# 粪菌移植技术及其应用进展

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**摘要**: 粪菌移植 (fecal microbiota transplantation, FMT) 技术起源于我国东晋时期, 近20年来发展迅速, 已经成为研究肠道菌群与疾病发生发展因果关系的主要方法; 同时, FMT技术在肠道疾病治疗中的应用也获得广泛认可, 并逐步扩展到其他疾病领域。然而, FMT操作较为复杂, 且无标准化方法, 其成功与否受到供体、受体、菌液处理和植入方式等多种因素的影响。鉴于肠道菌群与多种疾病之间存在密切关系, FMT在科学研究和临床应用领域已成为大家关注的焦点, 其相关研究也取得了系列的重要进展, 为帮助科研工作者更深入了解该项技术, 本文将概述FMT技术的发展历程, 总结科研和临床上常见的操作方法, 梳理其应用进展, 并展望其未来发展发向。

**关键词**: 肠道菌群; 粪菌移植; 操作流程; 临床治疗; 应用进展

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# The technology of fecal microbiota transplantation and its application progress

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**Abstract**: Fecal microbiota transplantation (FMT) technology originated in China during the Eastern Jin Dynasty and has rapidly developed over the past two decades, becoming a primary method for studying the causal relationship between gut microbiota and the occurrence and progression of diseases. At the same time, the therapeutic effects of FMT in the field of gastrointestinal diseases have gained widespread recognition and are gradually expanding into other disease areas. The FMT procedure is relatively complex, and there is currently no standardized method; its success is influenced by various factors, including the donor, recipient, processing of the fecal material, and the method of implantation. Given the increasingly recognized relationship between gut microbiota and various diseases, FMT has become a research hotspot in both scientific studies and clinical applications, achieving a series of significant advancements. To help researchers better understand this technology, this paper will outline the development history of FMT, summarize common operational methods in research and clinical settings, review its application progress, and look forward to future development directions.

**Key words**: gut microbiota; fecal microbiota transplantation; operational procedure; clinical treatment; application progress

## 1 粪菌移植发展历程

粪菌移植 (fecal microbiota transplantation, FMT) 是将供体的粪便移植到受体胃肠道, 从而直接改变受体肠道微生物群的技术方法[1]。目前, FMT已被广泛认可为确定微生物菌群是否在相关疾病中发挥作用的重要手段。此外, FMT也被定义为将健康供体粪便中的菌群移植到患者的胃肠道, 从而实现治疗因肠道菌

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群失调导致疾病的技术, 已逐渐成为一种疾病治疗的新方法[2]。

虽然FMT在临床的应用近年来才被广泛认知, 但其最早记录可追溯到公元4世纪的中国东晋时期, 葛洪在《肘后备急方》中就有“饮粪汁一升, 即活”的记载。书中描述了用人类粪便悬液 (称之为“黄汤”) 治疗食物中毒、严重腹泻的患者, 取得了较好的疗效[3]。16世纪时, 李时珍在《本草纲目》也记载了使用发酵粪液、新鲜粪悬液、干粪或婴儿粪便, 有效治疗腹泻、发热、疼痛、呕吐和便秘等腹部疾病的20多种处方[4]。17世纪, 意大利外科医生 Acquapendente 发明了“transfaunation”一词, 意思是将胃肠道内容物从健康动物转移到患病动物, 该技术在兽医学领域被广泛应用[5,6]。

在临床上, 1958年首例FMT获得成功, Eiseman医生等[7]用健康人的粪汁灌肠治愈了4例万古霉素和甲硝唑治疗无效的伪膜性肠炎患者。1989年, 柳叶刀杂志报道了Bennet等[8]用粪汁灌肠治愈1例溃疡性结肠炎 (ulcerative colitis, UC) 患者, 拓宽了FMT的治疗范围。2003年, Aas等[9]报道了用鼻胃管输入粪汁的方式治疗18名复发性艰难梭菌感染 (*Clostridium difficile* infection, CDI) 患者, 结果其中16名患者经过3个月的治疗后获得缓解。van Nood等[10]于2013年进行了首次FMT随机对照试验发现, 在复发性CDI患者中, 向十二指肠输注健康供体粪便比单独使用抗生素具有更显著的临床疗效。后续病例研究进一步证实了FMT治疗复发性和难治性CDI的治愈率已经达到90%左右[11]。2013年, 美国华盛顿大学Surawicz教授等[12]将FMT列入临床医学指南, 推荐用于治疗复发性CDI患者。随后, 2017年欧洲共识也同样推荐将FMT用于难治性复发性CDI患者[13]。2018年FMT被正式写入我国《炎症性肠病诊断与治疗的共识意见》[14]。

目前, FMT在临床上主要应用于CDI、炎症性肠病 (inflammatory bowel disease, IBD) 等肠道疾病患者, 但肠道菌群与其他疾病的关联性也被不断揭示, 进一步拓宽了FMT的临床应用范围, 如2型糖尿病、肝功能衰竭、癫痫、抑郁等疾病的治疗[15-19]。

## 2　FMT的实施过程

FMT在诸多疾病研究上均展现了有益的疗效, 但是其成功与否与供体、受体、菌液处理和植入方式等多个方面因素有关。然而迄今为止, 无论在临床应用还是基础研究中, FMT均无统一的标准化操作流程, 并且在不同的疾病类型和不同实验中方法差异性较大。为此, 本节对影响FMT的一些重要因素和应用较为广泛的操作方法进行介绍 (图1)。

**2.1　供体**　异体来源是临床应用的移植粪便的主要来源, 相比自体来源, 异体来源便于获取, 能够实现一对多治疗[15]。在临床研究上, 为尽量规避异源供体带来的交叉感染等风险, 多个国家或地区出台了相关指南或共识来规范健康供者的筛查标准, 提出对供体的筛选要遵循问卷、访谈、健康检查 (血液、粪便) 等流程[20]。美国和欧洲共识会议的指南都建议使用问卷对供体的年龄、病史、用药史、家族遗传等进行初步筛选, 以评估任何可能有害的行为; 通过筛选的供体还要进一步接受面试访谈。此外, 合适的供体还要接受血常规、血生化、血液病原体和粪常规、粪便病原体和微生物等检查[20-22]。另外, 供体粪便的初始状态还要依据布里斯托大便分类法进行评估, 选择“3型”或是“4型”的粪便作为移植对象[23]。目前, 肠道菌群移植临床应用管理中国专家共识 (2022版) 对供体的筛选提出了生理、心理、个人史、稳定性、持续性和限食耐受性6个维度, 对包括年龄、血液检查、粪便检查、呼气试验、既往病史及用药史、心理状况、菌群组成、供体持续性等

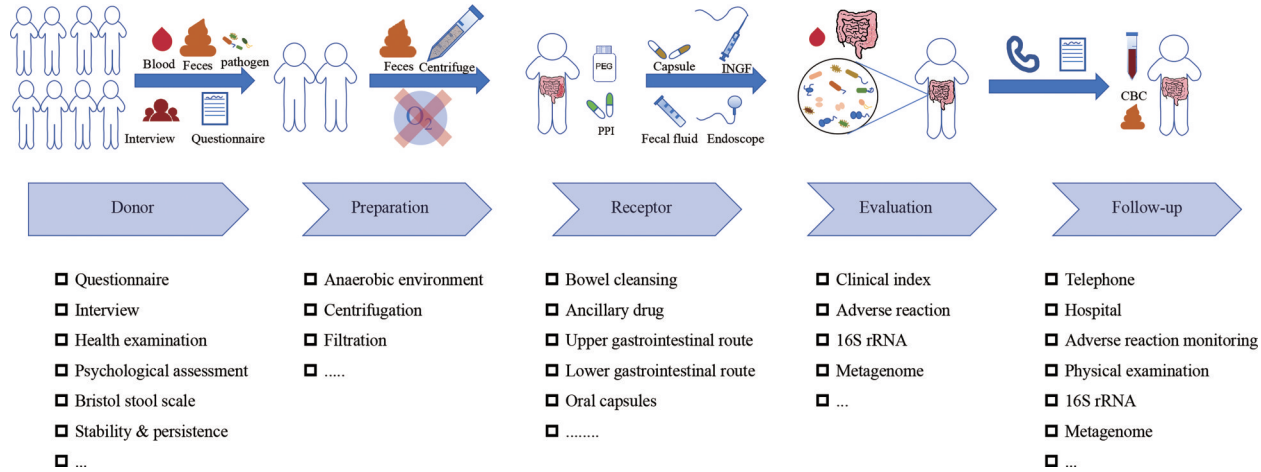


**Figure 1**　Operational procedures of fecal microbiota transplantation (FMT) in clinic. PPI: Proton pump inhibitor; INGF: Intermittent nasogastric feeding; CBC: Complete blood count

指标进行了较为严格的规定[24]。相较于国外研究, 中国对供体的年龄作出了更为严格的规定, 规定供体年龄范围为18～30岁, 但是儿科研究可选择最小年龄为3岁的供体。此外, 持续性指标的规定, 有助于选择经过严格质量控制、可长期多次提供的“标准供体”。

除去一些通用的筛选标准, 利用微生物组测序和机器学习可对FMT供体菌群进行精准化预测选择, 进而提升治疗效果。Smillie等[25]构建了一个机器学习模型来预测复发性CDI患者FMT后受体的菌群植入情况, 并开发了Strain Finder方法用于推断菌株基因型并随时间跟踪它们, 发现供体与受体的细菌丰度和细菌系统发育是植入成功的决定性因素。此外, 他们还在代谢综合征患者的FMT上验证了该模型的有效性。Xiao等[26]基于广义Lotka-Volterra模型构建生态框架评估FMT中的微生物动力学, 以复发性CDI作为原型疾病, 发现受体微生物多样性越高时, 对最佳供体的要求越高。此外, 他们还提出了一种基于网络的方法可除去病原体, 合理设计出真正个性化的益生菌鸡尾酒, 提升疗效及安全性。

Kazemian等[27]对供体及复发性CDI患者移植前后的粪便进行了宏基因组菌群测序, 在属水平上进行了随机森林模型训练, 发现供体中特异性细菌如*Clostridioides*属、*Desulfovibrio*属的存在及受体中*Yarrowia*属 (真菌) 和*Wigglesworthia*属 (细菌) 的存在可以提升FMT的成功率。此外, 他们还推测菌群可能通过胆汁酸和短链脂肪酸 (short chain fatty acids, SCFAs) 等代谢物发挥作用。除了对CDI患者的预测, 针对IBD患者也有部分研究。通过随访中重度克罗恩病和UC患者接受FMT后的菌群变化, 研究人员构建了基于供体与受体细菌结构和宿主参数 (如免疫标志物和胃肠道症状评分) 的随机森林分类模型。该模型可根据移植前参数实现对FMT后受体菌群结构的高预测性 (AUC > 85%), 从而评估FMT恢复菌群的效果[28]。

目前临床前研究的供体既包括人, 也包括大鼠和小鼠等实验动物, 以及牛、马、羊等大型牲畜, 收集的粪便主要用于疾病机制研究和药物研发等。对于实验动物常见的粪便收集方法是通过揉腹部诱导其自主排便后无菌试管收集, 也有部分实验选择盲肠、结肠等部分肠腔内容物或全肠菌群进行移植[2,29]。在动物实验中, 一般会连续多次采集粪便以满足实验所需。在采集时间上, 研究发现小鼠粪便细菌载量在夜间 (约晚上11点) 最高, 在清晨 (上午7点) 最低, 且拟杆菌门与厚壁菌门细菌峰值出现的时间不同[30]。也有研究认为粪便采集应固定在上午7～11点或者下午3～5点, 以减少昼夜节律效应[31]。

**2.2 受体** 临床治疗的FMT受体即为患者。患者在FMT之前应提前3天停用抗生素, 且移植前用聚乙二醇 (polyethylene glycol, PEG) 清洁肠道。若采用经上消化道途径, 在移植前晚及当天早晨服用奥美拉唑等质子泵抑制剂; 若采用经下消化道途径, 移植当天口服洛哌丁胺等抑制肠蠕动药物[32]。

目前以科学研究为目标的粪菌移植受体以小鼠为主。受体可选择无菌 (germ-free, GF) 动物, 也可选择经抗生素或泻药预处理的动物, 以提高粪菌移植的成功率。GF小鼠没有细菌、病毒、真菌、原生动物和寄生虫, 在接受外源性肠道微生物时没有竞争, 为分析宿主与供体微生物之间的关联提供了一种最直接有效的工具[33,34]。但是GF小鼠在FMT的研究上也并非没有缺点, 如其与野生型小鼠或者无特异病原体 (specific pathogen free, SPF) 小鼠肠道结构和生理条件不同: 如GF小鼠肠道黏蛋白、pH、尿素和氧气偏高, SCFAs含量偏低[34], 这些可能都对肠道微生物菌群植入产生较大的影响[35]。此外, 无菌状态可能会导致小鼠的异常发育或生理性改变, 如免疫及代谢系统和神经系统异常等[36,37], 因此选择GF小鼠模型需考虑规避其特异性改变对研究目标疾病的影响。

此外, GF小鼠在饲养、处理、运输上成本很高, 保持无菌的隔离器成本和管理费用昂贵, 并且常需采用细菌培养、血清病原体检测和基于测序的检测技术等来检查GF小鼠是否受到污染[38,39]。高昂的成本进一步限制了GF小鼠的广泛应用, 同时, 无菌状态在人类中是不太可能存在的, 因此使用GF小鼠的研究与临床之间还存在一定的差异。

通过抗生素预处理破坏受体菌群, 降低体内的肠道微生物负荷, 以减轻对供体移植的肠道微生物组的竞争, 得到“拟无菌”(antibiotic pre-treated, AP) 动物是目前研究中最普遍的受体模型[40]。抗生素预处理的AP动物获得简单, 相较于GF动物成本低、操作管理简单、对环境及设施要求低。Ji等[41]研究发现, 抗生素处理的小鼠的FMT有效性高于未经处理的SPF小鼠和服用泻药进行肠道洁净处理的小鼠。

抗生素对受体的肠道菌群有显著的影响, 不同的抗生素种类配比、给药途径和时间可能有不同的效果。不同的抗生素混合物以及给药途径可能显示出不同的疗效[42]。FMT之前, 广谱抗生素治疗常用于消耗受体的肠道微生物群, 但由于各类抗生素作用机制的差异, 可以选择性地减少不同的微生物。因此, 多种抗生素组成的鸡尾酒处理可能有助于允许人类肠道微生物组在受体小鼠中稳定植入[43], 其中氨苄西林、新霉素、甲

硝唑及万古霉素的四联抗生素是使用最广泛的抗生素组合[44-46]。

在给药方式中, 常见的有口服灌胃和添加至饮用水给药两种。其中, 灌胃能更好地控制给药剂量及时间, 但单次给药能维持的作用时间有限, 需采取间断重复灌胃[43-46]。抗生素添加在饮用水中可以延长抗生素作用时间, 以更彻底地清除肠道微生物, 但是难以确保摄入药品的剂量, 需刻意记录其饮水量以估算每日抗生素的摄入量, 但也需要考虑抗生素在饮用水中的放置时间与稳定性[47,48], 每周至少更换一到两次以保持新鲜[49]。另外, 抗生素的苦味会降低小鼠主动饮水量, 因此部分研究还补充了甜味剂, 如糖或Kool-aid饮料混合物, 以保障摄入量[50,51]。此外, 部分研究会将口服灌胃法与饮用水中的给药混合使用, 以加快清除受体菌群的效率[52,53]。抗生素的给药时间一般是3～14天, 具体时间与给药类型、给药浓度和给药方式相关。给药时间并非越长越有益, 据报道给药7天即可保证受体肠道微生物群耗尽, 时间过长会导致抗生素菌的过度生长或产生耐药性[54,55]。虽然AP动物应用广泛, 但在使用时仍需考虑其不良影响, 如抗生素可能促进耐抗生素菌株的生长, 增强病原体的肠道定植力, 提升炎症及感染风险[54,56]。此外, 部分抗生素使用存在毒性反应, 可能诱发心血管疾病、认知异常等[57,58]; 同时, 若目标疾病存在使用抗生素无法规避的影响, 则考虑采用其他受体模型。

使用泻药如PEG预处理清洁肠道是去除受体肠道微生物群的替代方法, 也是临床上患者FMT前常用的处理方法。但是与抗生素相比, 泻药只能暂时降低受体的肠道微生物的丰度[41,59]。PEG使用一般通过高剂量口服灌胃法进行肠道清洁, 一般每20～30 min重复使用一次, 大约4～5次后即可清理肠道和减少细菌负荷[60,61]。然而, PEG可能引起电解质紊乱、脱水以及结肠保护性黏液的变化等, 导致受体腹泻[62-64]。

此外, SPF动物由于不携带潜在感染或条件致病的病原体, 接近于未处理的人类肠道状态, 加之成本低, 近些年来常被用于单菌或多菌混合的移植实验和特定菌株的功能验证[65-67]。

**2.3　菌液制备及给药**　不同机构和实验室在菌液制备上存在差异, 但是整体过程和注意事项是相似的。首先, 粪便一般由10%甘油冷冻保存[68]。研究发现新鲜粪便与冷冻后解冻的粪便移植效果没有显著性差异, 但是反复冻融会使移植效果显著下降[31]。肠道菌群主要由厌氧菌组成, 因此无论是临床应用还是科学研究, 菌液制备需在厌氧条件下进行操作, 以保持细菌的活力[69]。科研上菌液的制备有过滤法、低速离心法及过滤加离心富集法等[70]。过滤法一般是将粪便加入生理盐水或者磷酸缓冲盐溶液 (phosphate buffered saline, PBS) 中, 经无菌纱布逐层过滤或者通过不同孔径的筛网过滤后取得; 离心法一般将粪便混悬液采用低速离心去除食物残渣; 部分研究将新鲜粪便经搅拌、过滤、匀质、再经过滤、离心后置于生理盐水中待用[71,72]。除上述较为简易的制备方法外, 临床上研究常将菌液制备成胶囊, 但该方法程序较复杂且费用高[73,74]。

在临床治疗上, FMT的移植途径主要包括上消化道途径 (经食管胃十二指肠镜给药、鼻胃管、鼻空肠管或鼻十二指肠管)、下消化道途径 (经结肠镜给药或保留灌肠) 和口服胶囊等[20]。经上消化道途径的FMT可用于结肠炎患者, 但存在置管期间不适、误吸风险以及无法评估结肠黏膜或收集黏膜组织样本的缺点。经结肠镜检查的FMT在将有益菌重新定植于整个结肠方面具有优势, 肠道清洁可以减少有机物和细菌孢子的残留, 以便观察整个结肠, 但这是一个相对危险、昂贵和有创的手术。通过保留灌肠进行的FMT比结肠镜检查更经济、创伤更小, 但供体粪便材料不能被输送到整个结肠, 仅限于远端结肠[75]。虽然保留灌肠的疗效曾受到质疑, 但在I期和II期复发性CDI临床试验中证明了其比安慰剂更有效、更安全[76,77]。口服胶囊FMT给药具有创伤小、患者接受度高的优势, 但存在费用高昂和胶囊本身影响菌群释放的缺点[67,75]。

关于各种FMT给药方法, 已有相关研究进行了对比。如Youngster等[78]报道声称, 上消化道和下消化道FMT对复发性CDI的治愈率无显著差异; 但Ramai等[79]发现在CDI患者中, 结肠镜给药的临床治愈高于上消化道途径。此外, Kao等[80]证明, 通过口服胶囊进行FMT在预防CDI复发方面与结肠镜给药的治疗结果相当。另外, 根据患者的病情、对治疗的反应和疗效, FMT给药既可以是一次性治疗, 也可以是多次强化治疗[81]。总之, 目前临床上没有强有力的证据证明何为最佳的FMT给药方法, 应该根据临床个体情况来决定合适的方法。

在科研实验中, 小鼠的FMT可以采用口服灌胃、灌肠、同笼饲养的方法进行[82]。此前人们推测, 由于口服灌胃需要通过酸性胃环境, 通过灌肠方式进行FMT可能会让肠道菌群更有效地定植[83]。但对小鼠FMT的研究表明, 对用抗生素治疗SPF小鼠分别进行口服灌胃和灌肠接种供体小鼠肠道菌群, 接种后微生物群落没有差异[84]。因此, 虽然灌肠在临床FMT使用的有效性和安全性方面更可取, 但在小鼠研究中, 出于方便通常选择口服灌胃的方式进行[85]。目前文献[86]报道的

实验中绝大多数研究 (90.4%) 选择口服给药, 只有少数 (2.9%) 使用直肠给药。

**2.4 菌群植入检测** 临床上FMT一般需要多轮移植来保证定植效果, 但对于科学研究是否需要多轮移植尚无定论, 但大部分研究认为当目标微生物较为复杂、致病或治疗周期较长时, 采用多次移植更能保证定植的效率[82,86]。FMT的临床疗效评价主要体现在对相应疾病症状的缓解或消除为主, 后续随访主要针对患者的状态以及客观化验检查指标, 对移植后的粪便微生物组成的检测不是必需的[24]。但基础研究一般通过16S rRNA测序、宏基因组等方式对其定植情况进行监测, 以保证成功移植和后续结论的可信度[87,88]。

在定植建立时间上, 通过FMT将人类肠道微生物群转移到GF小鼠中, 7天后属水平上90%左右的菌能够成功定植[89,90]。研究发现约50%～60%的供体微生物群在FMT 1周后能成功转移到受体AP小鼠中[91]。周志谟等[92]利用AP小鼠探究不同粪菌移植周期对小鼠肠道菌群恢复的影响, 发现两周的移植效果好于1周, 每天1次效果好于每周3次。肠道菌群主要由厚壁菌门、拟杆菌门、放线菌门、变形菌门、梭菌门和疣状菌门构成, 其中厚壁菌门和拟杆菌门占肠道菌群的90%以上。在定植能力上, 并非供体粪便中的所有细菌都具有相同的定植能力, Limketkai等[93]发现, 粪菌移植后厚壁菌门和拟杆菌门占比增加, 变形菌门占比下降, 说明变形菌门定植能力更差。与厚壁菌门相比, 拟杆菌门在定植方面更容易成功[44]。此外, 研究发现供体与受体原本的菌群物种组成与定植结果相关, 如果在FMT之前该物种同时存在于供体和受体中, 则供体菌株的定植能力更好, *Bacteroides* 和 *Fecalibacterium* 属菌群尤为显著。一些供体菌株可以取代同一物种的相关菌株, 但受体中本身不存在的新物种很难定植[94]。

在定植维持时间上, FMT的疗效往往可以持续数年。一项随访研究复发性CDI患者发现, 在FMT治疗 (平均22个月) 后, 82%的患者未出现复发现象[25,95]。Li等[94]研究发现供体和受体菌株广泛共存, 治疗后可持续3个月。供受体同种菌株的定植维持时间和定植成功率均高于新物种。Smillie等[25]为了研究细菌定植的持久性, 多次随访FMT后的CDI患者, 发现FMT后的第一次就诊中确定了125个供体来源的菌株, 到最后一次随访 (4个月后) 时, 这个数字下降到82株 (其中58株为供体衍生菌)。因此, 他们推断供体衍生的菌株可能会在FMT后患者的肠道中持续数月, 但是需要更大样本量的研究来更严格地评估其长期动态。

## 3 FMT在基础研究领域的应用

肠道微生物群是一个复杂、动态和空间异质的生态系统, 寄居着无数可相互作用以及与宿主相互作用的微生物。肠道菌群和宿主免疫代谢系统之间的复杂相互作用会影响其他器官相关的生理功能, 它们之间形成所谓的“轴”, 是宿主细胞和各种微生物群之间的多向通信系统[96-98]。粪菌移植实验可以直接评估供体粪便微生物群对受体的影响, 从而成为判断肠道菌群与其他器官是否可以形成互作轴的关键方法。此外, 在分析药物是否可以通过对肠道菌群的调控进而对疾病治疗发挥作用上, FMT也发挥着重要作用。

**3.1 FMT是判断肠道菌群是否影响其他器官的关键** 肠道菌群作为人体最大的微生态系统, 与宿主共生, 在正常的生理状态下会维持动态平衡。其基因总数约为人自身基因数目的150倍, 被认为是“第八大器官”[96]。目前, 肠道菌群已经被报道和肝脏、脑、心脏、脂肪、骨骼、肺、睾丸等器官形成“轴”, 其中FMT实验为这种关联提供了直接证据, 使肠道菌群成为相关疾病的“新靶点”[97,98] (表1[95-105], 图2)。

**3.2 FMT实验是明确药物是否通过肠道菌群发挥作用的公认手段** 近年来, 随着人们对肠道微生物群与药物互作关系、菌群与宿主共代谢认知的不断深化, 药物是否通过肠道菌群发挥作用具有多个层面的意义[99]。从药物代谢的角度来看, 肠道菌群能够代谢药物产生具有生物活性或毒性的代谢产物, 影响药物的生物利用度和毒性, 从而影响药物对疾病的治疗效果或其安全性[100]; 从菌群调控的角度来看, 药物能够调控肠道菌群的组成及其代谢物, 从而间接发挥治疗作用。FMT可通过将服药供体的菌群移植给受体, 重塑受体肠道菌群稳态, 进而验证药物通过调控肠道菌群间接改善疾病[106,107]。

中药决明子提取物和决明子总糖及两种糖苷可减少高脂饮食造成的非酒精性肝病的脂质积累、炎症反应和菌群紊乱。研究人员采用FMT实验将服用了药物的小鼠粪便上清给模型动物灌胃, 发现FMT组可以调节菌群紊乱, 改善肝脏炎症及脂质代谢, 恢复肠壁损伤[108]。Sung等[109]收集了正常饮食和白藜芦醇喂养的小鼠粪便, 将其上清通过口服灌胃 (3次, 隔天1次) 转移给两组肥胖小鼠, 研究结果显示与正常喂养的小鼠组相比, 移植了白藜芦醇喂养的供体粪便悬浮液的小鼠组葡萄糖清除率更高、炎症因子更低。Hao等[110]首次发现藻酸盐低聚糖 (AOS) 的粪便微生物群移植改善了肠道菌群紊乱及高脂饮食造成的生育能力下降。葛根素是一种天然化合物, 口服生物利用度有限, 但在治疗动脉粥样硬化 (AS) 方面显示出前景, 并可以显著降低普雷沃氏菌丰度。采用FMT实验发现, 移植葛根素饲喂的供体粪便上清, 可以通过调控肠道微生物群

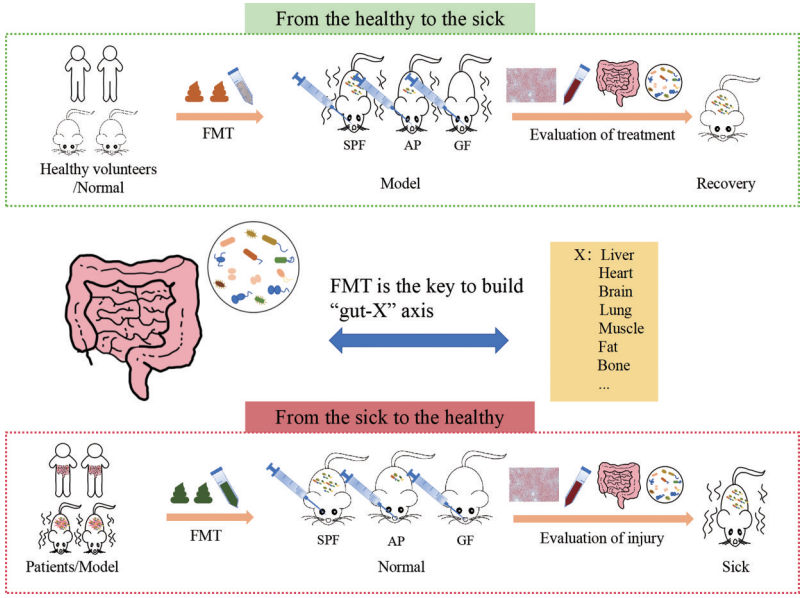


**Figure 2**　Process for building the association between gut microbiota and other organs by FMT. SPF: Specific pathogen free; AP: Antibiotic pre-treated; GF: Germ-free

来缓解AS[111]。

FMT实验可以通过评价移植后对受体小鼠疾病改善效果, 验证药物通过调控菌群间接发挥作用, 但对给药供体粪便的收集和处理中一般不能排除粪便中残留的原型药物及其代谢物的潜在影响, 因此部分研究会在抗生素抑菌动物或无菌动物上进行药效评估, 以排除粪便中残留的药源性成分的影响; 或者对药物所调控的特定菌群进行移植实验, 从而明确药物通过对菌群的调控发挥疗效的机制[108,111]。Wang等[112]建立正常、AP、FMT 3个模型探究红景天苷 (salidroside, SA) 对呋喃诱发的肠道损伤治疗作用的机制, 发现SA对AP小鼠的肠道损伤无治疗效果, 但服用过SA的小鼠粪便移植则可有效改善损伤, 并通过代谢组学进一步发现SA对菌群代谢物短链脂肪酸具有调控, 进而阐明了其作用机制。

## 4　FMT在临床治疗的应用

研究发现, 通过FMT将来自供体粪便的细菌或代谢物引入患病受体中, 重建肠道功能, 调节患者体内的微生态失衡, 对多种疾病的防治都有明显效果, 为疾病的治疗开辟了新思路和新疗法。但目前对FMT治疗疾病的机制探索尚不深入, 仅有部分研究利用组学技术对关键菌群或相关代谢物进行了分析。下面对FMT在各类疾病治疗中的应用进行简要介绍。

**4.1　肠道疾病**　FMT在临床治疗上主要用于治疗由致病性或条件性致病微生物引起的胃肠道疾病, 尤其适用于当肠道菌群因使用抗生素造成紊乱且对抗菌治疗无效时。针对十二指肠给药供体粪便对复发性CDI患者的治疗效果的一项评估发现除FMT组在输注当天出现轻度腹泻或腹部绞痛外, 无其他不良反应, 其有效率为93%, 远高于口服万古霉素 (31%) 或者万古霉素灌洗 (23%)[10]。对原发性和复发性CDI患者进行口服粪便微生物群冻干粉, 89%的患者获得了持续的治愈效果, 并且FMT后6个月菌群测序仍观察到强大的供体贡献。与复发性CDI相比, 原发性CDI与细菌群落的变化更相关[113]。对FMT用于治疗复发性和难治性CDI进行了系统评价和荟萃分析, 纳入37项研究, 发现治愈率在68%～100%, 远好于抗生素[114]。

研究发现, CDI患者在接受FMT后立刻出现了明显的治疗效果, 推测与受干扰的微生物群恢复正常化有关。微生物群分析表明, 在复发性CDI患者FMT后, 患者肠道中的*Bacteroidetes*、*Clostridium clusters* IV和XIVa、*Lactobacillus*和*Veillonella*等益生菌的丰度增加, 而*C. difficile*和*Escherichia coli*等致病菌的丰度降低, 使得患者肠道菌群的组成结构向正常人靠近[115]。另有研究发现, 在解决复发性和难治性CDI方面, FMT比使用万古霉素或甲硝唑的抗生素治疗更快、更有效, 并显著降低了重症患者的死亡率[116]。

此外, FMT在溃疡性结肠炎[117]、肠易激综合征[118-120]、短肠综合征[121]等临床试验中均取得了良好的治疗效果, 有效改善了疾病相关的临床指标和临床症状。

**4.2　神经和精神疾病**　目前关于肠道微生物引发神经退行性疾病的发病机制尚不十分清楚。一般认为, 来自异常肠道菌群的微生物毒素和其他代谢产物可能

**Table 1** Application of FMT in establishing the axis-association between gut microbiota and other organs

| Disease | Donor | Receptor | Cycle and frequency | Result | Reference |
|---|---|---|---|---|---|
| Alcohol-induced liver injury | Normal mice | Alcohol-sensitive receiver mice | 24 days, three times a week | FMT prevented alcohol-induced dysbacteriosis and liver inflammatory lesions and lipid accumulation | [95] |
| Depression | Patients with major depressive disorder or healthy volunteers | Flinders resistant line (FRL) rat, flinders sensitive line (FSL) rat | 3 weeks, three times a week | FRL rats transplanted with feces from disease donors showed more pronounced depressive-like behaviors and dysbiosis of the flora, and no behavioral differences were observed in FSL rats | [96] |
| Atherosclerosis | Normal mice | Atherosclerosis-prone mouse model [C1q/TNF-related protein 9-knockout (CTRP9-KO) mice] | 3 weeks, twice a week | Atherosclerotic lesions in the carotid arteries were decreased in transplanted CTRP9-KO mice | [97] |
| Metabolic syndrome | Normal fat diet mice | High fat diet mice | 12 weeks, five times a week | Weight gain was inhibited and the inflammatory state and metabolism of obesity were improved | [98] |
| Osteoporosis | Senile osteoporotic rats | Old female SD rats | 12 weeks, three times a week | The fecal microbiota was similar to the donor | [99] |
| Liver abscess | Normal mice | Mice infected with *Klebsiella pneumoniae* | 24 h, once | *K. pneumoniae*-caused liver abscess was inhibited | [100] |
| Disrupted spermatogenesis | Normal sheep and excessive-energy diet-induced metabolic syndrome (MetS) sheep | Normal mice | 8 weeks, once a day | Mice transplanted with feces from MetS sheep developed metabolic disorders and sperm damage | [101] |
| Radiation pneumonia | Normal mice | Wild-type C57BL/6J mice exposed to a single 15 Gy dose γ-ray local chest irradiation to mimic radiotherapy for lung cancer | 10 days, once a day | FMT reduced radiation pneumonia, scavenged oxidative stress and improved lung function in mouse models | [102] |
| Aging hematopoiesis | Young mice and old mice | Old AP mice | 4 weeks, once a day | FMT from young mice to aged mice and observed a significant increment in lymphoid differentiation and decrease in myeloid differentiation in aged recipient mice. FMT from young mice rejuvenated aged HSCs with enhanced short-term and long-term hematopoietic repopulation capacity | [103] |
| Frailty | Young mice and old mice | Young AP mice and old AP mice | 6 weeks, every other day | FMT from old mice into young mice reduced body weight and grip strength, and led to elevated inflammatory factors in young mice. FMT treatment in older mice not only improved frailty and muscle mass, but also improved intestinal ecological imbalances, intestinal barrier function, and systemic inflammation | [104] |
| Abdominal obesity | Normal mice | Abdominal obesity mice | 4 weeks, once a day | FMT has led to the repair of gut barrier damage and mitigation of metabolic inflammation, which ultimately ameliorated abdominal fat deposition | [105] |

直接与肠上皮相互作用并增加肠道屏障通透性, 从而导致肠道慢性低度炎症和免疫细胞激活[122]。另一方面, 透过受损肠道屏障的微生物群代谢物可以激活从肠道神经系统到中枢神经系统的神经通路, 从而影响血脑和肠道屏障的功能和发育, 促进中枢神经系统神经炎症和神经退行性病变的发展[122-124]。而通过FMT, 可以调整肠道菌群的组成, 改善肠道屏障, 降低有害代谢物的浓度, 对神经系统疾病起到治疗作用。

研究发现, 来自健康供体的肠道微生物群移植对孤独症谱系障碍 (autism spectrum disorder, ASD)、癫痫、抑郁症、帕金森病、阿尔茨海默病等神经退行性疾病均有有益的影响[125]。如肠道菌群失调和胃肠道问题会影响ASD患者[126], Kang等[127]对18名ASD儿童进行FMT, 在万古霉素口服14天后服用质子泵抑制剂, 移植前一天服用肠道冲洗剂, 而后进行口服或者灌肠给药, 移植后发现ASD儿童胃肠道中的*Bifidobacterium*、

*Prevotella* 和 *Desulfovibrio* 的丰度增加, 便秘、腹泻、消化不良和腹痛等症状得到改善, 孤独症的各项评价量表结果评分下降80%左右, 且效果可在随访的8周内维持。研究人员将1名小学女生的粪菌移植给1名有17年癫痫病史的克罗恩病女患者, 发现移植后可以有效防止该患者癫痫的复发, 并在12个月内将克罗恩病活动指数从361分降至104分[18]。研究认为FMT可用于治疗老年患者的抑郁症, 他们通过将患者健康6岁曾孙的粪菌移植给患者, 4天后患者嗜睡减少, 食欲改变并变得健谈; 2周后, 患者变得欣快, 体重增加, PHQ-9评分降至4分[19]。

**4.3　免疫系统疾病**　肠道菌群的代谢产物 (胆汁酸、维生素、短链脂肪酸、氨基酸等) 与肠道黏膜中免疫细胞表达的宿主代谢物敏感受体直接接触会导致黏膜免疫反应的启动和巨噬细胞、树突状细胞和T细胞的激活[128], 因此FMT对肠道菌群的改变可能会影响免疫系统并改善免疫介导的疾病。

研究发现, 通过肠镜将粪液输注至患者盲肠, 可以调节肠道菌群, 成功治愈难治性免疫检查点抑制剂相关的结肠炎。FMT后, 患者 $CD8^+$ T细胞密度显著降低, 结肠黏膜内调节性T细胞比例增加, FMT治疗后患者临床症状完全消退, 最终恢复正常的每日固体排便, 并没有进一步出血[129]。Jacob等[130]通过结肠镜检查对活动性溃疡性结肠炎患者进行了供体 (来源于OpenBiome粪便库) 粪便的单次递送, 4周后, 35%的患者达到临床治愈标准, 15%的患者症状得到缓解, 10%的患者黏膜发生了愈合。分析发现, FMT后患者黏膜 $CD4^+$ T细胞中IFN$\gamma$的产生显著减少, Th1和Treg也相应减少, 证明FMT可以调节患者的免疫和炎症反应。

此外, FMT在治疗自身免疫性疾病上也取得了许多成果。在临床试验中, FMT显著改善了乳糜泻[131]和类风湿性关节炎患者的症状[132], 对多发性硬化症[133,134]、银屑病关节炎[135,136]、1型糖尿病[137]展现出了相当的治疗潜力。

**4.4　肿瘤及其并发症**　FMT有望增加对免疫治疗耐药的癌症患者肠道微生物种群的多样性和组成。Kakihana等[138]认为FMT可以作为肠道急性移植物抗宿主病 (acute graft-*versus*-host disease, GvHD) 干细胞移植患者的一种安全的新型治疗选择。GvHD是接受来自基因不同的人的移植组织后的一种医疗并发症。在急性髓系白血病的GvHD患者中, FMT可增加外周效应调节性T细胞, 减少 *Streptococcus* 并增加肠道中的 *Bacteroides*、*Lactobacillus* 和 *Bifidobacterium*, 肠道菌群的正常化也给患者带来了胃肠道症状的恢复效果。

一项I期临床试验对10名抗程序性细胞死亡蛋白1 (programmed cell death protein 1, PD-1) 难治性转移性黑色素瘤患者进行FMT, 选择两名之前接受过抗PD-1单药治疗转移性黑色素瘤, 并且已经达到持久完全缓解至少1年的患者作为供体。通过口服粪便胶囊给药, 结肠镜检查观察3例患者的临床反应, 结果其中2例部分缓解、1例完全缓解。此外, FMT治疗与固有肠层和肿瘤微环境中免疫细胞浸润和基因表达谱的有利变化也具有相关性[139]。在患有复发性CDI且使用细胞毒化疗治疗的血液和实体恶性肿瘤患者中, 通过结肠镜检查将供体粪便单次滴入盲肠, 结果发现腹泻得到了缓解, 对CDI具有治疗作用, 并且没有发现感染性并发症, 仅有短暂性腹泻、便秘等轻微不良反应, 说明FMT是一种高效和安全的治疗选择, 即使是在化疗期间也可以考虑使用[140]。尽管目前看来FMT的安全性良好, 但有研究指出, 由于免疫功能低下患者存在感染风险, 因此在肿瘤环境中必须谨慎使用FMT[141]。

**4.5　代谢类疾病**　FMT对代谢综合征有一定的治疗作用。Vrieze等[15]将瘦削的人类供体粪便过滤后从十二指肠注入移植给代谢综合征患者, 6周后观察到受体的胰岛素敏感性得以增加 (葡萄糖清除率从26.2变为45.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$)。由此认为肠道微生物群可能被开发为治疗剂, 以增加人类的胰岛素敏感性。Kootte等[142]研究了采用瘦削的人类供体粪菌移植对患有代谢综合征的男性受体的影响。他们筛选BMI小于25的健康供体, 通过鼻十二指肠管进行输注, 6周后观察到受体的外周胰岛素敏感性得到改善, 糖化血红蛋白水平发生了降低, 但治疗效果的持续性较差, 18周后FMT已无治疗作用, 但这可能与他们恢复原本的饮食生活方式有关。

FMT在体重调节中起着重要作用。肠道微生物群落对于处理膳食多糖、促进肠腔中单糖的吸收和诱导肝脏脂肪从头合成至关重要。肠道微生物群还影响宿主饮食和能量储存的收集[143,144]。在FMT治疗CDI期间, 接受健康但超重供体粪便的受体女性体重显著增加, 即使通过控制饮食和锻炼, 受体女性的体重依然未见减轻[145]。研究发现接受FMT的神经性厌食症患者体重增加, FMT后26岁女性体重增加6.3 kg[146]。为此他们提出了一种假设: 体重的增加可能与某些微生物从食物中提取卡路里的能力有关。如通过对不消化的碳水化合物代谢产生SCFAs, 尽管饮食摄入量没有增加, 但能量摄取增加。

## 5　总结与展望

FMT技术有着悠久的历史背景, 其在近些年发展

迅速, 已经取得一系列创新性的研究成果并被用于临床治疗。但是目前在临床上的应用还不够普遍, 多数处在实验性治疗阶段, 仍需要长期反复的论证与试验证明其安全性和有效性。总结现有研究, 笔者认为FMT未来的研究重点可以在以下几个方面开展: 标准化是FMT发展的关键, 需统一供体筛选、样本制备及移植方法, 并扩大标准化粪菌库建设以提升规范化和应用范围; 目前对于移植后菌群稳定性的监测不足, 建议至少进行4周随访, 并采用微生物组学等技术进行菌群动态监控; 加强FMT不良反应评估, 特别是对免疫抑制患者的风险管理, 以制订科学治疗指南; 提倡精准个体化治疗, 通过筛选和组合益生菌提升FMT安全性和疗效, 利用AI技术实现个性化方案定制; 深化FMT机制研究, 解析关键菌群及其代谢物、基因等, 以推动其在更多疾病中的应用; 关注FMT伦理法律问题, 确保供体筛选、样本处理合规, 保护隐私并合理补偿供体。

FMT历经千年发展, 从古老疗法演变为现代治疗手段, 其临床应用已扩展至CDI、免疫性疾病等领域, 通过重建肠道菌群平衡展现其治疗潜力。实施过程是影响FMT结果的关键, 虽在供体筛选、受体处理、粪便制备、移植途径以及植入评估等方面取得了显著进展, 但仍需建立标准化流程。基础研究上, FMT是揭示肠道微生物与宿主健康的复杂关系的关键, 同时也是明确药物是否通过肠道菌群发挥作用的手段。然而, FMT仍面临供体筛选、安全性及伦理法律等挑战。未来随着科学技术的不断发展与研究的不断深入, FMT有望在医学领域发挥更大作用。

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## References

[1] Jia Q, Li H, Zhou H, et al. Role and effective therapeutic target of gut microbiota in heart failure [J]. Cardiovasc Ther, 2019, 2019: 5164298.

[2] Porcari S, Benech N, Valles-Colomer M, et al. Key determinants of success in fecal microbiota transplantation: from microbiome to clinic [J]. Cell Host Microbe, 2023, 31: 712-733.

[3] Ge H. Handbook of Prescriptions for Emergencies (肘后备急方) [M]. Tianjin: Tianjin Science and Technology Press, 2000: 36.

[4] Li SZ. Compendium of Materia Medica (本草纲目) [M]. Beijing: Huaxia Publishing House, 2011: 1921-1923.

[5] Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection [J]. Am J Gastroenterol, 2012, 107: 1079-1087.

[6] Borody TJ, Warren EF, Leis SM, et al. Bacteriotherapy using fecal flora: toying with human motions [J]. J Clin Gastroenterol, 2004, 38: 475-483.

[7] Eiseman B, Silen W, Bascom GS, et al. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis [J]. Surgery, 1958, 44: 854-859.

[8] Bennet JD, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora [J]. Lancet, 1989, 333: 164.

[9] Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered *via* a nasogastric tube [J]. Clin Infect Dis, 2003, 36: 580-585.

[10] van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile* [J]. N Engl J Med, 2013, 368: 407-415.

[11] Kassam Z, Lee CH, Yuan Y, et al. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis [J]. Am J Gastroenterol, 2013, 108: 500-508.

[12] Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections [J]. Am J Gastroenterol, 2013, 108: 478-498.

[13] Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice [J]. Gut, 2017, 66: 569-580.

[14] Wu KC, Liang J, Ran ZH, et al. Chinese consensus on diagnosis and treatment in inflammatory bowel disease (2018, Beijing) [J]. Chin J Pract Intern Med (中国实用内科杂志), 2018, 38: 796-813.

[15] Vrieze A, van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome [J]. Gastroenterology, 2012, 143: 913-916.e7.

[16] Udayappan SD, Hartstra AV, Dallinga-Thie GM, et al. Intestinal microbiota and faecal transplantation as treatment modality for insulin resistance and type 2 diabetes mellitus [J]. Clin Exp Immunol, 2014, 177: 24-29.

[17] Sharma A, Roy A, Premkumar M, et al. Fecal microbiota transplantation in alcohol-associated acute-on-chronic liver failure: an open-label clinical trial [J]. Hepatol Int, 2022, 16: 433-446.

[18] He Z, Cui BT, Zhang T, et al. Fecal microbiota transplantation cured epilepsy in a case with Crohn's disease: the first report [J]. World J Gastroenterol, 2017, 23: 3565-3568.

[19] Cai T, Shi X, Yuan LZ, et al. Fecal microbiota transplantation in an elderly patient with mental depression [J]. Int Psychogeriatr, 2019, 31: 1525-1526.

[20] Wang JW, Kuo CH, Kuo FC, et al. Fecal microbiota transplanta-

tion: review and update [J]. J Formos Med Assoc, 2019, 118: S23-S31.

[21] Wischmeyer PE, McDonald D, Knight R. Role of the microbiome, probiotics, and 'dysbiosis therapy' in critical illness [J]. Curr Opin Crit Care, 2016, 22: 347-353.

[22] Jayasinghe TN, Chiavaroli V, Holland DJ, et al. The new era of treatment for obesity and metabolic disorders: evidence and expectations for gut microbiome transplantation [J]. Front Cell Infect Microbiol, 2016, 6: 6-15.

[23] Madsen AMA, Halkjær SI, Christensen AH, et al. The effect of fecal microbiota transplantation on abdominal pain, stool frequency, and stool form in patients with moderate-to-severe irritable bowel syndrome: results from a randomized, double-blind, placebo-controlled study [J]. Scand J Gastroenterol, 2021, 56: 761-769.

[24] Society of Parenteral and Enteral Nutrition, Chinese Medical Association; Microecology Professional Committee of Shanghai Preventive Medicine Association. Chinese expert consensus on screening and management of fecal microbiota transplantation donors (2022 edition) [J]. Chin J Gastrointest Surg (中华胃肠外科杂志), 2022, 25: 757-765.

[25] Smillie CS, Sauk J, Gevers D, et al. Strain tracking reveals the determinants of bacterial engraftment in the human gut following fecal microbiota transplantation [J]. Cell Host Microbe, 2018, 23: 229-240.

[26] Xiao Y, Angulo MT, Lao S, et al. An ecological framework to understand the efficacy of fecal microbiota transplantation [J]. Nat Commun, 2020, 11: 3329.

[27] Kazemian N, Ramezankhani M, Sehgal A, et al. The trans-kingdom battle between donor and recipient gut microbiome influences fecal microbiota transplantation outcome [J]. Sci Rep, 2020, 10: 18349.

[28] Zou M, Jie Z, Cui B, et al. Fecal microbiota transplantation results in bacterial strain displacement in patients with inflammatory bowel diseases [J]. FEBS Open Bio, 2020, 10: 41-55.

[29] Zheng Y, Ding Y, Xu M, et al. Gut microbiota contributes to host defense against *Klebsiella* pneumoniae-induced liver abscess [J]. J Inflamm Res, 2021, 14: 5215-5225.

[30] Liang X, Bushman FD, FitzGerald GA. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock [J]. Proc Natl Acad Sci U S A, 2015, 112: 10479-10484.

[31] Ericsson AC, Gagliardi J, Bouhan D, et al. The influence of caging, bedding, and diet on the composition of the microbiota in different regions of the mouse gut [J]. Sci Rep, 2018, 8: 4065.

[32] Brown WR. Fecal microbiota transplantation in treating *Clostridium difficile* infection [J]. J Dig Dis, 2014, 15: 405-408.

[33] Li Y, Cao W, Gao NL, et al. Consistent alterations of human fecal microbes after transplantation into germ-free mice [J]. Genomics Proteomics Bioinformatics, 2022, 20: 382-393.

[34] Al-Asmakh M, Zadjali F. Use of germ-free animal models in microbiota-related research [J]. J Microbiol Biotechnol, 2015, 25: 1583-1588.

[35] Gillilland MG 3rd, Erb-Downward JR, Bassis CM, et al. Ecological succession of bacterial communities during conventionalization of germ-free mice [J]. Appl Environ Microbiol, 2012, 78: 2359-2366.

[36] Uzbay T. Germ-free animal experiments in the gut microbiota studies [J]. Curr Opin Pharmacol, 2019, 49: 6-10.

[37] Kennedy EA, King KY, Baldridge MT. Mouse microbiota models: comparing germ-free mice and antibiotics treatment as tools for modifying gut bacteria [J]. Front Physiol, 2018, 9: 1534.

[38] Fontaine CA, Skorupski AM, Vowles CJ, et al. How free of germs is germ-free? Detection of bacterial contamination in a germ free mouse unit [J]. Gut Microbes, 2015, 6: 225-233.

[39] Nicklas W, Keubler L, Bleich A. Maintaining and monitoring the defined microbiota status of gnotobiotic rodents [J]. ILAR J, 2015, 56: 241-249.

[40] Sarrabayrouse G, Landolfi S, Pozuelo M, et al. Mucosal microbial load in Crohn's disease: a potential predictor of response to faecal microbiota transplantation [J]. EBioMedicine, 2020, 51: 102611.

[41] Ji SK, Yan H, Jiang T, et al. Preparing the gut with antibiotics enhances gut microbiota reprogramming efficiency by promoting xenomicrobiota colonization [J]. Front Microbiol, 2017, 8: 1208.

[42] Johnson SA, Nicolson SW, Jackson S. The effect of different oral antibiotics on the gastrointestinal microflora of a wild rodent (*Aethomys namaquensis*) [J]. Comp Biochem Physiol A Mol Integr Physiol, 2004, 138: 475-483.

[43] Hintze KJ, Cox JE, Rompato G, et al. Broad scope method for creating humanized animal models for animal health and disease research through antibiotic treatment and human fecal transfer [J]. Gut Microbes, 2014, 5: 183-191.

[44] Ochoa-Repáraz J, Mielcarz DW, Ditrio LE, et al. Role of gut commensal microflora in the development of experimental autoimmune encephalomyelitis [J]. J Immunol, 2009, 183: 6041-6050.

[45] Kuss SK, Best GT, Etheredge CA, et al. Intestinal microbiota promote enteric virus replication and systemic pathogenesis [J]. Science, 2011, 334: 249-252.

[46] Stefka AT, Feehley T, Tripathi P, et al. Commensal bacteria protect against food allergen sensitization [J]. Proc Natl Acad Sci U S A, 2014, 111: 13145-13150.

[47] Zhang X, Zhao S, Song X, et al. Inhibition effect of glycyrrhiza polysaccharide (GCP) on tumor growth through regulation of the gut microbiota composition [J]. J Pharmacol Sci, 2018, 137: 324-332.

[48] Zhang S, Zeng L, Ma J, et al. Gut Prevotellaceae-GABAergic septohippocampal pathway mediates spatial memory impairment in high-fat diet-fed ovariectomized mice [J]. Neurobiol Dis,

2023, 177: 105993.

[49] Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis [J]. Science, 2013, 341: 569-573.

[50] Baldridge MT, Nice TJ, McCune BT, et al. Commensal microbes and interferon-$\lambda$ determine persistence of enteric murine norovirus infection [J]. Science, 2015, 347: 266-269.

[51] Emal D, Rampanelli E, Stroo I, et al. Depletion of gut microbiota protects against renal ischemia-reperfusion injury [J]. J Am Soc Nephrol, 2017, 28: 1450-1461.

[52] Reikvam DH, Erofeev A, Sandvik A, et al. Depletion of murine intestinal microbiota: effects on gut mucosa and epithelial gene expression [J]. PLoS One, 2011, 6: e17996.

[53] Parker A, Romano S, Ansorge R, et al. Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain [J]. Microbiome, 2022, 10: 68.

[54] Zhao ZX, Yuan X, Cui YY, et al. Melatonin mitigates oxazolone-induced colitis in microbiota-dependent manner [J]. Front Immunol, 2021, 12: 783806.

[55] Zhu W, Hong Y, Li Y, et al. Microbial and transcriptomic profiling reveals diet-related alterations of metabolism in metabolic disordered mice [J]. Front Nutr, 2022, 9: 923377.

[56] Huang C, Feng S, Huo F, et al. Effects of four antibiotics on the diversity of the intestinal microbiota [J]. Microbiol Spectr, 2022, 10: e0190421.

[57] Kappel BA, De Angelis L, Puetz A, et al. Antibiotic induced gut microbiota depletion exacerbates host hypercholesterolemia [J]. Pharmacol Res, 2023, 187: 106570.

[58] Dahiya D, Nigam PS. Antibiotic-therapy-induced gut dysbiosis affecting gut microbiota-brain axis and cognition: restoration by intake of probiotics and synbiotics [J]. Int J Mol Sci, 2023, 24: 3074.

[59] Jalanka J, Salonen A, Salojärvi J, et al. Effects of bowel cleansing on the intestinal microbiota [J]. Gut, 2015, 64: 1562-1568.

[60] Le Roy T, Debédat J, Marquet F, et al. Comparative evaluation of microbiota engraftment following fecal microbiota transfer in mice models: age, kinetic and microbial status matter [J]. Front Microbiol, 2019, 9: 3289.

[61] Wrzosek L, Ciocan D, Borentain P, et al. Transplantation of human microbiota into conventional mice durably reshapes the gut microbiota [J]. Sci Rep, 2018, 8: 6854.

[62] Yamano HO, Matsushita HO, Yoshikawa K, et al. Randomised clinical study comparing the effectiveness and physiological effects of hypertonic and isotonic polyethylene glycol solutions for bowel cleansing [J]. BMJ Open Gastroenterol, 2016, 3: e000101.

[63] Tropini C, Moss EL, Merrill BD, et al. Transient osmotic perturbation causes long-term alteration to the gut microbiota [J]. Cell, 2018, 173: 1742-1754.e17.

[64] Johansson ME, Gustafsson JK, Holmén-Larsson J, et al. Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis [J]. Gut, 2014, 63: 281-291.

[65] El-Baz AM, Shata A, Hassan HM, et al. The therapeutic role of lactobacillus and montelukast in combination with metformin in diabetes mellitus complications through modulation of gut microbiota and suppression of oxidative stress [J]. Int Immunopharmacol, 2021, 96: 107757.

[66] Qiao S, Liu C, Sun L, et al. Publisher Correction: Gut *Parabacteroides merdae* protects against cardiovascular damage by enhancing branched-chain amino acid catabolism [J]. Nat Metab, 2023, 5: 184.

[67] Le Roy T, Moens de Hase E, Van Hul M, et al. Dysosmobacter welbionis is a newly isolated human commensal bacterium preventing diet-induced obesity and metabolic disorders in mice [J]. Gut, 2022, 71: 534-543.

[68] Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review [J]. J Clin Gastroenterol, 2014, 48: 693-702.

[69] Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis [J]. Gastroenterology, 2015, 149: 110-118.e4.

[70] Guo YC, Huang CL, Lu YY, et al. Current status of fecal microbiota transplantation and its application in inflammatory bowel disease [J]. Int J Digest Dis (国际消化病杂志), 2018, 38: 294-296.

[71] He Z, Zhang FM. Principle, protocol and risk management of Chinese fecal microbiota bank [J]. Chin J Gastroenterol (胃肠病学), 2017, 22: 193-198.

[72] Shi XH. Feces therapy and fecal microecology [J]. Chin J Microecol (中国微生态学杂志), 2017, 29: 1362-1365.

[73] Da J, Xin C. Application of perioperative nursing of fecal microbiota transplantation in patients with inflammatory bowel disease [J]. J Southwest Med Univ (西南医科大学学报), 2018, 41: 563-566.

[74] Allegretti JR, Kassam Z, Osman M, et al. The 5D framework: a clinical primer for fecal microbiota transplantation to treat *Clostridium difficile* infection [J]. Gastrointest Endosc, 2018, 87: 18-29.

[75] Vindigni SM, Surawicz CM. Fecal microbiota transplantation [J]. Gastroenterol Clin North Am, 2017, 46: 171-185.

[76] Orenstein R, Dubberke E, Hardi R, et al. Safety and durability of RBX2660 (microbiota suspension) for recurrent *Clostridium difficile* infection: results of the PUNCH CD study [J]. Clin Infect Dis, 2016, 62: 596-602.

[77] Dubberke ER, Lee CH, Orenstein R, et al. Results from a randomized, placebo-controlled clinical trial of a RBX2660-a microbiota-based drug for the prevention of recurrent *Clostridium*

*difficile* infection [J]. Clin Infect Dis, 2018, 67: 1198-1204.

[78] Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing *Clostridium difficile* infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study [J]. Clin Infect Dis, 2014, 58: 1515-1522.

[79] Ramai D, Zakhia K, Fields PJ, et al. Fecal microbiota transplantation (FMT) with colonoscopy is superior to enema and nasogastric tube while comparable to capsule for the treatment of recurrent *Clostridioides difficile* infection: a systematic review and meta-analysis [J]. Dig Dis Sci, 2021, 66: 369-380.

[80] Kao D, Roach B, Silva M, et al. Effect of oral capsule- *vs* colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: a randomized clinical trial [J]. JAMA, 2017, 318: 1985-1993.

[81] Emanuelsson F, Claesson BE, Ljungström L, et al. Faecal microbiota transplantation and bacteriotherapy for recurrent *Clostridium difficile* infection: a retrospective evaluation of 31 patients [J]. Scand J Infect Dis, 2014, 46: 89-97.

[82] Bokoliya SC, Dorsett Y, Panier H, et al. Procedures for fecal microbiota transplantation in murine microbiome studies [J]. Front Cell Infect Microbiol, 2021, 11: 711055.

[83] Hu J, Chen L, Tang Y, et al. Standardized preparation for fecal microbiota transplantation in pigs [J]. Front Microbiol, 2018, 9: 1328.

[84] Lützhøft DO, Sánchez-Alcoholado L, Tougaard P, et al. Short communication: gut microbial colonization of the mouse colon using faecal transfer was equally effective when comparing rectal inoculation and oral inoculation based on 16S rRNA sequencing [J]. Res Vet Sci, 2019, 126: 227-232.

[85] Park JC, Im SH. Of men in mice: the development and application of a humanized gnotobiotic mouse model for microbiome therapeutics [J]. Exp Mol Med, 2020, 52: 1383-1396.

[86] Secombe KR, Al-Qadami GH, Subramaniam CB, et al. Guidelines for reporting on animal fecal transplantation (graft) studies: recommendations from a systematic review of murine transplantation protocols [J]. Gut Microbes, 2021, 13: 1979878.

[87] Johnson JS, Spakowicz DJ, Hong BY, et al. Evaluation of 16S rRNA gene sequencing for species and strainlevel microbiome analysis [J]. Nat Commun, 2019, 10: 5029.

[88] Knights D, Kuczynski J, Charlson ES, et al. Bayesian community-wide culture-independent microbial source tracking [J]. Nat Methods, 2011, 8: 761-763.

[89] Turnbaugh PJ, Ridaura VK, Faith JJ, et al. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice [J]. Sci Transl Med, 2009, 1: 6ra14.

[90] Staley C, Kaiser T, Beura LK, et al. Stable engraftment of human microbiota into mice with a single oral gavage following antibiotic conditioning [J]. Microbiome, 2017, 5: 87.

[91] Ericsson AC, Personett AR, Turner G, et al. Variable colonization after reciprocal fecal microbiota transfer between mice with low and high richness microbiota [J]. Front Microbiol, 2017, 8: 196.

[92] Zhou ZM, Zhang YJ, Liu MX, et al. Influence of different fecal microbiota transplantation cycles on the recovery of intestinal microbiota in the antibiotic cocktail-pretreated mice [J]. J Hyg Res (卫生研究), 2023, 52: 585-590.

[93] Limketkai BN, Hendler S, Ting PS, et al. Fecal microbiota transplantation for the critically ill patient [J]. Nutr Clin Pract, 2019, 34: 73-79.

[94] Li SS, Zhu A, Benes V, et al. Durable coexistence of donor and recipient strains after fecal microbiota transplantation [J]. Science, 2016, 352: 586-589.

[95] Mamo Y, Woodworth MH, Wang T, et al. Durability and long-term clinical outcomes of fecal microbiota transplant treatment in patients with recurrent *Clostridium difficile* infection [J]. Clin Infect Dis, 2018, 66: 1705-1711.

[96] Adak A, Khan MR. An insight into gut microbiota and its functionalities [J]. Cell Mol Life Sci, 2019, 76: 473-493.

[97] Zhang T, Cheng JK, Hu YM. Gut microbiota as a promising therapeutic target for age-related sarcopenia [J]. Ageing Res Rev, 2022, 81: 101739.

[98] Nguyen NM, Cho J, Lee C. Gut microbiota and Alzheimer's disease: how to study and apply their relationship [J]. Int J Mol Sci, 2023, 24: 4047.

[99] Zhang YY, Wang JH, Hao HH. Advances in gut microbiota-drug interactions [J]. Acta Microbiol Sin (微生物学报), 2023, 63: 4536-4554.

[100] Wang ZY, Shen HR, Han YX, et al. Interactions between gut microbiota-producing enzymes and natural drugs affect disease progression [J]. Acta Pharm Sin (药学学报), 2024, 59: 2183-2191.

[101] Ferrere G, Wrzosek L, Cailleux F, et al. Fecal microbiota manipulation prevents dysbiosis and alcohol-induced liver injury in mice [J]. J Hepatol, 2017, 66: 806-815.

[102] Knudsen JK, Michaelsen TY, Bundgaard-Nielsen C, et al. Faecal microbiota transplantation from patients with depression or healthy individuals into rats modulates mood-related behaviour [J]. Sci Rep, 2021, 11: 21869.

[103] Kim ES, Yoon BH, Lee SM, et al. Fecal microbiota transplantation ameliorates atherosclerosis in mice with C1q/TNF-related protein 9 genetic deficiency [J]. Exp Mol Med, 2022, 54: 103-114.

[104] Lai ZL, Tseng CH, Ho HJ, et al. Fecal microbiota transplantation confers beneficial metabolic effects of diet and exercise on diet-induced obese mice [J]. Sci Rep, 2018, 8: 15625.

[105] Wang N, Ma S, Fu L. Gut microbiota dysbiosis as one cause of osteoporosis by impairing intestinal barrier function [J]. Calcif Tissue Int, 2022, 110: 225-235.

[106] Weersma RK, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome [J]. Gut, 2020, 69: 1510-1519.

[107] Zuo WF, Pang Q, Yao LP, et al. Gut microbiota: a magical multifunctional target regulated by medicine food homology species [J]. J Adv Res, 2023, 52: 151-170.

[108] Luo H, Wu H, Wang L, et al. Hepatoprotective effects of Cassiae Semen on mice with non-alcoholic fatty liver disease based on gut microbiota [J]. Commun Biol, 2021, 4: 1357.

[109] Sung MM, Kim TT, Denou E, et al. Improved glucose homeostasis in obese mice treated with resveratrol is associated with alterations in the gut microbiome [J]. Diabetes, 2017, 66: 418-425.

[110] Hao Y, Feng Y, Yan X, et al. Gut microbiota-testis axis: FMT mitigates high-fat diet-diminished male fertility *via* improving systemic and testicular metabolome [J]. Microbiol Spectr, 2022, 10: e0002822.

[111] Li ZH, Weng J, Yan J, et al. Puerarin alleviates atherosclerosis *via* the inhibition of *Prevotella copri* and its trimethylamine production [J]. Gut, 2024, 73: 1934-1943.

[112] Wang Z, Li L, Li W, et al. Salidroside alleviates furan-induced impaired gut barrier and inflammation *via* gut microbiota-SCFA-TLR4 signaling [J]. J Agric Food Chem, 2024, 72: 16484-16495.

[113] Haifer C, Paramsothy S, Borody TJ, et al. Long-term bacterial and fungal dynamics following oral lyophilized fecal microbiota transplantation in *Clostridioides difficile* infection [J]. mSystems, 2021, 6: e00905-20.

[114] Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection [J]. Aliment Pharmacol Ther, 2017, 46: 479-493.

[115] Fuentes S, van Nood E, Tims S, et al. Reset of a critically disturbed microbial ecosystem: faecal transplant in recurrent *Clostridium difficile* infection [J]. ISME J, 2014, 8: 1621-1633.

[116] Borody TJ, Eslick GD, Clancy RL. Fecal microbiota transplantation as a new therapy: from *Clostridioides difficile* infection to inflammatory bowel disease, irritable bowel syndrome, and colon cancer [J]. Curr Opin Pharmacol, 2019, 49: 43-51.

[117] Ding X, Li Q, Li P, et al. Long-term safety and efficacy of fecal microbiota transplant in active ulcerative colitis [J]. Drug Saf, 2019, 42: 869-880.

[118] Johnsen PH, Hilpüsch F, Cavanagh JP, et al. Faecal microbiota transplantation *versus* placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial [J]. Lancet Gastroenterol Hepatol, 2018, 3: 17-24.

[119] Huang HL, Chen HT, Luo QL, et al. Relief of irritable bowel syndrome by fecal microbiota transplantation is associated with changes in diversity and composition of the gut microbiota [J]. J Dig Dis, 2019, 20: 401-408.

[120] Xu J, Gordon JI. Honor thy symbionts [J]. Proc Natl Acad Sci U S A, 2003, 100: 10452-10459.

[121] Davidovics ZH, Vance K, Etienne N, et al. Fecal transplantation successfully treats recurrent *D*-lactic acidosis in a child with short bowel syndrome [J]. JPEN J Parenter Enteral Nutr, 2017, 41: 896-897.

[122] Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice [J]. Sci Transl Med, 2014, 6: 263ra158.

[123] Erny D, Hrabě de Angelis AL, Jaitin D, et al. Host microbiota constantly control maturation and function of microglia in the CNS [J]. Nat Neurosci, 2015, 18: 965-977.

[124] Liang S, Wu X, Jin F. Gut-brain psychology: rethinking psychology from the microbiota-gut-brain axis [J]. Front Integr Neurosci, 2018, 12: 33.

[125] Antushevich H. Fecal microbiota transplantation in disease therapy [J]. Clin Chim Acta, 2020, 503: 90-98.

[126] Rosenfeld CS. Microbiome disturbances and autism spectrum disorders [J]. Drug Metab Dispos, 2015, 43: 1557-1571.

[127] Kang DW, Adams JB, Gregory AC, et al. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study [J]. Microbiome, 2017, 5: 10.

[128] Steinert A, Radulovic K, Niess J. Gastro-intestinal tract: the leading role of mucosal immunity [J]. Swiss Med Wkly, 2016, 146: w14293.

[129] Wang Y, Wiesnoski DH, Helmink BA, et al. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis [J]. Nat Med, 2018, 24: 1804-1808.

[130] Jacob V, Crawford C, Cohen-Mekelburg S, et al. Single delivery of high-diversity fecal microbiota preparation by colonoscopy is safe and effective in increasing microbial diversity in active ulcerative colitis [J]. Inflamm Bowel Dis, 2017, 23: 903-911.

[131] van Beurden YH, van Gils T, van Gils NA, et al. Serendipity in refractory celiac disease: full recovery of duodenal villi and clinical symptoms after fecal microbiota transfer [J]. J Gastrointestin Liver Dis, 2016, 25: 385-388.

[132] Zeng J, Peng L, Zheng W, et al. Fecal microbiota transplantation for rheumatoid arthritis: a case report [J]. Clin Case Rep, 2021, 9: 906-909.

[133] Al KF, Craven LJ, Gibbons S, et al. Fecal microbiota transplantation is safe and tolerable in patients with multiple sclerosis: a pilot randomized controlled trial [J]. Mult Scler J Exp Transl Clin, 2022, 8: 20552173221086662.

[134] Engen PA, Zaferiou A, Rasmussen H, et al. Single-arm, non-randomized, time series, single-subject study of fecal microbiota transplantation in multiple sclerosis [J]. Front Neurol, 2020, 11: 978.

[135] Kragsnaes MS, Sødergren ST, Kjeldsen J, et al. Experiences and perceptions of patients with psoriatic arthritis participating in a trial of fecal microbiota transplantation: a nested qualitative

study [J]. BMJ Open, 2021, 11: e039471.

[136] Kragsnaes MS, Kjeldsen J, Horn HC, et al. Safety and efficacy of faecal microbiota transplantation for active peripheral psoriatic arthritis: an exploratory randomised placebo-controlled trial [J]. Ann Rheum Dis, 2021, 80: 1158-1167.

[137] de Groot P, Nikolic T, Pellegrini S, et al. Faecal microbiota transplantation halts progression of human new-onset type 1 diabetes in a randomised controlled trial [J]. Gut, 2021, 70: 92-105.

[138] Kakihana K, Fujioka Y, Suda W, et al. Fecal microbiota transplantation for patients with steroid-resistant acute graft-*versus*-host disease of the gut [J]. Blood, 2016, 128: 2083-2088.

[139] Baruch EN, Youngster I, Ben-Betzalel G, et al. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients [J]. Science, 2021, 371: 602-609.

[140] Hefazi M, Patnaik MM, Hogan WJ, et al. Safety and efficacy of fecal microbiota transplant for recurrent *Clostridium difficile* infection in patients with cancer treated with cytotoxic chemotherapy: a single-institution retrospective case series [J]. Mayo Clin Proc, 2017, 92: 1617-1624.

[141] Wardill HR, Secombe KR, Bryant RV, et al. Adjunctive fecal microbiota transplantation in supportive oncology: emerging indications and considerations in immunocompromised patients [J]. EBioMedicine, 2019, 44: 730-740.

[142] Kootte RS, Levin E, Salojärvi J, et al. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition [J]. Cell Metab, 2017, 26: 611-619.e6.

[143] Ridaura VK, Faith JJ, Rey FE, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice [J]. Science, 2013, 341: 1241214.

[144] Turnbaugh PJ, Gordon JI. The core gut microbiome, energy balance and obesity [J]. J Physiol, 2009, 587: 4153-4158.

[145] Alang N, Kelly CR. Weight gain after fecal microbiota transplantation [J]. Open Forum Infect Dis, 2015, 2: ofv004.

[146] de Clercq NC, Frissen MN, Davids M, et al. Weight gain after fecal microbiota transplantation in a patient with recurrent underweight following clinical recovery from anorexia nervosa [J]. Psychother Psychosom, 2019, 88: 58-60.