是一种以思维紊乱、感知障碍、言行异常为主要临床表现的重性精神障碍。目前的抗精神病药物主要针对精神分裂症的阳性症状有效，但对阴性和认知症状的改善效果有限，并且常伴有显著的不良反应。在精神分裂症患者中，特定的肠道微生物组成发生改变，例如瘤胃球菌属和罗氏菌属的相对丰度降低，而韦荣球菌属的丰度则显著升高，并且这些变化可能与大脑结构和功能的改变存在相关性^[214]。有研究发现^[215]，口服短双歧杆菌 A-1 亚株（ 1.0×10^{11} CFU/d，连续 4 周）可改善精神分裂症患者焦虑和抑郁症状。添加富含低聚果糖的菊粉益生元治疗，可以有选择性地增加精神分裂症患者的血浆丁酸盐水平，从而发挥抗炎作用^[216-217]。12 周的益生菌（双歧杆菌、乳酸菌和肠球菌三联活菌散）和膳食纤维补充剂（低聚糖、菊粉等）的组合被证明对奥氮平诱导的首发精神分裂症药物初治患者体重增加和代谢紊乱有积极影响^[218]。补充益生菌复合制剂（嗜酸乳杆菌、两歧双歧杆菌、罗伊氏乳杆菌和发酵乳杆菌， 8×10^9 CFU/d）和维生素 D（50 000 IU，每 2 周 1 次）12 周对慢性精神分裂症患者的阳性和阴性症状量表总分及其代谢特征和认知功能有积极影响，具有较高的治疗安全性^[219]。

16.4 孤独症谱系障碍 孤独症谱系障碍（ASD）是一种发病于婴幼儿时期的严重大脑发育障碍，以社会交往和沟通障碍、兴趣范围狭窄和重复刻板行为为主要临床表现。有接近半数的孤独症患儿出现腹痛、腹泻、便秘和胃食管反流等胃肠道并发症。有研究显示^[220]，ASD 儿童体内肠道菌群发生改变，拟杆菌门、类杆菌、双歧杆菌、瘤胃球菌等的相对丰度明

显下降。服用 4 个月益生菌制剂后, ASD 患儿肠道微生物结构重塑, 肠道中拟杆菌门/厚壁菌门比例恢复正常, 双歧杆菌属和脱硫弧菌属丰度下降, 乳酸杆菌属丰度升高^[221]。ASD 儿童接受 4 周的植物乳植杆菌 PS128 胶囊(2 粒/d, 每粒含 PS128 菌 3×10^{10} CFU)治疗后, 多动/冲动行为、破坏性行为得到改善^[222]。ASD 儿童连续 3 个月服用含嗜酸乳杆菌、鼠李糖乳酪杆菌和长双歧杆菌三种益生菌的配方奶粉(5 g, 每克奶粉含益生菌 1.0×10^7 CFU)后, 粪便中双歧杆菌和乳酸杆菌丰度增加, 孤独症症状的严重程度、行为特征和胃肠道症状得到明显改善^[223]。另有研究表明^[224], 补充脆弱拟杆菌也有助于改善 ASD 样的行为障碍, 包括刻板行为、沟通障碍、焦虑和感觉运动障碍等。

在各类精神疾病中, 益生菌及益生元制剂初步展现了应用价值, 干预配方具有疾病特异性和症状靶向性。通常选用多种益生菌复方制剂(剂量通常在 $10^8 \sim 10^{11}$ CFU/d), 主要涉及长双歧杆菌、短双歧杆菌、瑞士乳杆菌、干酪乳杆菌、植物乳杆菌、嗜酸乳杆菌、鼠李糖乳杆菌、乳酸片球菌、乳酸乳球菌等, 搭配 2'-岩藻糖基乳糖、S-腺苷甲硫氨酸、4G-β-D-半乳糖基蔗糖、低聚果糖、菊粉等一种或多种益生元。然而, 在不同疾病、年龄的患者群体中, 如何选择安全、有效的益生菌及其干预时间, 仍需大样本的临床研究加以确认。

17 肠菌移植在微生态失衡中的应用

肠菌移植(FMT)是指将健康者粪便菌群移植至患者肠道中, 重建肠道微生态平衡, 以治疗特定肠道及肠道外疾病。目前 FMT 明确的适应证是复发性艰难梭菌感染(CDI), 且 FMT 治疗 CDI 在 2013 年被写入美国医学指南^[225]。FMT 可治疗炎症型肠病、肠易激综合征、慢性疲劳综合征、肥胖症、T2DM、顽固性便秘、原发性硬化性胆管炎、肝性脑病、孤独症、抑郁等胃肠道和非胃肠道相关疾病, 并能增加免疫检查点抑制剂的疗效。FMT 的途径包括: 鼻胃管、胃镜、鼻肠管、结肠镜、灌肠等。有学者认为^[226]移植途径的选择应取决于病变部位以及所患疾病的特点, 如代谢综合征倾向于经十二指肠输注等。新鲜粪便标本处理临床上使用较多的是阿姆斯特丹方案: 即取供者的新鲜粪便 200~300 g 溶解于 500 mL 无菌等渗盐水中, 经搅拌离心过滤后, 形成均一溶液, 再将新鲜粪菌液在 6 h 内注入患者的肠道内。关于 FMT 治疗相关疾病的作用机制仍在深入研究中。针对不同疾病, FMT 在供者选择标准、制剂(粪菌

悬液)制备、移植前抗菌药物的使用时机与种类、移植途径及流程等方面尚缺乏统一标准。然而, 作为肠道微生态的诊疗手段, FMT 的应用前景依然广阔。由于 FMT 筛选、移植流程复杂, 用人工组合菌群移植(synthetic microbiota transplantation, SMT)可能成为今后 FMT 或肠道菌群干预的发展的新方向。此外, SER-109^[227]的成功上市也标志着 FMT 进入到胶囊时代, 提升了 FMT 的可及性和患者的接受度, 同时也让成分、剂量更为清晰, 符合 GMP 生产标准的活体生物药物进入到临床应用范畴。

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