DOI: 10.14188/j.1671-8852.2024.0492
文章编号 1671-8852(2025)02-0226-06

肠道菌群在肠源性急性呼吸窘迫综合征中的发病机制及其治疗应用进展

张雨婷 穆素成
复旦大学附属中山医院急诊科/复旦大学应急救援与急危重症研究所 上海 200032

摘要 急性呼吸窘迫综合征(ARDS)是一种以严重低氧血症为特征的呼吸系统疾病,是脓毒症最常见的并发症之一。以肠道功能障碍为始动因素如肠道损伤、肠道免疫功能紊乱、肠道菌群失调以及肠道代谢等引起的ARDS常被认为是肠源性ARDS,其常常表现为肠道完整性、通透性的改变,并影响肠道菌群的构成及其代谢物的生成。本综述旨在总结肠源性ARDS与肠道菌群的关联,阐述目前基于肠道功能改善ARDS的治疗措施,从而为肠源性ARDS治疗方案提供新的思路和方向。

关键词 肠源性急性呼吸窘迫综合征;肠道菌群;代谢产物;脓毒症
中图分类号 R563
文献标识码 A
开放科学(资源服务)标识码(OSID):

Pathogenesis and treatments of gut microbiota in gut-deprived acute respiratory distress syndrome

ZHANG Yuting, MU Sucheng
Dept. of Emergency, Zhongshan Hospital Fudan University & Institute of Emergency Rescue and Critical Care, Fudan University, Shanghai 200032, China

Abstract

Acute respiratory distress syndrome (ARDS) is a respiratory disease characterized by severe hypoxemia and is regarded as one of the most common complications of sepsis. ARDS caused by intestinal dysfunction, such as intestinal injury, intestinal immune dysfunction, intestinal microbiota disorder, and intestinal metabolism, is often considered to be gut-derived ARDS. It is often manifested as changes in intestinal integrity and permeability and affects the composition of the gut microbiota as well as the production of metabolites. The purpose of this review is to summarize the relationship between gut-derived ARDS and gut microbiota, providing new ideas for the treatment of ARDS patients by altering their gut microbiota and its metabolites.

Key Words Gut-Deprived ARDS; Gut Microbiota; Metabolites; Sepsis

急性呼吸窘迫综合征(acute respiratory distress syndrome,ARDS)是以顽固性低氧血症与肺水肿为特点的严重炎症反应综合征,是脓毒症最常见的并发症之一[1]。据统计,全世界每年有超过

课题来源:国家重点研发计划(编号:2021YFC2501800);上海市青年科技英才扬帆计划(编号:23YF1405000)
作者简介:张雨婷,女,1999—,医学硕士生,主要从事脓毒症与急性呼吸窘迫综合征相关研究,E-mail:yutingzhang0094@163.com
通信作者:穆素成,男,1992—,医学博士,助理研究员,主要从事脓毒症与急性呼吸窘迫综合征发病机制相关研究,E-mail:mu.sucheng@zs-hospital.sh.cn

300万人罹患ARDS，约占ICU收治患者的10%[2]，其死亡率高达39.6%[3]。随着对ARDS发病机制研究的深入，肠道在ARDS发病及诊疗过程中的作用日益受到重视[4]。探索肠源性ARDS的发病机制，并基于此总结肠源性ARDS的疾病进程及防治手段，对降低ARDS患者死亡率具有十分重要的意义。

1　肠源性ARDS

1.1　ARDS的定义　急性呼吸窘迫综合征是一种非心源性肺水肿所致的急性呼吸系统疾病，其特征是肺部炎症及肺泡毛细血管通透性增高引起的急性顽固性低氧血症，通常伴有双侧影像学浸润表现[1,5]。2012年提出的ARDS柏林标准强调了胸部影像学和氧合障碍严重程度的重要性[6]，2023年发布的ARDS全球新定义将ARDS的诊断范围扩展至接受无创支持及资源有限地区的ARDS患者，为ARDS的早期识别、诊疗干预及临床研究提供了明确的标准及依据[7-8]。ARDS的发病机制十分复杂，早期学者认为主要是由创伤、大量输血、感染性休克或肺炎等疾病引起[5]。近年来，肠道在ARDS发病及发展过程中的影响日益受到重视[9]。肠源性损伤因素通过影响机体的全身炎症，在危重症患者ARDS及多器官功能障碍（Multiple Organ Dysfunction Syndrome，MODS）的病理生理学中发挥着关键作用[4,10]。

1.2　肠源性ARDS的发病机制　肠道是人体最大的免疫器官，近几十年来，肠道是MODS的始发器官和中心器官的观点逐渐得到学术界的广泛认同[11-12]。肠源性ARDS目前尚无准确定义，多数学者认为，以肠道功能障碍为始动因素如肠道损伤、肠道免疫功能紊乱、肠道菌群失调以及肠道代谢等引起的ARDS即可认为是肠源性ARDS[9,13-14]。肠道微生物群在人体微环境中起着至关重要的作用，而肠道菌群失调是危重症患者典型的肠道病理生理学现象[15]。肠道微生物多样性减少或生态失调与许多疾病的发生有关，细菌移位被认为是ARDS及MODS发生的机制之一[16]。肠源性ARDS发生时，肠黏膜屏障的通透性和肠道上皮细胞凋亡率显著增加，这导致肠道菌群改变生物学行为并移位，从而进一步加重继发的肺损伤[17]。肺-肠轴理论是目前解释肠道与肺部之间生理与病理密切关联的重要理论之一[18]，它强调肠道及肠道菌群通过局部调控和远端效应发挥调节免疫和炎症反应的作用，并以此影响呼吸系统疾病[19]。肠道菌群紊乱常体现在有益的肠道微生物代谢产物减少、肠道屏障功能受损以及肠上皮通透性增加，这直接引起细菌的细胞壁成分如脂多糖甚至整个细菌进入血液或淋巴循环，从而诱导全身炎症反应的发生[20]及呼吸系统疾病的进展[21]。已有研究[22]报道，ARDS患者肺部微生物组富含肠源性菌群，肠杆菌科和巴氏杆菌的相对丰度增加[23]，揭示了肠源性ARDS的可能发病机制。

2　肠源性ARDS发病机制分类

2.1　肠道损伤引起的ARDS　当肠道由于机械、物理、化学或生理因素发生直接损伤时，肠道内容物如肠腔内细菌及其产物的外漏可引起局部或系统性炎症反应[24]，同时，肠道炎性细胞因子（TNF-α、IL-6和IL-1β）对肌球蛋白轻链激酶的激活也与ARDS的发病有关[25]。肠道通透性增加启动黏膜免疫系统的局部激活，促使损伤相关的分子模式与共生肠道微生物相关分子模式的产生，并通过门静脉循环和肠系膜淋巴管移位进入肺部及体循环，激活高表达Toll样受体的细胞（如单核巨噬细胞、T细胞、B淋巴细胞等）炎症介质的释放，触发炎症免疫应答，最终导致随后的全身感染和对远端器官的损伤，从而引起肺部级联炎症反应导致ARDS与MODS[26]。此外，肠黏膜的损伤会导致有害物质的产生，如内毒素、激素或炎症介质（如IFN-γ、IL-6、IL-4和TNF-α等），并破坏肠道屏障的完整性。当有害物质被肠系膜淋巴管吸收后会进入血液并激活内皮细胞和免疫细胞，最终导致全身炎症和ARDS[27]。

2.2　肠道菌群紊乱引起的ARDS　肠道菌群紊乱主要体现在菌群丰度与多样性的下降、有益微生物和有害微生物平衡的破坏以及某些特定微生物种群相对增加或减少[28]。Gao等[29]研究发现，抗生素可使流感小鼠肠道菌群的多样性和种类减少，肺和肠组织黏膜损伤加重。口服头孢菌素会破坏肠道微生物稳态，使双歧杆菌和乳杆菌的比例显著降低、肠球菌和念珠菌的比例增加[30]，并通过介导内皮屏障相关蛋白（Claudin 5、Occludin和ZO-1）和炎症相关蛋白（TLR4、p38和NF-κB），加重肺血管内皮损伤、炎性细胞聚集和间充质水肿，从而引起肠源性ARDS[31-33]。

Dickson及其团队[14]报道了在盲肠结扎穿孔的肠源性脓毒症小鼠模型中,紊乱的肠道菌群通过肠系膜淋巴管在肺部富集,同时在脓毒症小鼠及ARDS患者肺泡灌洗液检测到肠道特有的拟杆菌属细菌,且该细菌的含量与患者全身炎症反应强度相关。笔者所在研究团队[34]通过对监护室重症患者粪便、肺泡灌洗液和血液中分离培养的细菌作宏基因组同源性分析发现,肠道菌群中异常增殖的肠球菌及肺炎克雷伯菌通过菌群易位进一步引起患者继发肺部及血流感染,增加肠源性ARDS患者死亡风险。

而针对重症患者的治疗手段,如肠内肠外营养、机械通气、口服的质子泵抑制剂以及阿片类药物的使用,都会对肠道菌群造成不同程度的破坏[9,35]。笔者所在团队的一项单中心观察性研究[36]发现,脓毒症及ARDS患者肠道菌群中变形菌门的相对丰度随时间推移显著增加,而厚壁菌门的相对丰度则明显降低。克雷伯菌属作为与继发感染高度相关的菌属,在脓毒症及ARDS发病第3周的患者,尤其是死亡患者肠道中的相对丰度显著增加。

2.3 肠道菌群代谢产物相关的ARDS 肠道菌群代谢产物主要包括肠道菌群产生的短链脂肪酸(short chain fatty acids,SCFAs)、胆汁酸、氨基酸代谢物等。肠道菌群代谢产物在维持肠道的健康、免疫调节以及代谢平衡中具有重要意义[37],当其相对含量失调时,常常导致机体免疫功能紊乱,进而导致肠源性疾病的发生[38]。

SCFAs包括丁酸、乙酸、丙酸等8种脂肪酸,它们能够激活G蛋白偶联受体,发挥维护肠黏膜的完整性以及促进肠上皮细胞的增殖和修复等作用[39]。丁酸是肠道菌群产生的关键代谢物,已有大量研究证明丁酸盐可通过影响免疫细胞迁移、黏附和细胞因子表达,以及细胞增殖、活化和凋亡等,在ARDS患者的发病机制中具有不可忽视的调节作用[40]。丁酸能够通过促进胸腺外调节性T细胞的产生发挥抗炎与调节免疫反应的作用[41]。此外,丁酸盐还能够促进M2巨噬细胞的极化,并显著增强黏蛋白MUC-2和杯状细胞的表达,从而修复肠道屏障,降低肠源性继发损伤[42]。同样,当丙酸酯、异丁酸酯以及丁酸盐等代谢产物减少时,ARDS小鼠外周血的肺和肠道微生物群紊乱相关促炎因子(包括IFN-γ、IL-17)显著上调[43],而丁酸处理肠上皮细胞后,促炎因子如Toll样受体2、IL-6、TNF、TLR4、血管内皮生长因子被显著下调[44]。这一抗炎效应同样作用在肺部微生物群,因此具有减轻肺部炎症的效果[45]。丙酸可通过激活Keap1/Nrf2通路抑制氧化应激,直接减轻ARDS小鼠肺损伤[46]。通过与肺泡巨噬细胞GPR43结合,丙酸能够阻碍NLRP3炎症小体的激活,抑制TNF-α、IL-1β以及IL-6的合成与释放,从而抑制肺泡巨噬细胞炎症和氧化应激,减轻肺损伤[47]。

除SCFAs外,精氨酸与胆汁酸亦是在肠源性ARDS患者发生剧烈改变的肠道菌群代谢产物。作为免疫细胞的重要营养物质及一氧化氮关键合成底物,精氨酸通过参与免疫调节及一氧化氮代谢减轻ARDS患者肺损伤[48]。笔者所在团队的一项观察性研究[36]发现,重症肠源性ARDS死亡患者在住院期间初级胆汁酸增加、次级胆汁酸减少,其伴随的肠道菌群多样性降低和肺炎克雷菌属增加,均是患者死亡的高危因素。而初级胆汁酸的增加,可能通过分泌磷脂酶A2途径、对炎症和局部免疫的生物学效应以及直接的细胞毒性加重ARDS患者肺损伤[49]。

3 基于肠道菌群及其代谢物的肠源性ARDS治疗方案进展

3.1 选择性消化道去污染疗法与粪菌移植 重症患者肠道微生物群紊乱与肠源性ARDS患者发病与预后密切相关。选择性消化道去污染疗法(selective decontamination of the digestive tract,SDD)与粪便微生物移植(fecal microbiota transplant,FMT)通过改善肠道菌群起到减轻肠源性ARDS、改善其重症患者预后的作用。一项基于随机临床试验的Meta分析报告称,使用SDD与死亡率和呼吸机相关性肺炎发病率的降低有关[50],但最新的一项纳入19个监护室5 982例重症患者的长期随机化对照研究[51]表明,SDD并未显著降低住院死亡率,研究者指出,研究结果的差异可能与SDD疗法糊剂及口服悬液在消化道中停留时长的不确定性以及重症患者肠道菌群的异质性相关。

相对于SDD较低的国际使用率与较大的临床不确定性,FMT用于改善肠道菌群的治疗方案正向着规范化与标准化的方向迈进[52]。在ICU艰难梭菌感染患者中,FMT可以达到较好的疗效,82%的病人在术后平均22个月内未出现艰难梭菌的再次感染[53]。此外,FMT显著改善监护室患者肠道菌群构成与腹泻症状[54],从而促进肠道屏障的恢

复，用于肠源性疾病的治疗并改善预后。另一项研究[55]显示，对于超广谱β-内酰胺酶或产碳青霉烯酶肠杆菌科携带者，抗生素联合FMT治疗同样有助于减少肠道的菌群富集，从而改善肠源性疾病预后。此外，Littmann等[56]在进行粪菌移植治疗艰难梭菌感染时，发现T、B细胞缺陷的*Rag*1$^{-/-}$小鼠对FMT治疗毫无应答，这说明粪菌移植的起效需要基于T、B细胞而发挥作用。在进一步靶向射频消融掉免疫细胞亚群后发现，CD4^{+}Foxp3^{+}T细胞是粪菌移植发挥抗艰难梭菌感染的重要细胞亚群[57]。FMT在改善炎症损伤方面效果显著，它能够明显改善肺和回肠的病理损伤、有助于免疫功能的恢复、减少肺组织中凋亡细胞的比例、抑制肺及回肠组织的氧化应激反应[57]。FMT还具有重塑微生物群的作用，它通过增加丁酸的水平来缓解肠道菌群的失调，因此常在炎症性疾病中发挥作用，肠源性ARDS也囊括其中[58]。

3.2　补充特定菌群或代谢产物　直接补充肠源性ARDS患者肠道失衡菌群是改善肺损伤的可行性方法之一。Sapra等[59]的研究证明，乳酸杆菌能够通过降低中性粒细胞及炎性细胞因子在小鼠的肺与血清中的表达，发挥改善肺部血管的通透性、减少肺部水肿的作用。同样，补充肠道菌群代谢产物亦可起到减轻肺损伤的效果。丁酸盐通过促进M1巨噬细胞极化、促进杯状细胞生成，以及减少INF-γ和IL-17等促炎因子的释放改善肠道屏障及调节免疫细胞功能，从而缓解ARDS患者的肺损伤[39-41]。而补充代谢物精氨酸亦能够减轻COVID-19相关ARDS患者的免疫抑制、减少机械通气持续时间、降低患者死亡率[60]。此外，吲哚作为色氨酸代谢中的关键代谢产物，能够通过调节细胞因子，起到改善炎症和损伤的作用[61]。烟酸通过增强调节性T细胞及IL-10的产生，表现出抗炎和免疫调节特性[62]，胆碱也能够减轻细菌易位引起的炎症，从而发挥抗炎作用[19]。

3.3　传统中药复方　传统中医认为，ARDS的发病机制主要是毒热内蕴、淤血阻滞、正气不足和肺气不通[63]。中药在肠道的作用与肠道菌群关系颇为密切，已有多项研究证明，采用中药复方改善肠道菌群对多类疾病均具有一定疗效[64-65]。扶正解毒方能经肺-肠轴调节氨基酸代谢，纠正LPS诱导的ARDS患者体内甘氨酸等5种氨基酸的失衡。笔者所在团队在盲肠结扎穿孔术构建的肠源性大鼠肺损伤模型实验中发现，补充宣白承气汤可提高大鼠的存活率，改善受损的肠道功能，并使肠道有益菌群厚壁菌门和放线菌门的相对丰度增加[66]。最近的一项研究指出，酒黄芩能够明显减轻ARDS小鼠肺与结肠组织的病理损伤，改善患者的肺和肠道功能，并增加肠道中SCFAs的产生[67]。鉴于中药对肠道菌群调节的广泛实践，其在肠源性ARDS治疗中的应用前景被寄予厚望，有望成为未来治疗策略中的关键组成部分。

4　总结与展望

肠源性ARDS是多种ARDS类型中关键且重要的一种，其发病机制与肠道功能、肠道菌群及其代谢物密切相关。通过粪菌移植、单种菌株补给、代谢物补充以及传统中医药等方案能够有效改善肠道功能、减轻肠道损伤、调节肠道菌群稳态及菌群代谢物水平，有助于肠源性ARDS相关器官损伤的减轻，从而提高ARDS患者的生存率。然而，应用肠道菌群及其代谢物改善肠源性ARDS的治疗方法尚属于动物实验与临床试验阶段，要将其充分应用到临床诊疗中，未来仍需要更多的临床研究提供证据支持。

参考文献

[1] Meyer N J, Gattinoni L, Calfee C S. Acute respiratory distress syndrome[J]. Lancet, 2021, 398(10300): 622-637.

[2] Abe T, Madotto F, Pham T, et al. Epidemiology and patterns of tracheostomy practice in patients with acute respiratory distress syndrome in ICUs across 50 countries[J]. Crit Care, 2018, 22(1): 195.

[3] Fernando S M, Ferreyro B L, Urner M, et al. Diagnosis and management of acute respiratory distress syndrome[J]. CMAJ, 2021, 193(21): E761-e768.

[4] Mittal R, Coopersmith C M. Redefining the gut as the motor of critical illness[J]. Trends Mol Med, 2014, 20(4): 214-223.

[5] Angus D C, Seymour C W, Bibbins-Domingo K. Caring for patients with acute respiratory distress syndrome: Summary of the 2023 ESICM practice guidelines[J]. JAMA, 2023, 330(4): 368-371.

[6] Ranieri V M, Rubenfeld G D, Thompson B T, et al. Acute respiratory distress syndrome: The Berlin Definition[J]. JAMA, 2012, 307(23): 2526-2533.

[7] 袁雪燕，刘玲，邱海波 . 2023急性呼吸窘迫综合征全球新标准：进步与局限[J]. 中华医学杂志，2024，104(15): 1216-1220.
Yuan X Y, Liu L, Qiu H B. New 2023 global defini-

tion of acute respiratory distress syndrome: Progress and limitation[J]. Natl Med J China, 2024, 104(15): 1216-1220.

[8] Matthay M A, Arabi Y, Arroliga A C, et al. A new global definition of acute respiratory distress syndrome [J]. Am J Respir Crit Care Med, 2024, 209(1): 37-47.

[9] Dickson R P. The microbiome and critical illness[J]. Lancet Respir Med, 2016, 4(1): 59-72.

[10] Gatt M, Reddy B S, MacFie J. Review article: Bacterial translocation in the critically ill: Evidence and methods of prevention[J]. Aliment Pharmacol Ther, 2007, 25(7): 741-757.

[11] Shankar-Hari M, Phillips G S, Levy M L, et al. Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (sepsis-3)[J]. JAMA, 2016, 315(8): 775-787.

[12] Klingensmith N J, Coopersmith C M. The gut as the motor of multiple organ dysfunction in critical illness[J]. Crit Care Clin, 2016, 32(2): 203-212.

[13] Ziaka M, Exadaktylos A. Exploring the lung-gut direction of the gut-lung axis in patients with ARDS[J]. Crit Care, 2024, 28(1): 179.

[14] Dickson R P, Singer B H, Newstead M W, et al. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome[J]. Nat Microbiol, 2016, 1(10): 16113.

[15] He S Y, Lin F Y, Hu X Y, et al. Gut microbiome-based therapeutics in critically ill adult patients-a narrative review[J]. Nutrients, 2023, 15(22): 4734.

[16] Mustansir Dawoodbhoy F, Patel B K, Patel K, et al. Gut microbiota dysbiosis as a target for improved post-surgical outcomes and improved patient care: A review of current literature[J]. Shock, 2021, 55(4): 441-454.

[17] Kontopoulou K, Iosifidis E, Antoniadou E, et al. The clinical significance of carbapenem-resistant *Klebsiella pneumoniae* rectal colonization in critically ill patients: From colonization to bloodstream infection[J]. J Med Microbiol, 2019, 68(3): 326-335.

[18] Wang H, Liu J S, Peng S H, et al. Gut-lung crosstalk in pulmonary involvement with inflammatory bowel diseases[J]. World J Gastroenterol, 2013, 19(40): 6794-6804.

[19] Zhang D W, Lu J L, Dong B Y, et al. Gut microbiota and its metabolic products in acute respiratory distress syndrome[J]. Front Immunol, 2024, 15: 1330021.

[20] Li M H, Zhang R F, Li J, et al. The role of C-type lectin receptor signaling in the intestinal microbiota-inflammation-cancer axis[J]. Front Immunol, 2022, 13: 894445.

[21] Spiljar M, Merkler D, Trajkovski M. The immune system bridges the gut microbiota with systemic energy homeostasis: Focus on TLRs, mucosal barrier, and SCFAs[J]. Front Immunol, 2017, 8: 1353.

[22] Kyo M, Nishioka K, Nakaya T, et al. Unique patterns of lower respiratory tract microbiota are associated with inflammation and hospital mortality in acute respiratory distress syndrome[J]. Respir Res, 2019, 20(1): 246.

[23] Dickson R P, Schultz M J, van der Poll T, et al. Lung microbiota predict clinical outcomes in critically ill patients[J]. Am J Respir Crit Care Med, 2020, 201(5): 555-563.

[24] Villablanca E J, Selin K, Hedin C R H. Mechanisms of mucosal healing: Treating inflammatory bowel disease without immunosuppression?[J]. Nat Rev Gastroenterol Hepatol, 2022, 19(8): 493-507.

[25] Lorentz C A, Liang Z, Meng M, et al. Myosin light chain kinase knockout improves gut barrier function and confers a survival advantage in polymicrobial sepsis[J]. Mol Med, 2017, 23: 155-165.

[26] Uzzan M, Corcos O, Martin J C, et al. Why is SARS-CoV-2 infection more severe in obese men? The gut lymphatics - Lung axis hypothesis[J]. Med Hypotheses, 2020, 144: 110023.

[27] Ma Y G, Yang X Y, Chatterjee V, et al. The gut-lung axis in systemic inflammation. Role of mesenteric lymph as a conduit[J]. Am J Respir Cell Mol Biol, 2021, 64(1): 19-28.

[28] Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease[J]. Nat Rev Microbiol, 2021, 19(1): 55-71.

[29] Gao J, Chen H F, Xu L Y, et al. Effects of intestinal microorganisms on influenza-infected mice with antibiotic-induced intestinal dysbiosis, through the TLR7 signaling pathway[J]. Front Biosci (Landmark Ed), 2023, 28(3): 43.

[30] Wang J F, Shi C Y, Ying H Z. Cephalosporins-induced intestinal dysbiosis exacerbated pulmonary endothelial barrier disruption in *Streptococcus pneumoniae*-infected mice[J]. Front Cell Infect Microbiol, 2022, 12: 997368.

[31] Ding Y P, Feng Q J, Chen J S, et al. *TLR4*/NF-κB signaling pathway gene single nucleotide polymorphisms alter gene expression levels and affect ARDS occurrence and prognosis outcomes[J]. Medicine, 2019, 98(26): e16029.

[32] Zhang D, Xu C J, Zhang J T, et al. Plasma TNFRSF11B as a new predictive inflammatory marker of sepsis-ARDS with endothelial dysfunction[J]. J Proteome Res, 2023, 22(11): 3640-3651.

[33] Sanwal R, Mintsopoulos V, Ditmans M, et al. Ultrasound-guided transfection of claudin-5 improves

lung endothelial barrier function in lung injury without impairing innate immunity[J]. Am J Physiol Lung Cell Mol Physiol, 2023, 325(2): L135-L142.

[34] Mu S C, Xiang H, Wang Y Z, et al. The pathogens of secondary infection in septic patients share a similar genotype to those that predominate in the gut[J]. Crit Care, 2022, 26(1): 68.

[35] Haak B W, Levi M, Wiersinga W J. Microbiota-targeted therapies on the intensive care unit [J]. Curr Opin Crit Care, 2017, 23(2): 167-174.

[36] Long X Y, Mu S C, Zhang J, et al. Global signatures of the microbiome and metabolome during hospitalization of septic patients[J]. Shock, 2023, 59(5): 716-724.

[37] Wang J J, Zhu N N, Su X M, et al. Gut-microbiota-derived metabolites maintain gut and systemic immune homeostasis[J]. Cells, 2023, 12 (5): 793.

[38] Belvoncikova P, Maronek M, Gardlik R. Gut dysbiosis and fecal microbiota transplantation in autoimmune diseases[J]. Int J Mol Sci, 2022, 23(18): 10729.

[39] Tan J K, Macia L, MacKay C R. Dietary fiber and SCFAs in the regulation of mucosal immunity[J]. J Allergy Clin Immunol, 2023, 151(2): 361-370.

[40] Sultan M, Wilson K, Abdulla O A, et al. Endocannabinoid anandamide attenuates acute respiratory distress syndrome through modulation of microbiome in the gut-lung axis[J]. Cells, 2021, 10(12): 3305.

[41] Deitch E A. Gut lymph and lymphatics: A source of factors leading to organ injury and dysfunction[J]. Ann N Y Acad Sci, 2010, 1207(Suppl 1): E103-E111.

[42] Liang L P, Liu L, Zhou W Y, et al. Gut microbiota-derived butyrate regulates gut mucus barrier repair by activating the macrophage/WNT/ERK signaling pathway[J]. Clin Sci (Lond), 2022, 136(4): 291-307.

[43] Alghetaa H, Mohammed A, Zhou J H, et al. Resveratrol-mediated attenuation of superantigen-driven acute respiratory distress syndrome is mediated by microbiota in the lungs and gut[J]. Pharmacol Res, 2021, 167: 105548.

[44] Yin J H, Zhou C, Yang K Q, et al. Mutual regulation between butyrate and hypoxia-inducible factor-1α in epithelial cell promotes expression of tight junction proteins [J]. Cell Biol Int, 2020, 44(6): 1405-1414.

[45] Ayres J S, Trinidad N J, Vance R E. Lethal inflammasome activation by a multidrug-resistant pathobiont upon antibiotic disruption of the microbiota[J]. Nat Med, 2012, 18: 799-806.

[46] Mohammed A, Alghetaa H K, Zhou J H, et al. Protective effects of Δ(9)-tetrahydrocannabinol against enterotoxin-induced acute respiratory distress syndrome are mediated by modulation of microbiota[J]. Br J Pharmacol, 2020, 177(22): 5078-5095.

[47] Zhang Y D, Zhang L B, Mao L J, et al. Intestinal microbiota-derived propionic acid protects against zinc oxide nanoparticle-induced lung injury[J]. Am J Respir Cell Mol Biol, 2022, 67(6): 680-694.

[48] Pontes-Arruda A, Demichele S, Seth A, et al. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: A meta-analysis of outcome data[J]. JPEN J Parenter Enteral Nutr, 2008, 32(6): 596-605.

[49] De Luca D, Alonso A, Autilio C. Bile acid-induced lung injury: Update of reverse translational biology[J]. Am J Physiol Lung Cell Mol Physiol, 2022, 323(1): L93-L106.

[50] Plantinga N L, de Smet A M G A, Oostdijk E A N, et al. Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: Individual patient data meta-analysis[J]. Clin Microbiol Infect, 2018, 24(5): 505-513.

[51] Myburgh J A, Seppelt I M, Goodman F, et al. Effect of selective decontamination of the digestive tract on hospital mortality in critically ill patients receiving mechanical ventilation: A randomized clinical trial[J]. JAMA, 2022, 328(19): 1911-1921.

[52] Carvalho T. First oral fecal microbiota transplant therapy approved[J]. Nat Med, 2023, 29(7): 1581-1582.

[53] Han S, Shannahan S, Pellish R. Fecal microbiota transplant: Treatment options for *Clostridium* difficile infection in the intensive care unit[J]. J Intensive Care Med, 2016, 31(9): 577-586.

[54] Li Q R, Wang C Y, Tang C, et al. Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: A case report[J]. Crit Care, 2015, 19(1): 37.

[55] Leo S, Lazarevic V, Girard M, et al. Metagenomic characterization of gut microbiota of carriers of extended-spectrum beta-lactamase or carbapenemase-producing Enterobacteriaceae following treatment with oral antibiotics and fecal microbiota transplantation: Results from a multicenter randomized trial[J]. Microorganisms, 2020, 8(6): 941.

[56] Littmann E R, Lee J J, Denny J E, et al. Host immunity modulates the efficacy of microbiota transplantation for treatment of *Clostridioides difficile* infection[J]. Nat Commun, 2021, 12(1): 755.

[57] Hua F, Cui E H, Lv L, et al. Fecal microbiota transplantation from HUC-MSC-treated mice alleviates acute lung injury in mice through anti-inflammation and gut microbiota modulation[J]. Front Microbiol, 2023, 14: 1243102.

（下转第 251 页）