

结直肠癌术后腹泻发病机制的研究进展

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摘 要

结直肠癌(Colorectal cancer, CRC)是全球第三大常见恶性肿瘤, 手术作为其主要治疗手段, 术后约有20%~50%的患者出现腹泻, 严重影响康复进程与后续治疗。本综述重点阐释术后腹泻的多种发病机制: 胆汁酸性腹泻源于回盲部及末端回肠切除导致的胆汁酸吸收障碍及肠肝反馈失调; 低位前切除综合征与直肠储存、感觉及动力功能障碍有关; 化疗致肠黏膜炎由5-氟尿嘧啶和伊立替康等药物引起肠上皮损伤及炎症反应所致; 放射性肠病则是因辐射直接损伤肠黏膜及微血管结构所引发; 靶向与免疫治疗相关腹泻涉及EGFR/VEGF信号通路抑制及免疫检查点抑制剂诱发的肠炎; 肠道微生态失调则通过短链脂肪酸减少、菌群结构改变及代谢异常等多个途径参与腹泻发生。文章系统梳理上述机制的病理生理基础, 以期对早期诊断工具的研发和个体化治疗策略的优化提供理论参考。

关键词

结直肠癌, 术后腹泻, 发病机制

Research Progress on the Pathogenesis of Postoperative Diarrhea in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is the third most common malignant tumor worldwide. Surgery, as the primary treatment, is followed by diarrhea in approximately 20%~50% of patients, which significantly impacts recovery and subsequent therapies. This review elaborates on the multiple pathogenesis

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of postoperative diarrhea: bile acid diarrhea results from bile acid malabsorption and disrupted enterohepatic feedback due to resection of the ileocecal region and terminal ileum; low anterior resection syndrome is associated with dysfunction in rectal storage, sensation, and motility; chemotherapy-induced intestinal mucositis is caused by damage to the intestinal epithelium and inflammatory responses triggered by agents such as 5-fluorouracil and irinotecan; radiation enteropathy arises from direct injury to the intestinal mucosa and microvascular architecture caused by radiation; targeted and immunotherapy-related diarrhea involves EGFR/VEGF signaling pathway inhibition and immune checkpoint inhibitor-induced enteritis; and intestinal dysbiosis contributes to diarrhea through multiple pathways, including reduced short-chain fatty acids, altered microbial composition, and metabolic abnormalities. This article systematically outlines the pathophysiological basis of these mechanisms, aiming to provide a theoretical reference for the development of early diagnostic tools and the optimization of personalized treatment strategies.

Keywords

Colorectal Cancer, Postoperative Diarrhea, Pathogenesis

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1. 引言

结直肠癌(Colorectal cancer, CRC)是全球第三大常见恶性肿瘤,2022年新发病例超过190万,其发病率和死亡率均维持在较高水平[1]。随着筛查手段的改进、手术技术的进步以及辅助治疗策略的多样化,结直肠癌患者的生存机会正逐步提升。数据显示,结直肠癌手术根治后的总体生存率可达78%,其中I~IIIA期患者的5年生存率甚至超过90%[1]-[3]。然而,术后功能性肠紊乱,尤其是腹泻,发生率为20%~50%,严重影响患者的术后生活质量和康复进程[4]。

腹泻通常定义为排便次数显著多于平日习惯(一般>3次/日),粪便量增加(>200克/日),质地变稀(含水量>85%),并可伴黏液、脓血或未消化食物。根据病因和机制,腹泻可分为分泌性、渗透性、渗出性、动力异常性及脂肪泻等多种类型[5]-[8]。腹泻不仅导致患者体力衰弱,还可能引起脱水、电解质紊乱、营养不良等并发症,甚至影响后续化疗等抗肿瘤治疗的进行。其发生机制复杂,常见原因包括胆汁酸性腹泻、低位前切除综合征、化疗致肠黏膜炎、放射性肠病、靶向与免疫治疗相关腹泻及肠道微生态失调等[9]。不同类型的腹泻在临床表现、发生机制及处理原则上存在差异,因此准确识别其具体类别对实施个体化治疗至关重要。

综上所述,结直肠癌术后腹泻的形成涉及多种机制。下文将重点探讨胆汁酸性腹泻、低位前切除综合征、化疗致肠黏膜炎、放射性肠病、靶向与免疫相关腹泻及肠道微生态失调等主要发病机制,以深化对结直肠癌术后腹泻病理生理过程的理解,并为未来预防与治疗策略的优化提供思路。

2. 结直肠癌术后腹泻的发病机制的研究现状

2.1. 胆汁酸性腹泻

在结直肠癌患者术后,腹泻是较为常见的并发症之一,其中胆汁酸性腹泻尤其值得关注,特别是在右半结肠切除术后。其核心机制在于回肠对胆汁酸的重吸收功能受损,同时肝脏与肠道之间的胆汁酸反馈调节出现异常。结果就是,肝脏持续过量生成胆汁酸,大量初级和次级胆汁酸进入结肠,刺激结肠分

泌液体并加速蠕动,从而引发腹泻,且症状常在进食后加重[10][11]。多项研究进一步表明,右半结肠切除后的慢性腹泻往往与胆汁酸吸收不良密切相关,且常合并小肠细菌过度生长,小肠中过度增殖的细菌可使胆汁酸发生解共轭,进一步加剧胆汁酸的吸收障碍[12][13]。

从分子机制上来看,末端回肠上皮细胞中表达的 Farnesoid X 受体(FXR)在这一反馈调节中扮演关键角色。FXR 作为一种核受体,主要分布于肝脏和末端回肠,能够感知肠腔内胆汁酸水平,若肠腔内胆汁酸水平过高,则会促进成纤维细胞生长因子 19 (FGF19)的释放。FGF19 经血液循环至肝脏,抑制 CYP7A1 酶的活性,从而负反馈抑制胆汁酸的合成,维持其稳态[14]-[17]。然而,若末端回肠因切除而导致 FXR 表达下降,其对胆汁酸的感知能力减弱,FGF19 生成减少,肝脏合成胆汁酸的调控便会失控,生成大量胆汁酸。过量胆汁酸进入结肠后,可通过激活 G 蛋白偶联胆汁酸受体 1 (GPBAR1)及囊性纤维化跨膜传导调节因子(CFTR)等通道,导致肠道水分分泌过多,还可直接损伤结肠上皮细胞膜,进一步加剧肠道的分泌与蠕动,最终导致腹泻[10][18]-[20]。这一过程与术中末端回肠切除的长度以及回盲瓣是否保留密切相关。

2.2. 低位前切除综合征

低位前切除综合征是直肠癌患者接受保肛手术后常见的肠道功能障碍症候群。根据其症状特点,低位前切除综合征可分为以下三种临床表型:储便障碍型,主要表现为大便失禁、排便急迫和排便频率增加等;排便障碍型,以排便费力、排便不尽感及需手助排便等为特征;以及混合障碍型,兼具上述两类症状。低位前切除综合征严重影响患者术后生活质量,甚至对临床结局产生不良影响[21]-[23]。

低位前切除综合征中腹泻的发生并非单一因素所致,主要涉及三方面功能紊乱,包括储存功能紊乱、感觉功能紊乱和动力协调功能紊乱[24]。具体而言,手术切除部分或全部直肠后,吻合形成的“新直肠”容量减小、顺应性降低,导致储便能力下降;同时肛门直肠区域感觉过敏,加之盆底神经及括约肌可能受损,引起排便协调障碍,共同导致患者术后出现频繁排便、排便急迫感甚至大便泄漏等[22][23]。

首先是储存功能障碍。正常直肠具有良好弹性和扩张能力,可舒张以临时储存粪便。手术切除病变直肠后,乙状结肠或降结肠与残留直肠或肛管吻合所形成的“新直肠”管腔较窄,且缺乏直肠壶腹的弹性扩张能力,储便能力显著下降。即使少量粪便进入也会产生较高压力,迅速诱发强烈便意,导致排便次数增多[25]-[27]。此外,高分辨率结肠测压研究显示,直乙交界区存在特定的周期性逆行收缩,有助于延缓直肠充盈[28][29]。手术切除该区域后,逆行收缩减弱,结肠顺行性推进运动占主导,使粪便快速进入“新直肠”,进一步加重储存功能障碍,引发腹泻样症状[30]。

其次为感觉功能异常。直肠壁内含丰富神经感受器,能精确感知粪便性状和容量。手术或放疗可能损伤这些感受器,导致“新直肠”感觉异常,患者难以准确辨别气体与粪便,对直肠扩张的感知过度敏感,低容量即可触发便意[21]。同时,肛门抑制反射失调,进一步导致排便频次增加和急迫感[21]。肿瘤位置较低、广泛系膜切除或术前新辅助放疗均可加剧此类感觉过敏[23]。

再者是动力协调障碍。肛门括约肌包括内括约肌(不随意肌,维持静息肛门闭合)和外括约肌(随意肌,负责主动收缩),手术操作(如吻合器使用或组织牵拉)可能造成其损伤,导致肌力减弱,控便能力下降[31]。此外,手术可能影响结肠神经支配,促使结肠尤其是降结肠蠕动加快,食物残渣过快进入“新直肠”,水分吸收不充分,引发腹泻样症状[31]。若患者曾接受放疗,盆底组织纤维化可进一步损害肛门括约肌的控便功能[21][32]。

2.3. 化疗致肠黏膜炎

在结肠癌患者的化疗过程中,化疗致肠黏膜炎是最令人担忧的毒性反应之一,其不仅可导致脱水、

电解质紊乱和营养不良, 还可能引起化疗药物减量、治疗推迟甚至中止, 严重影响抗肿瘤疗效及患者生存结局[33]-[35]。研究表明, 化疗致黏膜炎的发病机制十分复杂, 以 5-氟尿嘧啶(5-FU)及伊立替康为基础的化疗方案, 既会直接损伤肠道上皮细胞, 也会激活炎症通路、扰乱离子转运平衡、改变肠道菌群, 并引发胆碱能刺激, 最终导致以分泌性腹泻为主、兼具渗透性因素的混合型腹泻[34] [36] [37]。

5-FU 引起黏膜炎和腹泻的主要机制在于其抑制细胞分裂并诱导凋亡, 导致肠绒毛萎缩、隐窝结构异常和肠道屏障功能受损。与此同时, 炎症因子如 $\text{TNF-}\alpha$ 、 $\text{IL-1}\beta$ 等大量释放, 进一步加剧组织损伤和细胞死亡[35] [36]。5-FU 在体内代谢为活性产物后, 可掺入正在合成的 RNA 中, 干扰 RNA 功能及其加工过程, 并能抑制胸苷酸合成酶(TS), 阻碍 DNA 的合成与修复。由于肠道基底层的上皮干细胞和增殖细胞需持续分裂以补充脱落的黏膜细胞, 它们对 DNA/RNA 合成抑制极为敏感, 因而 5-FU 可直接引发这类细胞凋亡。细胞死亡和组织损伤会释放损伤相关分子模式(DAMPs), 激活黏膜固有免疫细胞, 被激活的细胞大量释放促炎细胞因子(如 $\text{TNF-}\alpha$ 、 $\text{IL-1}\beta$ 、 IL-6), 形成“炎症风暴”, 进一步加重组织损伤。随着死亡上皮细胞无法及时更新, 肠黏膜逐渐变薄, 物理屏障遭到破坏, 肠道内正常菌群及其产物易位至黏膜下层, 引发继发感染和更强烈的炎症反应, 最终导致广泛黏膜炎、糜烂和溃疡, 临床表现为腹泻等[38]-[40]。

伊立替康引起的腹泻则呈现双相特征, 包括用药期间或刚结束时的早发性腹泻, 以及给药数小时至数天后出现的迟发性腹泻[36]。早发性腹泻的机制在于静脉注射的伊立替康经肝脏排泄入胆汁并进入肠道, 其活性代谢物 SN-38 在肠腔内浓度较高, 直接损伤肠黏膜。而迟发性腹泻则与肝脏代谢途径相关, 肝脏将有毒的 SN-38 与葡萄糖醛酸结合为无活性的 SN-38G, 经胆汁排入肠道后, 肠道细菌(尤其是革兰氏阴性菌)产生的 β -葡萄糖醛酸苷酶可将其重新水解为有毒的 SN-38。SN-38 主要攻击肠道隐窝处的增殖细胞, 使吸收性肠细胞和杯状细胞再生受阻。作为代偿, 隐窝细胞异常增殖, 但这些新生细胞功能不成熟, 以分泌功能为主, 吸收功能严重不足, 导致水和电解质大量分泌至肠腔而无法被重吸收, 从而引发严重分泌性腹泻。此外, 肠黏膜损伤所引起的炎症反应, 以及伊立替康对胆盐重吸收的干扰, 均可进一步加重腹泻症状[41] [42]。

2.4. 放射性肠病

放射性肠病是直肠癌放射治疗后常见的消化道并发症, 临床主要表现为腹泻、里急后重、便血及腹痛等。其不仅给患者带来显著痛苦, 严重降低其生活质量, 若未能有效控制, 还可能迫使放疗计划中断, 进而影响肿瘤的局部控制效果及患者的长期生存预后[43]。

放射性肠病所致腹泻的病理机制涉及多因素、多环节的级联反应, 核心在于电离辐射对肠道组织造成的直接与间接损伤。辐射首先作用于肠黏膜, 特别是隐窝内快速增殖的干细胞, 通过直接细胞毒性作用引起 DNA 双链断裂, 干扰细胞复制与分裂, 诱发隐窝干细胞大量凋亡。同时, 辐射使组织液电离, 产生大量高活性自由基(如 $\cdot\text{OH}$), 攻击细胞膜脂质、蛋白质和核酸, 造成氧化应激损伤。受损及死亡细胞释放信号, 募集大量炎症细胞浸润, 并释放肿瘤坏死因子- α ($\text{TNF-}\alpha$)、白细胞介素- 1β ($\text{IL-1}\beta$)等炎性因子, 加剧组织水肿与黏膜破坏。急性损伤导致肠黏膜物理屏障功能严重受损, 肠道对水分的吸收能力下降, 同时血浆成分(水分、电解质和蛋白质)经破损黏膜渗入肠腔, 形成渗出性腹泻[44]。

除直接上皮损伤外, 辐射对肠壁微血管内皮细胞的损害是慢性腹泻及更严重并发症的关键机制。内皮细胞对辐射高度敏感, 辐射可致其肿胀、凋亡, 并上调黏附分子表达, 进一步募集炎症细胞, 形成恶性循环。更重要的是, 功能失调的内皮细胞由抗凝转为促凝状态, 促进微血栓形成, 造成微血管闭塞, 引发肠壁慢性缺血缺氧, 严重阻碍黏膜上皮的再生与修复。长此以往, 反复的炎症刺激与缺血缺氧可激活局部成纤维细胞, 通过 $\text{TGF-}\beta$ /SMAD 信号通路促使其向肌成纤维细胞转化, 进而导致瘢痕组织形成、肠壁纤维化及硬化[45] [46]。此外, 放疗还可能扰乱肠道菌群平衡, 共同参与腹泻的发生与发展

[47]。

2.5. 靶向与免疫治疗相关腹泻

随着结直肠癌治疗进入精准医疗时代, 靶向药物(如抗 EGFR 药物西妥昔单抗、抗 VEGF 药物贝伐珠单抗)以及免疫检查点抑制剂(ICIs, 如 PD-1/PD-L1 抑制剂)的应用日益广泛。然而, 这些新型疗法同样会引发腹泻, 值得临床关注[48] [49]。

靶向治疗所致腹泻的机制因药物类别不同而异。EGFR 信号通路在肠道隐窝基底部的干细胞和增殖细胞的分裂和更新中起关键作用。抗 EGFR 药物在抑制肿瘤信号的同时, 也会抑制该通路在正常肠组织中的功能, 导致肠上皮细胞增殖与更新减缓, 无法及时补充因生理更替而脱落的衰老细胞[50]。肠绒毛由成熟的肠上皮细胞构成, 由于底层细胞更新受阻, 绒毛顶端的衰老细胞脱落后难以被新生细胞替代, 造成肠绒毛缩短甚至萎缩, 从而减少肠道吸收水分的有效表面积[51]。同时, 绒毛结构的变短及细胞间连接的受损削弱了肠道黏膜的物理屏障功能, 增加了肠道通透性, 大量水分和电解质渗入到肠腔, 共同促成腹泻的发生[52]。此外, EGFR 信号通路还参与调解肠上皮细胞的离子通道, 其受抑制后可导致氯离子分泌增加和钠离子吸收减少, 使得大量水分滞留于肠腔, 形成分泌性腹泻[53]。另一方面, VEGF 信号通路是维持血管内皮细胞存活、增殖和血管通透性的关键。抗 VEGF 药物在靶向肿瘤血管生成的同时, 也会干扰正常组织中的该信号通路, 引起肠道黏膜内成熟毛细血管退化、萎缩, 甚至微血栓形成[54]。肠道黏膜的血流灌注因此下降, 导致肠上皮细胞因缺氧而死亡脱落, 进而削弱肠道吸收功能、破坏黏膜屏障完整性, 最终诱发腹泻[51]。

免疫相关腹泻是 ICIs 最常见的不良反应之一, 其本质是免疫相关性肠炎。ICIs 通过解除 T 细胞受到的抑制, 激活机体免疫系统以攻击肿瘤, 但同时也可能导致免疫系统异常攻击正常组织, 其中肠道是最常受累的器官之一[55]。活化的细胞毒性 T 细胞与辅助性 T 细胞大量浸润肠黏膜, 诱发显著的炎症反应, 组织学上可见大量炎性细胞浸润, 甚至导致隐窝脓肿和上皮细胞凋亡[56]。这些病理改变破坏肠道屏障功能, 影响水分吸收, 并可能伴有大量炎性渗出, 临床表现为水样泻, 严重时可出现血性腹泻和结肠炎。相较于其他类型的腹泻, 免疫治疗相关性腹泻起病可能更急、程度更重, 且可能合并免疫性肝炎、皮炎等其他器官的免疫相关不良事件, 需要及时地采用免疫抑制治疗进行干预[55]。

2.6. 肠道微生物失调

近年来, 肠道菌群在维持肠道稳态中的核心作用备受关注, 其微生态已被视为结直肠癌术后腹泻的一个重要的发病机制。手术应激、麻醉、抗生素使用、饮食改变以及放化疗等因素, 均可导致肠道菌群在多样性、组成和功能上发生显著紊乱, 这种失调通过多种途径诱发或加重腹泻症状[57]。

首先, 菌群结构失衡常表现为有益菌(如厚壁菌门、毛螺菌科、双歧杆菌等)的减少和潜在致病菌(如变形菌门、革兰氏阴性杆菌等)的过度增殖。有益菌能够发酵膳食纤维产生短链脂肪酸(SCFAs, 如丁酸、乙酸、丙酸), 这些物质是结肠上皮细胞的主要能量来源, 对于维持肠上皮屏障的完整性, 调节炎症反应和促进水钠吸收至关重要。菌群失调导致 SCFAs(尤其是丁酸)的产量显著下降, 从而削弱肠道屏障功能、增加肠道通透性, 引发低度炎症并损害吸收功能, 最终导致渗透性腹泻[58]。

其次, 菌群失调还会引起代谢功能异常。某些细菌(如拟杆菌属、梭菌属)的 β -葡萄糖醛酸苷酶的活性升高, 可将伊立替康的无活性代谢物 SN-38G 在肠道内重新活化为有毒的 SN-38, 直接损伤肠黏膜[59]。此外, 菌群失调也可能干扰胆汁酸代谢。部分细菌表达的胆汁盐水解酶能将结合型胆汁酸解离为游离型胆汁酸, 后者更易被细菌进一步转化为次级胆汁酸[60]。过量的次级胆汁酸对结肠黏膜具有更强的刺激分泌和细胞毒性作用, 从而形成胆汁酸性腹泻的恶性循环。

3. 结论与展望

结直肠癌术后腹泻是一个多因素、异质性显著的临床难题, 其发病机制复杂且个体差异明显。主要病因涵盖胆汁酸性腹泻、低位前切除综合征、化疗致肠黏膜炎、放射性肠病、靶向与免疫相关腹泻, 以及肠道微生态失调等多个方面。临床上, 患者常多种机制并存并相互影响, 给诊断与治疗带来了极大的挑战。

为实现对结直肠癌术后腹泻的精准预防与管理, 未来可以从以下几个方向深入探索: 多组学指导的生物标志物的发掘, 当前腹泻的诊断多依赖临床症状, 缺乏客观、量化的预测与分型工具, 未来应积极利用宏基因组学、代谢组学和蛋白质组学等技术, 系统分析患者手术前后粪便菌群、血清胆汁酸谱、短链脂肪酸及炎症因子谱的动态变化, 筛选出可用于早期预测不同腹泻亚型的发生风险、严重程度及治疗反应性的生物标志物集群[61][62]; 肠道菌群在多重损伤中的枢纽作用与干预策略, 肠道微生态失调是贯穿手术、放化疗及靶向免疫治疗的共同病理基础, 需要深入探索菌群在不同机制中的特异性作用, 明确关键菌株缺失或代谢通路改变的核心驱动因素, 进而研究特定益生菌、益生元或菌群移植在重建健康微生态、缓解特定类型腹泻方面的疗效与机制[63]; 新型治疗相关毒性的机制解析与防治策略, 随着靶向与免疫治疗的广泛应用, 其相关腹泻的精细分子与免疫机制尚未完全明确, 亟需构建更贴近临床的前期模型, 阐明例如 ICIs 引发结肠炎的免疫细胞活化途径及关键细胞因子等, 为开发特异性高、副作用小的免疫调节方案提供靶点, 避免因腹泻而中断有效的抗肿瘤治疗[64]; 构建基于人工智能的个体化风险预测模型, 调整患者的手术方式、放疗剂量与野区、化疗/靶向/免疫治疗方案、术前基线菌群特征及宿主遗传背景等多维度数据, 利用机器学习算法开发和验证个体化腹泻风险预测模型, 从而实现高危患者的早期识别和预防性干预, 最终改善患者的长期生活治疗和肿瘤治疗结局。

参考文献

- [1] Bray, F.M., Laversanne, M., Sung, H., Ferlay, J., Siegel, R.L., Soerjomataram, I., *et al.* (2024) Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, **74**, 229-263. <https://doi.org/10.3322/caac.21834>
- [2] Sato, T. and Watanabe, M. (2017) The Present Status and Developments of Laparoscopic Surgery for Colorectal Cancer. *Journal of the Anus, Rectum and Colon*, **1**, 1-6. <https://doi.org/10.23922/jarc.2016-010>
- [3] Singh, M., Morris, V.K., Bandey, I.N., Hong, D.S. and Kopetz, S. (2024) Advancements in Combining Targeted Therapy and Immunotherapy for Colorectal Cancer. *Trends in Cancer*, **10**, 598-609. <https://doi.org/10.1016/j.trecan.2024.05.001>
- [4] Ohta, H., Miyake, T., Ueki, T., Kojima, M., Kawasaki, M., Tatsuta, T., *et al.* (2022) Predictors and Clinical Impact of Postoperative Diarrhea after Colorectal Cancer Surgery: A Prospective, Multicenter, Observational Study (SHISA-1602). *International Journal of Colorectal Disease*, **37**, 657-664. <https://doi.org/10.1007/s00384-022-04097-8>
- [5] Chu, C., Rotondo-Trivette, S. and Michail, S. (2020) Chronic Diarrhea. *Current Problems in Pediatric and Adolescent Health Care*, **50**, Article 100841. <https://doi.org/10.1016/j.cppeds.2020.100841>
- [6] Burgers, K., Lindberg, B. and Bevis, Z.J. (2020) Chronic Diarrhea in Adults: Evaluation and Differential Diagnosis. *American Family Physician*, **101**, 472-480.
- [7] Corinaldesi, R., Stanghellini, V., Barbara, G., Tomassetti, P. and De Giorgio, R. (2012) Clinical Approach to Diarrhea. *Internal and Emergency Medicine*, **7**, 255-262. <https://doi.org/10.1007/s11739-012-0827-4>
- [8] Camilleri, M., Sellin, J.H. and Barrett, K.E. (2017) Pathophysiology, Evaluation, and Management of Chronic Watery Diarrhea. *Gastroenterology*, **152**, 515-532.e2. <https://doi.org/10.1053/j.gastro.2016.10.014>
- [9] 谭常青, 赖州. 5124 例腹泻患者临床治疗效果回顾性分析[J]. 中国药房, 2012, 23(26): 2453-2454.
- [10] Marasco, G., Cremon, C., Barbaro, M.R., Falangone, F., Montanari, D., Capuani, F., *et al.* (2022) Pathophysiology and Clinical Management of Bile Acid Diarrhea. *Journal of Clinical Medicine*, **11**, Article 3102. <https://doi.org/10.3390/jcm11113102>
- [11] Fani, B., Bertani, L., Paglianiti, I., Fantechi, L., De Bortoli, N., Costa, F., *et al.* (2018) Pros and Cons of the Sehcet Test in Bile Acid Diarrhea: A More Appropriate Use of an Old Nuclear Medicine Technique. *Gastroenterology Research and*

- Practice*, **2018**, 1-9. <https://doi.org/10.1155/2018/2097359>
- [12] Larsen, H.M., Krogh, K., Borre, M., Gregersen, T., Mejlbj Hansen, M., Arveschoug, A.K., *et al.* (2023) Chronic Loose Stools Following Right-Sided Hemicolectomy for Colon Cancer and the Association with Bile Acid Malabsorption and Small Intestinal Bacterial Overgrowth. *Colorectal Disease*, **25**, 600-607. <https://doi.org/10.1111/codi.16409>
 - [13] BouSaba, J. and Camilleri, M. (2023) Bile Acid Diarrhea—As Bad as It Gets? *Current Opinion in Gastroenterology*, **39**, 184-191. <https://doi.org/10.1097/mog.0000000000000916>
 - [14] Pattni, S.S., Brydon, G.W., Dew, T. and Walters, J.R.F. (2012) Fibroblast Growth Factor 19 and 7 α -Hydroxy-4-Cholesten-3-One in the Diagnosis of Patients with Possible Bile Acid Diarrhea. *Clinical and Translational Gastroenterology*, **3**, e18. <https://doi.org/10.1038/ctg.2012.10>
 - [15] Pattni, S.S., Brydon, W.G., Dew, T., Johnston, I.M., Nolan, J.D., Srinivas, M., *et al.* (2013) Fibroblast Growth Factor 19 in Patients with Bile Acid Diarrhoea: A Prospective Comparison of FGF19 Serum Assay and Sehcet Retention. *Alimentary Pharmacology & Therapeutics*, **38**, 967-976. <https://doi.org/10.1111/apt.12466>
 - [16] Zhou, H. and Hylemon, P.B. (2014) Bile Acids Are Nutrient Signaling Hormones. *Steroids*, **86**, 62-68. <https://doi.org/10.1016/j.steroids.2014.04.016>
 - [17] Amigo, L., Husche, C., Zanlungo, S., Lütjohann, D., Arrese, M., Miquel, J.F., *et al.* (2011) Cholecystectomy Increases Hepatic Triglyceride Content and Very-Low-Density Lipoproteins Production in Mice. *Liver International*, **31**, 52-64. <https://doi.org/10.1111/j.1478-3231.2010.02361.x>
 - [18] Chadwick, V.S., Gaginella, T.S., Carlson, G.L., *et al.* (1979) Effect of Molecular Structure on Bile Acid-Induced Alterations in Absorptive Function, Permeability, and Morphology in The Perfused Rabbit Colon. *Journal of Laboratory and Clinical Medicine*, **94**, 661-674.
 - [19] Mekhjian, H.S., Phillips, S.F. and Hofmann, A.F. (1971) Colonic Secretion of Water and Electrolytes Induced by Bile Acids: Perfusion Studies in Man. *Journal of Clinical Investigation*, **50**, 1569-1577. <https://doi.org/10.1172/jci106644>
 - [20] Bampton, P.A., Dinning, P.G., Kennedy, M.L., Lubowski, D.Z. and Cook, I.J. (2002) The Proximal Colonic Motor Response to Rectal Mechanical and Chemical Stimulation. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **282**, G443-G449. <https://doi.org/10.1152/ajpgi.00194.2001>
 - [21] 张斌, 韩加刚, 楼征, 马腾辉, 张林, 王延磊, 等. 低位前切除综合征诊治中国专家共识(2025 版) [J]. 中国普通外科杂志, 2025, 34(8): 1603-1617.
 - [22] Nguyen, T.H. and Chokshi, R.V. (2020) Low Anterior Resection Syndrome. *Current Gastroenterology Reports*, **22**, Article No. 48. <https://doi.org/10.1007/s11894-020-00785-z>
 - [23] Ryoo, S. (2023) Low Anterior Resection Syndrome. *Annals of Gastroenterological Surgery*, **7**, 719-724. <https://doi.org/10.1002/ags3.12695>
 - [24] Zhang, R., Luo, W., Qiu, Y., Chen, F., Luo, D., Yang, Y., *et al.* (2023) Clinical Management of Low Anterior Resection Syndrome: Review of the Current Diagnosis and Treatment. *Cancers*, **15**, Article 5011. <https://doi.org/10.3390/cancers15205011>
 - [25] Brock, H., Lambrineas, L., Ong, H.I., Chen, W.Y., Das, A., Edsell, A., *et al.* (2023) Preventative Strategies for Low Anterior Resection Syndrome. *Techniques in Coloproctology*, **28**, Article No. 10. <https://doi.org/10.1007/s10151-023-02872-5>
 - [26] Cura Pales, C.G., An, S., Cruz, J.P., Kim, K. and Kim, Y. (2019) Postoperative Bowel Function after Anal Sphincter-Preserving Rectal Cancer Surgery: Risks Factors, Diagnostic Modalities, and Management. *Annals of Coloproctology*, **35**, 160-166. <https://doi.org/10.3393/ac.2019.08.10>
 - [27] Kakodkar, R., Gupta, S. and Nundy, S. (2006) Low Anterior Resection with Total Mesorectal Excision for Rectal Cancer: Functional Assessment and Factors Affecting Outcome. *Colorectal Disease*, **8**, 650-656. <https://doi.org/10.1111/j.1463-1318.2006.00992.x>
 - [28] Rosen, H., Sebesta, C.G. and Sebesta, C. (2023) Management of Low Anterior Resection Syndrome (LARS) Following Resection for Rectal Cancer. *Cancers*, **15**, Article 778. <https://doi.org/10.3390/cancers15030778>
 - [29] Lin, A.Y., Varghese, C., Paskaranandavadivel, N., Seo, S., Du, P., Dinning, P., *et al.* (2022) Faecal Incontinence Is Associated with an Impaired Rectosigmoid Brake and Improved by Sacral Neuromodulation. *Colorectal Disease*, **24**, 1556-1566. <https://doi.org/10.1111/codi.16249>
 - [30] Varghese, C., Wells, C.I., Bissett, I.P., O'Grady, G. and Keane, C. (2022) The Role of Colonic Motility in Low Anterior Resection Syndrome. *Frontiers in Oncology*, **12**, Article 975386. <https://doi.org/10.3389/fonc.2022.975386>
 - [31] Miyo, M., Akizuki, E., Okuya, K., Noda, A., Ishii, M., Miura, R., *et al.* (2025) Diagnosis and Treatment of Low Anterior Resection Syndrome. *Journal of the Anus, Rectum and Colon*, **9**, 1-9. <https://doi.org/10.23922/jarc.2024-069>
 - [32] Bregendahl, S., Emmertsen, K.J., Lous, J. and Laurberg, S. (2013) Bowel Dysfunction after Low Anterior Resection with and without Neoadjuvant Therapy for Rectal Cancer: A Population-Based Cross-Sectional Study. *Colorectal Disease*,

- 15, 1130-1139. <https://doi.org/10.1111/codi.12244>
- [33] Bossi, P., Antonuzzo, A., Cherny, N.I., Rosengarten, O., Pernot, S., Trippa, F., *et al.* (2018) Diarrhoea in Adult Cancer Patients: ESMO Clinical Practice Guidelines. *Annals of Oncology*, **29**, iv126-iv142. <https://doi.org/10.1093/annonc/mdy145>
- [34] Stein, A., Voigt, W. and Jordan, K. (2010) Review: Chemotherapy-Induced Diarrhea: Pathophysiology, Frequency and Guideline-Based Management. *Therapeutic Advances in Medical Oncology*, **2**, 51-63. <https://doi.org/10.1177/1758834009355164>
- [35] O'Reilly, M., Mellotte, G., Ryan, B. and O'Connor, A. (2020) Gastrointestinal Side Effects of Cancer Treatments. *Therapeutic Advances in Chronic Disease*, **11**, 1-7. <https://doi.org/10.1177/2040622320970354>
- [36] Ribeiro, R.A., Wanderley, C.W.S., Wong, D.V.T., Mota, J.M.S.C., Leite, C.A.V.G., Souza, M.H.L.P., *et al.* (2016) Irinotecan- and 5-Fluorouracil-Induced Intestinal Mucositis: Insights into Pathogenesis and Therapeutic Perspectives. *Cancer Chemotherapy and Pharmacology*, **78**, 881-893. <https://doi.org/10.1007/s00280-016-3139-y>
- [37] 郭锦瑞, 詹臻, 康安, 王小龙. 化疗致肠黏膜炎的病理机制及药物干预策略研究进展[J]. 中国临床药理学与治疗学, 2014, 19(5): 573-578.
- [38] Dahlgren, D., Sjöblom, M., Hellström, P.M. and Lennernäs, H. (2021) Chemotherapeutics-Induced Intestinal Mucositis: Pathophysiology and Potential Treatment Strategies. *Frontiers in Pharmacology*, **12**, Article 681417. <https://doi.org/10.3389/fphar.2021.681417>
- [39] Sonis, S.T., Elting, L.S., Keefe, D., Peterson, D.E., Schubert, M., Hauer-Jensen, M., *et al.* (2004) Perspectives on Cancer Therapy-Induced Mucosal Injury. *Cancer*, **100**, 1995-2025. <https://doi.org/10.1002/cncr.20162>
- [40] Lee, C.S. (2014) Gastro-Intestinal Toxicity of Chemotherapeutics in Colorectal Cancer: The Role of Inflammation. *World Journal of Gastroenterology*, **20**, 3751-3761. <https://doi.org/10.3748/wjg.v20.i14.3751>
- [41] Stringer, A.M., Gibson, R.J., Bowen, J.M., Logan, R.M., Ashton, K., Yeoh, A.S.J., *et al.* (2009) Irinotecan-Induced Mucositis Manifesting as Diarrhoea Corresponds with an Amended Intestinal Flora and Mucin Profile. *International Journal of Experimental Pathology*, **90**, 489-499. <https://doi.org/10.1111/j.1365-2613.2009.00671.x>
- [42] Xu, S., Lan, H., Huang, C., Ge, X. and Zhu, J. (2024) Mechanisms and Emerging Strategies for Irinotecan-Induced Diarrhea. *European Journal of Pharmacology*, **974**, Article 176614. <https://doi.org/10.1016/j.ejphar.2024.176614>
- [43] Shadad, A.K. (2013) Gastrointestinal Radiation Injury: Symptoms, Risk Factors and Mechanisms. *World Journal of Gastroenterology*, **19**, 185-198. <https://doi.org/10.3748/wjg.v19.i2.185>
- [44] Mollà, M. and Panés, J. (2007) Radiation-Induced Intestinal Inflammation. *World Journal of Gastroenterology*, **13**, 3043-3046. <https://doi.org/10.3748/wjg.v13.i22.3043>
- [45] Venkatesulu, B.P., Mahadevan, L.S., Aliru, M.L., Yang, X., Bodd, M.H., Singh, P.K., *et al.* (2018) Radiation-Induced Endothelial Vascular Injury. *JACC: Basic to Translational Science*, **3**, 563-572. <https://doi.org/10.1016/j.jacbs.2018.01.014>
- [46] Yu, Z., Xu, C., Song, B., Zhang, S., Chen, C., Li, C., *et al.* (2023) Tissue Fibrosis Induced by Radiotherapy: Current Understanding of the Molecular Mechanisms, Diagnosis and Therapeutic Advances. *Journal of Translational Medicine*, **21**, Article No. 708. <https://doi.org/10.1186/s12967-023-04554-0>
- [47] 王跃, 谭艳琼, 杨玲, 许家素. 肠道菌群失调促进放射性肠炎发生的研究进展[J]. 中国微生态学杂志, 2023, 35(5): 612-614+620.
- [48] Fakih, M. and Vincent, M. (2010) Adverse Events Associated with Anti-EGFR Therapies for the Treatment of Metastatic Colorectal Cancer. *Current Oncology*, **17**, 18-30. <https://doi.org/10.3747/co.v17is1.615>
- [49] Miroddi, M., Sterrantino, C., Simonelli, I., Ciminata, G., Phillips, R.S. and Calapai, G. (2015) Risk of Grade 3-4 Diarrhea and Mucositis in Colorectal Cancer Patients Receiving Anti-EGFR Monoclonal Antibodies Regimens: A Meta-Analysis of 18 Randomized Controlled Clinical Trials. *Critical Reviews in Oncology/Hematology*, **96**, 355-371. <https://doi.org/10.1016/j.critrevonc.2015.06.004>
- [50] Bowen, J.M. (2013) Mechanisms of TKI-Induced Diarrhea in Cancer Patients. *Current Opinion in Supportive & Palliative Care*, **7**, 162-167. <https://doi.org/10.1097/spc.0b013e32835ec861>
- [51] Liu, J., Yan, S., Du, J., Teng, L., Yang, R., Xu, P., *et al.* (2024) Mechanism and Treatment of Diarrhea Associated with Tyrosine Kinase Inhibitors. *Heliyon*, **10**, e27531. <https://doi.org/10.1016/j.heliyon.2024.e27531>
- [52] Rodrigues, D., Herpers, B., Ferreira, S., Jo, H., Fisher, C., Coyle, L., *et al.* (2022) A Transcriptomic Approach to Elucidate the Mechanisms of Gefitinib-Induced Toxicity in Healthy Human Intestinal Organoids. *International Journal of Molecular Sciences*, **23**, Article 2213. <https://doi.org/10.3390/ijms23042213>
- [53] Van Seville, Y.Z.A., Gibson, R.J., Wardill, H.R. and Bowen, J.M. (2015) ERBB Small Molecule Tyrosine Kinase Inhibitor (TKI) Induced Diarrhoea: Chloride Secretion as a Mechanistic Hypothesis. *Cancer Treatment Reviews*, **41**, 646-652. <https://doi.org/10.1016/j.ctrv.2015.05.011>

-
- [54] Kamba, T., Tam, B.Y.Y., Hashizume, H., Haskell, A., Sennino, B., Mancuso, M.R., *et al.* (2006) VEGF-Dependent Plasticity of Fenestrated Capillaries in the Normal Adult Microvasculature. *American Journal of Physiology-Heart and Circulatory Physiology*, **290**, H560-H576. <https://doi.org/10.1152/ajpheart.00133.2005>
 - [55] Zoghbi, M., Burk, K.J., Haroun, E., Saade, M. and Carreras, M.T.C. (2024) Immune Checkpoint Inhibitor-Induced Diarrhea and Colitis: An Overview. *Supportive Care in Cancer*, **32**, Article No. 680. <https://doi.org/10.1007/s00520-024-08889-2>
 - [56] Zhou, W., Huang, Y., Lai, J., Lu, J., Feely, M. and Liu, X. (2018) Anti-Inflammatory Biologics and Anti-Tumoral Immune Therapies-Associated Colitis: A Focused Review of Literature. *Gastroenterology Research*, **11**, 174-188. <https://doi.org/10.14740/gr1041w>
 - [57] Lederer, A., Chikhladze, S., Kohnert, E., Huber, R. and Müller, A. (2021) Current Insights: The Impact of Gut Microbiota on Postoperative Complications in Visceral Surgery—A Narrative Review. *Diagnostics*, **11**, Article 2099. <https://doi.org/10.3390/diagnostics11112099>
 - [58] Liu, P., Wang, Y., Yang, G., Zhang, Q., Meng, L., Xin, Y., *et al.* (2021) The Role of Short-Chain Fatty Acids in Intestinal Barrier Function, Inflammation, Oxidative Stress, and Colonic Carcinogenesis. *Pharmacological Research*, **165**, Article 105420. <https://doi.org/10.1016/j.phrs.2021.105420>
 - [59] Mahdy, M.S., Azmy, A.F., Dishisha, T., Mohamed, W.R., Ahmed, K.A., Hassan, A., *et al.* (2023) Irinotecan-Gut Microbiota Interactions and the Capability of Probiotics to Mitigate Irinotecan-Associated Toxicity. *BMC Microbiology*, **23**, Article No. 53. <https://doi.org/10.1186/s12866-023-02791-3>
 - [60] Staley, C., Weingarden, A.R., Khoruts, A. and Sadowsky, M.J. (2017) Interaction of Gut Microbiota with Bile Acid Metabolism and Its Influence on Disease States. *Applied Microbiology and Biotechnology*, **101**, 47-64. <https://doi.org/10.1007/s00253-016-8006-6>
 - [61] Xie, T., Jiang, Z., Wen, C., Shen, D., Bian, J., Liu, S., *et al.* (2021) Blood Metabolomic Profiling Predicts Postoperative Gastrointestinal Function of Colorectal Surgical Patients under the Guidance of Goal-Directed Fluid Therapy. *Aging*, **13**, 8929-8943. <https://doi.org/10.18632/aging.202711>
 - [62] Nalluri-Butz, H., Bobel, M.C., Nugent, J., Boatman, S., Emanuelson, R., Melton-Meaux, G., *et al.* (2022) A Pilot Study Demonstrating the Impact of Surgical Bowel Preparation on Intestinal Microbiota Composition Following Colon and Rectal Surgery. *Scientific Reports*, **12**, Article No. 10559. <https://doi.org/10.1038/s41598-022-14819-1>
 - [63] Kaźmierczak-Siedlecka, K., Daca, A., Fic, M., van de Wetering, T., Folwarski, M. and Makarewicz, W. (2020) Therapeutic Methods of Gut Microbiota Modification in Colorectal Cancer Management—Fecal Microbiota Transplantation, Prebiotics, Probiotics, and Synbiotics. *Gut Microbes*, **11**, 1518-1530. <https://doi.org/10.1080/19490976.2020.1764309>
 - [64] Tang, L., Wang, J., Lin, N., Zhou, Y., He, W., Liu, J., *et al.* (2021) Immune Checkpoint Inhibitor-Associated Colitis: From Mechanism to Management. *Frontiers in Immunology*, **12**, Article 800879. <https://doi.org/10.3389/fimmu.2021.800879>