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Hans汉斯

利福昔明在终末期肝病患者中的应用

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摘　要

终末期肝病唯一有效的治疗方式为肝移植，但价格昂贵、肝源短缺等原因限制了肝移植在临床上的实际应用，故改善生活质量及预后在终末期肝病患者的治疗中具有重要的意义。利福昔明作为一种难以被吸收的口服抗生素，对胃肠道具有良好的药理作用。可通过调节肠道微生物和免疫平衡及其代谢产物的生成、减少小肠细菌过度生长、维持肠道通透性和屏障功能等作用，从而直接或间接地在一定程度上延缓终末期肝病的发展、治疗或预防终末期肝病患者所并发的门静脉高压、肝性脑病、腹水、自发性腹膜炎、肝肾综合征、肌肉减少症等。本文就利福昔明在终末期肝病患者的应用及作用机制进行综述。

关键词

利福昔明，抗生素，终末期肝病，并发症，肠道微生物

The Application of Rifaximin in Patients with End Stage Liver Disease

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Abstract

The only effective treatment for end-stage liver disease is liver transplantation. However, the high price and shortage of liver sources limit the practical clinical application of liver transplantation. Therefore, improving the quality of life and prognosis is of great significance in the treatment of patients with end-stage liver disease. Rifaximin, as an oral antibiotic that is difficult to absorb, has good pharmacological effects on the gastrointestinal tract. It can directly or indirectly delay the

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development of end-stage liver disease to a certain extent by regulating intestinal microbial, immune balance and the production of metabolites, reducing small intestinal bacterial overgrowth, maintaining intestinal permeability and barrier function to treat or prevent portal hypertension, hepatic encephalopathy, ascites, spontaneous peritonitis, hepatorenal syndrome, sarcopenia, etc, in patients with end-stage liver disease. This article reviews the application and mechanism of action of rifaximin in patients with end-stage liver disease.

Keywords

Rifaximin, Antibiotic, End Stage Liver Disease, Complications, Gut Microbiota

1. 利福昔明的特点

1.1. 药理作用

1) 利福昔明是一种利福霉素，特异性地结合细菌 DNA 依赖性的 RNA 聚合酶的 β 亚基，进而抑制细菌转录，从而产生抗菌作用；具有利福霉素所具有的以下特点：a) 抗菌谱广，由于利福霉素的作用位点是细菌的 RNA 聚合酶，故利福霉素对大多数革兰阳性菌及革兰阴性菌具有抗菌作用[1]；b) 副作用小：利福昔明对人类 RNA 聚合酶几乎没有或没有活性，故使用时对人类产生的副作用较小，在包括小孩在内的群体中具有良好的安全性[1] [2]。2) 利福昔明的独特性：a) 利福昔明是一种口服抗生素，在胃肠道中缺乏吸收且具有高胆汁溶解度，故其在胃肠道及粪便中的浓度高、生物利用度高，对胃肠道具有良好的药理作用[3] [4]。b) 耐药性低：利福霉素与 RNA 聚合酶的结合不太紧密，当细菌的生物负荷过大时，利福霉素难以有效地结合全部的 RNA 聚合酶，故利福霉素的耐药性发生率较高。但利福昔明作为一种在胃肠道难以吸收的利福霉素，难以作用于胃肠道以外，大大减少了其耐药性及不良反应的发生[1]。

1.2. 临床应用

自 1987 年在意大利获得批准以来，利福昔明已陆续在临床上应用于肝性脑病、肠易激综合征、不同原因所致腹泻、溃疡性结肠炎、艰难梭菌感染和小肠细菌过度生长等疾病[5] [6]。在预防抑郁[7]、预防昼夜节律紊乱引起的认知障碍[8]、减少镰状细胞病所并发的疼痛性血管闭塞危象[9]、治疗回肠储袋－肛管吻合术并发储袋炎[10]等疾病中，利福昔明也具有一定的作用。

2. 终末期肝病

终末期肝病指各种慢性肝病的终末期阶段，包括肝硬化急性失代偿、慢性肝功能衰竭、慢加急性肝功能衰竭、肝细胞癌，预后差、死亡率高[11]。终末期肝病的常见病因有：乙型病毒性肝炎、丙型病毒性肝炎、酒精性、非酒精性脂肪肝性、自身免疫性、胆汁淤积性[12]，不同病因下的终末期肝病均存在肝实质的慢性损伤、炎症反应的持续激活以及肝脏纤维化[13]。终末期肝病常合并肝性脑病、腹腔积液、不同类型及部位的感染、食管胃底静脉曲张、肝肾综合征、肌肉减少症等并发症，导致患者的生活质量下降、病死率升高，在世界范围内，终末期肝病并发症每年造成大约 100 万人死亡[14] [15] [16]。

肝移植是治疗终末期肝病唯一有效的方法，但由于肝源短缺、价格高昂等原因限制了肝移植的实际

临床应用[17]，因此改善终末期肝病患者的生活质量及短期预后在终末期肝病患者的临床治疗中尤为重要。利福昔明通过降低或治疗终末期肝病相关的并发症以及在一定程度上减轻终末期肝病的进展，目前已在终末期肝病患者中得到了广泛的应用[18]。

3. 利福昔明在终末期肝病患者中的应用

3.1. 肠道微生物

肝脏排出胆汁进入肠道，肠道血液通过门静脉进入肝脏，肠－肝轴使得物质，包括部分有害物质，在肠道与肝脏中实现肠肝循环，健康的肝脏可代谢其中的有害物质[19]。肠道微生物紊乱可导致肠道屏障功能受损、通透性增加、诱导肠道炎症、激活更多的 TOLL 样受体 4 (TLR4)表达，从而致使肠道菌群易位、肠道内的炎症驱动因子及炎症因子增加，进而经肠道吸收至血液内的有害物质增多，部分通过肠肝循环进入肝脏，介导肝脏疾病的进展[20] [21]。肠－肝轴和肠道微生物紊乱是各种类型的终末期肝病具有的共同特征，小肠细菌过度生长在终末期肝病患者中的发生率也明显高于健康人，可导致肠道微生物失衡[22]。

利福昔明可通过以下机制改善肠道微生物对终末期肝病造成的不利影响：调节肠道微生物群的功能和丰度但不改变其组成类型，减少有害细菌(如克雷伯氏菌、链球菌)的丰度，增加有益细菌(如双歧杆菌)的丰度、抑制小肠细菌过度生长、减少细菌易位，从而直接及间接地减少内毒素血症和炎症[23] [24]；利福昔明可通过减弱细菌内毒素介导的炎症介质释放、抑制 TLR4 的表达、介导上皮细胞生理学改变和细菌附着或内化的改变以减少炎症性细胞因子增多和炎症进展[25] [26]；利福昔明可通过激活妊娠素 X 受体(PXR)以促进肠道上皮创面愈合、肠道屏障修复、维持肠道免疫平衡[27]。

3.2. 肝纤维化

终末期肝病是各种肝病的晚期阶段，在疾病的发生发展过程中，肝脏组织不断地进行损伤－修复，肝星状细胞及其他多种细胞、细胞因子和信号通路都参与其中，导致细胞外基质过度沉积，从而产生肝纤维化，涉及肠－肝轴的通路可介导肝纤维化的进展[28]。

一项纳入 1886 例研究对象，采用随机双盲、使用安慰剂进行对照的 2 期单中心试验研究，证明利福昔明可减少酒精性相关性肝病患者的肝纤维进展[29]。在动物实验中，显示利福昔明可激活肠道孕烷 X 受体来恢复肠道紧密连接蛋白，以改善肠道通透性；以及直接抑制肠源性脂多糖诱导的肠道屏障功能障碍、肠道紧密连接蛋白耗竭，起到改善肝纤维化的作用[30]。在另外的动物实验中，利福昔明被证明可以通过直接影响肠上皮细胞 ZO-1 的表达，来改善肠道通透性，从而改善肝纤维化，而这个作用，在与血管紧张素-II 受体阻滞剂联合使用时，显示出更强的效果[31]。

3.3. 门静脉高压

门静脉高压是终末期肝病患者普遍存在的并发症，指肝门静脉压力病理性增加，其相关的临床表现包括：胃食管静脉曲张、腹腔积液、肝性脑病、脾脏增大、肝肾综合征等，胃食管静脉曲张所并发的消化道大出血是终末期肝病患者死亡的常见原因[32]。用于测量门静脉压力的最常见参数是门静脉与下腔静脉之间的压力梯度，即肝静脉压力梯度(HVPG)，HVPG 的正常值为 1~5 mmHg，当 HVPG > 10 mmHg 时，发展为静脉曲张出血、腹水和肝性脑病等临床并发症的可能性增大[33]。

终末期肝病的肝脏结构及功能变化引起的肝内血管阻力增加、以及其激活的神经－体液调节系统作用下所产生的高动力循环状态，共同导致门静脉高压。细菌内毒素及细菌产物可直接引起血管收缩导致门静脉压力增高[34]；另外，细菌及其产物通过模式识别受体(较常见为 TLR4)激活免疫细胞、致使细胞

因子和趋化因子上调，从而激活炎症反应，亦可导致门静脉压力升高。终末期肝病患者肠道微生物失衡、小肠细菌过度生长、肠道通透性增加、肠道屏障功能减弱，致使肠道菌群易位、更多的内毒素、炎症因子等进入循环，进一步引起肝脏的损伤及门静脉高压的进展[35] [36]。

利福昔明可通过调节肠道菌群丰度、减少小肠细菌过度生长、维持肠道屏障功能及通透性，并减少肠道菌群易位、减少更多的细菌产物和炎症相关因子吸收入血，从而直接或间接地减轻终末期肝病所致的门静脉高压[37]。临床实验研究证实，利福昔明可引起酒精性终末期肝病患者肝静脉压力梯度值显着降低、静脉曲张出血及腹腔积液相关的入院人数减少，在与普萘洛尔联合使用时，比普萘洛尔单药疗法更能有效降低门静脉压力[38] [39] [40]。

3.4. 肝性脑病

肝性脑病是终末期肝病常见的并发症，表现为不同程度的神经精神异常，根据严重程度，可分为隐形肝性脑病和显性肝性脑病[41]，隐形肝性脑病缺乏临床神经系统体征，需要进行心理测试或电生理学评估以发现；显性肝性脑病可出现性格改变、时间和空间迷失、谵妄、昏睡和昏迷[42]。

肝性脑病的病理生理学机制还未完全被阐明，目前多数研究认为，高氨血症是导致肝性脑病发生的主要因素。氨来源于蛋白质代谢，通常在肝脏进行代谢，转化为尿素后通过肾脏和肌肉骨骼系统排出，部分通过尿素循环在肠道微生物的作用下再次转化为氨。终末期肝病患者氨的代谢减少，同时，门体分流导致循环中的氨增多[43]；另外，终末期肝病患者的肠道微生物改变以及其影响的内毒素血症和全身炎症的发展、肠道屏障损伤、肠－肝循环可介导肝性脑病的进展；同时，肝脏疾病的进展可导致循环铁代谢障碍及大脑中铁浓度增高，诱发活性氧介导的神经元细胞凋亡，从而加速中枢神经系统退行性疾病的进程[44] [45]。

终末期肝病的治疗方法中，经颈静脉肝内门体分流术(TIPS)可以有效治疗终末期肝病患者出现的静脉曲张出血和腹水，然而，TIPS 放置会增加发生肝性脑病(HE)的风险[46]。在一项纳入 197 名的接受 TIPS 治疗肝硬化患者，采用随机、双盲、多中心、安慰剂对照的研究，利福昔明在这些患者中具有良好的耐受性，降低了其患显性肝性脑病的风险[47]。

多项研究表示，利福昔明可通过增加紧密连接蛋白的表达、抑制其降解以增强肠道屏障功能；可调节肠道通透性以降低患者内毒素活性、减少肠源性炎症、限制全身炎症进展；可减轻微生物毒力，调节细菌代谢途径的表达；可调节肠道微生物丰度但不改变其组成；降低血浆氨水平以达到改善肝性脑病的作用，并且不会改变肠道菌群中耐药基因的类型，故不会出现抗菌药物耐药性的问题；利福昔明可以纠正柠檬酸铁铵诱导的铁过载和细菌脂多糖诱导的铁沉积，可有效减少神经元细胞损伤和凋亡[23] [24] [45] [48]。

利福昔明已被批准用作肝性脑病二级预防的一线治疗，与在肝性脑病中同样广泛应用的乳果糖相比，两者治疗效果无明显差异，两者联合使用可提高治疗终末期肝病并发肝性脑病的临床疗效、减少肝性脑病的复发及肝性脑病相关的再入院风险、降低死亡率、改善肝性脑病的预后[49]。

3.5. 腹水

腹水是终末期肝病最常见且较早出现的并发症，部分腹水对常用治疗药物反应不佳，称为难治性腹水[50]。终末期肝病由于肝脏结构的破坏，导致肝内血管阻力和肝窦压力增加从而产生门静脉高压，一方面，门脉高压直接导致肝窦内的静水压增加，液体渗出到腹腔中产生腹水；另一方面，门脉高压可产生更多的一氧化氮等内源性血管舒张物质，导致终末期肝病患者的全身血管舒张，有效循环血容量减少，从而引起肾素－血管紧张素－醛固酮系统(RAAS)、交感神经系统(SNS)等可产生水钠潴留作用的神经体

液调节系统激活[51] [52]。

终末期肝病并发腹水常用的治疗方法包括限制钠的摄入及使用利尿剂以减少水钠潴留、补充白蛋白以维持胶体渗透压、腹腔穿刺抽液、经颈静脉肝内门体分流术、肝移植[53]。除此之外，已有研究表明，利福昔明可通过调节肠道细菌的结构和功能以改善全身炎症状态、改善全身血流动力学和肾功能、降低门静脉压力和内毒素活性、减少肝肾综合征和急性肾损伤的发生，从而产生减少腹水、降低难治性腹水的发生率并提高患有难治性腹水的终末期患者的生存率的作用[54] [55]。利福昔明在与普萘洛尔联合使用时，能更好地降低门静脉压力，从而减少腹水生成[40]；在和利尿剂联合使用时，可增强对难治性腹水患者的利尿作用[56]。

3.6. 自发性腹膜炎

自发性腹膜炎指腹腔内无明确感染源的腹水感染和炎症，是终末期肝病患者最常见的感染类型[11]。终末期肝病患者的腹水中的中性粒细胞计数 ≥ 250 个细胞/mm^3 或腹水培养见病原体，且腹腔内未发现明显感染源，可诊断为自发性腹膜炎。多种病原体可引发自发性腹膜炎，致病菌主要来源于肠道菌群易位，最常见的为革兰阴性菌，如大肠杆菌、克雷伯杆菌[50]。自发性腹膜炎可导致终末期肝病的入院率和死亡率大大增加，因此，治疗和预防自发性腹膜炎的发生尤为重要。

利福昔明可通过以下方面对自发性腹膜炎产生有益作用：调节肠道菌群的丰度，但不改变肠道微生物的组成成分、减少肠道菌群易位；调节肠道微生物的功能变化、促进肠道菌群产生更多的有利代谢物以改善血流动力学；减轻内毒素活性及减少内毒素血症的产生；调节自发性腹膜炎患者体内的与炎症相关的免疫反应[57] [58]。

既往常使用诺氟沙星治疗和预防终末期肝病所并发的自发性腹膜炎，已有多个研究表明，使用利福昔明治疗及预防自发性腹膜炎复发的效果及安全性优于诺氟沙星，且能显著降低不良反应的发生率及死亡率[58] [59]。

3.7. 肝肾综合征

肝肾综合征是肝硬化患者并发的急性功能性肾损伤，是终末期肝病常见且严重的并发症之一，具有较高的死亡率[60]。近年来，肝病患者中急性肾损伤的定义发生了一定的变化，但定义中的共同主题是使用血清肌酐的相对变化值而不是绝对定义值。无结构性肾损伤、基础肾脏疾病及肾损伤药物应用证据的终末期肝病患者，当肾功能变化符合急性肾损伤标准时可考虑诊断为肝肾综合征[61]。

肝肾综合征的发病机制：终末期肝病患者白蛋白合成减少、门脉高压等使液体积聚在组织间隙及腹盆腔内，导致有效血容量减少，同时产生的更多血管活性物质导致微小血管扩张，进一步减少有效血容量，进而引起肾脏血流量下降；有效循环血流量减少激活系统性血管收缩系统，引起肾脏血管收缩[62] [63]；终末期肝病患者肠道通透性改变，导致肠道细菌及肠道炎症因子易位、模式相关受体(如 TLR4)的过度表达，引起肾脏功能障碍[64]。

利福昔明可通过调节肠道通透性、减少肠道细菌易位、调节血清代谢物、改善全身血流动力学、降低 TLR4 的表达、调节全身免疫及炎症反应，从而改善肝肾综合征[58] [65]。在临床试验研究中，利福昔明被证明可降低终末期肝病患者并发急性肾损伤的发生率、降低肝肾综合征需要肾脏置换治疗的风险[54]。

3.8. 肌肉减少症

肌肉减少症指肌肉质量与功能的损失，在终末期肝病患者中较常见，导致患者的生活质量下降、与短期及长期的不良预后相关，一个对 22 项研究进行的荟萃分析证实，肌肉减少症是终末期肝病患者死亡

率增加的独立预测因素，死亡率随着肌少症严重程度的加重或持续时间的延长而增加[66] [67]。

肠道菌群紊乱、肠道通透性及肠道屏障的损伤及细菌易位引起的内毒素血症及炎症反应导致蛋白质分解代谢引起肌肉损失[68]；另外，肠道菌群紊乱所促进的高氨血症，可通过负反馈抑制生成氨的肌肉生长，以及高氨血症导致实验动物中可增强肌肉蛋白质分解代谢并抑制其生长的肌生长抑制素水平增加，其升高的水平与肌肉减少症的严重程度相关[69] [70]；此外，小肠细菌过度生长可竞争进入肠道的营养物质，导致营养不良，引起肌肉生成减少[71]。利福昔明可通过调节肠道微生物，从而起到治疗及预防肌肉减少症的作用[72]。

4. 小结

终末期肝病即各种肝病的终末期阶段，死亡率高，治疗及预防终末期肝病的并发症、延缓终末期肝病的进展，在减少终末期肝病的病死率、改善预后及生活质量中尤为重要。利福昔明是一种口服的、难以被吸收的、在胃肠道具有高利用度的抗生素，目前已被批准用于终末期肝病并发肝性脑病二级预防的一线治疗，同时，利福昔明在改善肝纤维化、治疗或预防终末期肝病所并发的门静脉高压、腹水、自发性腹膜炎、肝肾综合征、肌肉减少症中具有一定的作用。

利福昔明可通过调节肠道微生物群的功能和丰度但不改变其组成类型、抑制小肠细菌过度生长、减少细菌易位，从而直接及间接地减少内毒素血症和炎症；利福昔明可通过减弱细菌内毒素介导的炎症介质释放、抑制 TLR4 的表达、减少炎症因子增多和炎症进展；利福昔明可通过激活 PXR 以促进肠道屏障修复、改善肠道通透性，从而对全身循环及脏器具有一定的影响。利福昔明通过上述机制，是否对终末期肝病相关的疾病进程及并发症治疗或预防具有更多的作用，有待进一步探究。

参考文献

[1] Rothstein, D.M. (2016) Rifamycins, Alone and in Combination. *Cold Spring Harbor Perspectives in Medicine*, **6**, a027011. https://doi.org/10.1101/cshperspect.a027011

[2] Ojetti, V., Lauritano, E.C., Barbaro, F., Migneco, A., Ainora, M.E., Fontana, L., Gabrielli, M. and Gasbarrini, A. (2009) Rifaximin Pharmacology and Clinical Implications. *Expert Opinion on Drug Metabolism & Toxicology*, **5**, 675-682. https://doi.org/10.1517/17425250902973695

[3] Koo, H.L. and DuPont, H.L. (2010) Rifaximin: A Unique Gastrointestinal-Selective Antibiotic for Enteric Diseases. *Current Opinion in Gastroenterology*, **26**, 17-25. https://doi.org/10.1097/MOG.0b013e328333dc8d

[4] Caraceni, P., Vargas, V., Solà, E., Alessandria, C., de Wit, K., Trebicka, J., Angeli, P., Mookerjee, R.P., Durand, F., Pose, E., Krag, A., Bajaj, J.S., Beuers, U., Ginès, P. and Liverhope Consortium (2021) The Use of Rifaximin in Patients with Cirrhosis. *Hepatology*, **74**, 1660-1673. https://doi.org/10.1002/hep.31708

[5] Kogawa, A.C. and Salgado, H.R.N. (2018) Status of Rifaximin: A Review of Characteristics, Uses and Analytical Methods. *Critical Reviews in Analytical Chemistry*, **48**, 459-466. https://doi.org/10.1080/10408347.2018.1447355

[6] Barkin, J.A., Keihanian, T., Barkin, J.S., Antequera, C.M. and Moshiree, B. (2019) Preferential Usage of Rifaximin for the Treatment of Hydrogen-Positive Small Intestinal Bacterial Overgrowth. *Revista de Gastroenterología del Perú*, **39**, 111-115. https://doi.org/10.14309/00000434-201610001-01074

[7] Li, H., Xiang, Y., Zhu, Z., Wang, W., Jiang, Z., Zhao, M., Cheng, S., Pan, F., Liu, D., Ho, R.C.M. and Ho, C.S.H. (2021) Rifaximin-Mediated Gut Microbiota Regulation Modulates the Function of Microglia and Protects against CUMS-Induced Depression-Like Behaviors in Adolescent Rat. *Journal of Neuroinflammation*, **18**, Article No. 254. https://doi.org/10.1186/s12974-021-02303-y

[8] Meng, D., Yang, M., Hu, L., Liu, T., Zhang, H., Sun, X., Wang, X., Chen, Y., Jin, Y. and Liu, R. (2022) Rifaximin Protects against Circadian Rhythm Disruption-Induced Cognitive Impairment through Preventing Gut Barrier Damage and Neuroinflammation. *Journal of Neurochemistry*, **163**, 406-418. https://doi.org/10.1111/jnc.15701

[9] Dutta, D., Li, K., Methe, B. and Lim, S.H. (2020) Rifaximin on Intestinally-Related Pathologic Changes in Sickle Cell Disease. *American Journal of Hematology*, **95**, E83-E86. https://doi.org/10.1002/ajh.25722

[10] Poo, S., Sriranganathan, D. and Segal, J.P. (2022) Network Meta-Analysis: Efficacy of Treatment for Acute, Chronic, and Prevention of Pouchitis in Ulcerative Colitis. *European Journal of Gastroenterology & Hepatology*, **34**, 518-528.

https://doi.org/10.1097/MEG.0000000000002362

[11] Chinese Society of Infectious Diseases and Chinese Medical Association (2022) Expert Consensus on Diagnosis and Treatment of End-Stage Liver Disease Complicated Infection (2021 Version). *Chinese Journal of Hepatology*, **30**, 147-158.

[12] Paik, J.M., Golabi, P., Younossi, Y., Mishra, A. and Younossi, Z.M. (2020) Changes in the Global Burden of Chronic Liver Diseases from 2012 to 2017: The Growing Impact of NAFLD. *Hepatology*, **72**, 1605-1616. https://doi.org/10.1002/hep.31173

[13] Parola, M. and Pinzani, M. (2019) Liver Fibrosis: Pathophysiology, Pathogenetic Targets and Clinical Issues. *Molecular Aspects of Medicine*, **65**, 37-55. https://doi.org/10.1016/j.mam.2018.09.002

[14] European Association for the Study of the Liver and European Association for the Study of the Liver (2019) EASL Clinical Practice Guidelines on Nutrition in Chronic Liver Disease. *Journal of Hepatology*, **70**, 172-193.

[15] Carrion, A.F. and Martin, P. (2021) Keeping Patients with End-Stage Liver Disease Alive While Awaiting Transplant: Management of Complications of Portal Hypertension. *Clinical Liver Disease*, **25**, 103-120. https://doi.org/10.1016/j.cld.2020.08.007

[16] Haep, N., Florentino, R.M., Squires, J.E., Bell, A. and Soto-Gutierrez, A. (2021) The Inside-Out of End-Stage Liver Disease: Hepatocytes Are the Keystone. *Seminars in Liver Disease*, **41**, 213-224. https://doi.org/10.1055/s-0041-1725023

[17] Shi, M., Meng, F.P. and Wang, F.S. (2021) Progress in Basic and Clinical and Clinical Research of a Cell Therapy for End-Stage Liver Disease. *Chinese Journal of Hepatology*, **29**, 179-182.

[18] Zeng, X., Sheng, X., Wang, P.Q., Xin, H.G., Guo, Y.B., Lin, Y., *et al*. (2021) Low-Dose Rifaximin Prevents Complications and Improves Survival in Patients with Decompensated Liver Cirrhosis. *Hepatology International*, **15**, 155-165. https://doi.org/10.1007/s12072-020-10117-y

[19] Tilg, H., Adolph, T.E. and Trauner, M. (2022) Gut-Liver Axis: Pathophysiological Concepts and Clinical Implications. *Cell Metabolism*, **34**, 1700-1718. https://doi.org/10.1016/j.cmet.2022.09.017

[20] Trebicka, J., Macnaughtan, J., Schnabl, B., Shawcross, D.L. and Bajaj, J.S. (2021) The Microbiota in Cirrhosis and Its Role in Hepatic Decompensation. *Journal of Hepatology*, **75**, S67-S81. https://doi.org/10.1016/j.jhep.2020.11.013

[21] Kang, Y., Kuang, X., Yan, H., Ren, P., Yang, X., Liu, H., Liu, Q., Yang, H., *et al*. (2023) A Novel Synbiotic Alleviates Autoimmune Hepatitis by Modulating the Gut Microbiota-Liver Axis and Inhibiting the Hepatic TLR4/NF-*κ*B/NLRP3 Signaling Pathway. *mSystems*, **8**, e0112722. https://doi.org/10.1128/msystems.01127-22

[22] Maslennikov, R., Pavlov, C. and Ivashkin, V. (2018) Small Intestinal Bacterial Overgrowth in Cirrhosis: Systematic Review and Meta-Analysis. *Hepatology International*, **12**, 567-576. https://doi.org/10.1007/s12072-018-9898-2

[23] Patel, V.C., Lee, S., McPhail, M.J.W., Da Silva, K., Guilly, S., Zamalloa, A., *et al*. (2022) Rifaximin-*α* Reduces Gut-Derived Inflammation and Mucin Degradation in Cirrhosis and Encephalopathy: RIFSYS Randomised Controlled Trial. *Journal of Hepatology*, **76**, 332-342. https://doi.org/10.1016/j.jhep.2021.09.010

[24] Kaji, K., Takaya, H., Saikawa, S., Furukawa, M., Sato, S., Kawaratani, H., *et al*. (2017) Rifaximin Ameliorates Hepatic Encephalopathy and Endotoxemia without Affecting the Gut Microbiome Diversity. *World Journal of Gastroenterology*, **23**, 8355-8366. https://doi.org/10.3748/wjg.v23.i47.8355

[25] Brown, E.L., Xue, Q., Jiang, Z.D., Xu, Y. and Dupont, H.L. (2010) Pretreatment of Epithelial Cells with Rifaximin Alters Bacterial Attachment and Internalization Profiles. *Antimicrobial Agents and Chemotherapy*, **54**, 388-396. https://doi.org/10.1128/AAC.00691-09

[26] Mencarelli, A., Renga, B., Palladino, G., Claudio, D., Ricci, P., Distrutti, E., *et al*. (2011) Inhibition of NF-*κ*B by a PXR-Dependent Pathway Mediates Counter-Regulatory Activities of Rifaximin on Innate Immunity in Intestinal Epithelial Cells. *European Journal of Pharmacology*, **668**, 317-324. https://doi.org/10.1016/j.ejphar.2011.06.058

[27] de Wit, K., Beuers, U., Mukha, A., Stigter, E.C.A., Gulersonmez, M.C., Ramos Pittol, J.M., *et al*. (2023) Rifaximin Stimulates Nitrogen Detoxification by PXR-Independent Mechanisms in Human Small Intestinal Organoids. *Liver International*, **43**, 649-659. https://doi.org/10.1111/liv.15491

[28] Wang, F.D., Zhou, J. and Chen, E.Q. (2022) Molecular Mechanisms and Potential New Therapeutic Drugs for Liver Fibrosis. *Frontiers in Pharmacology*, **13**, Article ID: 787748. https://doi.org/10.3389/fphar.2022.787748

[29] Israelsen, M., Madsen, B.S., Torp, N., Johansen, S., Hansen, C.D., Detlefsen, S., *et al*. (2023) Rifaximin-*α* for Liver Fibrosis in Patients with Alcohol-Related Liver Disease (GALA-RIF): A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial. *The Lancet Gastroenterology and Hepatology*, **8**, 523-532. https://doi.org/10.1016/S2468-1253(23)00010-9

[30] Enomoto, M., Kaji, K., Nishimura, N., Fujimoto, Y., Murata, K., Takeda, S., Tsuji, Y., *et al*. (2022) Rifaximin and Lubiprostone Mitigate Liver Fibrosis Development by Repairing Gut Barrier Function in Diet-Induced Rat Steatohepatitis.

Digestive and Liver Disease, **54**, 1392-1402. https://doi.org/10.1016/j.dld.2022.04.012

[31] Fujinaga, Y., Kawaratani, H., Kaya, D., Tsuji, Y., Ozutsumi, T., Furukawa, M., *et al*. (2020) Effective Combination Therapy of Angiotensin-II Receptor Blocker and Rifaximin for Hepatic Fibrosis in Rat Model of Nonalcoholic Steatohepatitis. *International Journal of Molecular Sciences*, **21**, Article No. 5589. https://doi.org/10.3390/ijms21155589

[32] Jothimani, D., Rela, M. and Kamath, P.S. (2023) Liver Cirrhosis and Portal Hypertension: How to Deal with Esophageal Varices? *Medical Clinics of North America*, **107**, 491-504. https://doi.org/10.1016/j.mcna.2023.01.002

[33] Ferral, H., Fimmel, C.J., Sonnenberg, A., Alonzo, M.J. and Aquisto, T.M. (2021) Transjugular Liver Biopsy with Hemodynamic Evaluation: Correlation between Hepatic Venous Pressure Gradient and Histologic Diagnosis of Cirrhosis. *Journal of Clinical Imaging Science*, **11**, Article No. 25. https://doi.org/10.25259/JCIS_233_2020

[34] Iwakiri, Y. and Trebicka, J. (2021) Portal Hypertension in Cirrhosis: Pathophysiological Mechanisms and Therapy. *JHEP Reports*, **3**, Article ID: 100316. https://doi.org/10.1016/j.jhepr.2021.100316

[35] Rayes, N., Pilarski, T., Stockmann, M., Bengmark, S., Neuhaus, P. and Seehofer, D. (2012) Effect of Pre- and Probiotics on Liver Regeneration after Resection: A Randomised, Double-Blind Pilot Study. *Beneficial Microbes*, **3**, 237-244. https://doi.org/10.3920/BM2012.0006

[36] Arab, J.P., Martin-Mateos, R.M. and Shah, V.H. (2018) Gut-Liver Axis, Cirrhosis and Portal Hypertension: The Chicken and the Egg. *Hepatology International*, **12**, 24-33. https://doi.org/10.1007/s12072-017-9798-x

[37] Kalambokis, G.N. and Tsianos, E.V. (2012) Rifaximin Reduces Endotoxemia and Improves Liver Function and Disease Severity in Patients with Decompensated Cirrhosis. *Hepatology*, **55**, 655-656. https://doi.org/10.1002/hep.24751

[38] Vlachogiannakos, J., Saveriadis, A.S., Viazis, N., Theodoropoulos, I., Foudoulis, K., Manolakopoulos, S., Raptis, S. and Karamanolis, D.G. (2009) Intestinal Decontamination Improves Liver Haemodynamics in Patients with Alcohol-Related Decompensated Cirrhosis. *Alimentary Pharmacology & Therapeutics*, **29**, 992-999. https://doi.org/10.1111/j.1365-2036.2009.03958.x

[39] Salehi, S., Tranah, T.H., Lim, S., Heaton, N., Heneghan, M., Aluvihare, V., Patel, V.C. and Shawcross, D.L. (2019) Rifaximin Reduces the Incidence of Spontaneous Bacterial Peritonitis, Variceal Bleeding and All-Cause Admissions in Patients on the Liver Transplant Waiting List. *Alimentary Pharmacology & Therapeutics*, **50**, 435-441. https://doi.org/10.1111/apt.15326

[40] Lim, Y.L., Kim, M.Y., Jang, Y.O., Baik, S.K. and Kwon, S.O. (2017) Rifaximin and Propranolol Combination Therapy Is More Effective than Propranolol Monotherapy for the Reduction of Portal Pressure: An Open Randomized Controlled Pilot Study. *Gut and Liver*, **11**, 702-710. https://doi.org/10.5009/gnl16478

[41] Patidar, K.R. and Bajaj, J.S. (2015) Covert and Overt Hepatic Encephalopathy: Diagnosis and Management. *Clinical Gastroenterology and Hepatology*, **13**, 2048-2061. https://doi.org/10.1016/j.cgh.2015.06.039

[42] Ridola, L., Faccioli, J., Nardelli, S., Gioia, S. and Riggio, O. (2020) Hepatic Encephalopathy: Diagnosis and Management. *Journal of Translational Internal Medicine*, **8**, 210-219. https://doi.org/10.2478/jtim-2020-0034

[43] Coronel-Castillo, C.E., Contreras-Carmona, J., Frati-Munari, A.C., Uribe, M. and Méndez-Sánchez, N. (2020) Efficacy of Rifaximin in the Different Clinical Scenarios of Hepatic Encephalopathy. *Revista de Gastroenterología de México*, **85**, 56-68. https://doi.org/10.1016/j.rgmxen.2019.09.003

[44] Tamai, Y., Iwasa, M., Eguchi, A., Shigefuku, R., Kamada, Y., Miyoshi, E. and Takei, Y. (2021) Rifaximin Ameliorates Intestinal Inflammation in Cirrhotic Patients with Hepatic Encephalopathy. *JGH Open*, **5**, 827-830. https://doi.org/10.1002/jgh3.12596

[45] Zhang, Z., Yuan, Q., Hu, X., Liao, J. and Kuang, J. (2022) Rifaximin Protects SH-SY5Y Neuronal Cells from Iron Overload-Induced Cytotoxicity via Inhibiting STAT3/NF-κB Signaling. *Cell Biology International*, **46**, 1062-1073. https://doi.org/10.1002/cbin.11776

[46] Liang, A., Brar, S., Almaghrabi, M., Khan, M.Q., Qumosani, K. and Teriaky, A. (2023) Primary Prevention of Hepatic Encephalopathy Post-TIPS: A Systematic Review and Meta-Analysis. *Medicine* (*Baltimore*), **102**, e35266. https://doi.org/10.1097/MD.0000000000035266

[47] LBureau, C., Thabut, D., Jezequel, C., Archambeaud, I., D'Alteroche, L., Dharancy, S., *et al*. (2021) The Use of Rifaximin in the Prevention of Overt Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt: A Randomized Controlled Trial. *Annals of Internal Medicine*, **174**, 633-640. https://doi.org/10.7326/M20-0202

[48] Yu, X., Jin, Y., Zhou, W., Xiao, T., Wu, Z., Su, J., *et al*. (2022) Rifaximin Modulates the Gut Microbiota to Prevent Hepatic Encephalopathy in Liver Cirrhosis without Impacting the Resistome. *Frontiers in Cellular and Infection Microbiology*, **11**, Article ID: 761192. https://doi.org/10.3389/fcimb.2021.761192

[49] Fu, J., Gao, Y. and Shi, L. (2022) Combination Therapy with Rifaximin and Lactulose in Hepatic Encephalopathy: A Systematic Review and Meta-Analysis. *PLOS ONE*, **17**, e0267647. https://doi.org/10.1371/journal.pone.0267647

[50] Aithal, G.P., Palaniyappan, N., China, L., Härmälä, S., Macken, L., Ryan, J.M., *et al*. (2021) Guidelines on the Man-

agement of Ascites in Cirrhosis. *Gut*, **70**, 9-29. https://doi.org/10.1136/gutjnl-2020-321790

[51] Zaccherini, G., Tufoni, M., Iannone, G. and Caraceni, P. (2021) Management of Ascites in Patients with Cirrhosis: An Update. *Journal of Clinical Medicine*, **10**, Article No. 5226. https://doi.org/10.3390/jcm10225226

[52] Pedersen, J.S., Bendtsen, F. and Møller, S. (2015) Management of Cirrhotic Ascites. *Therapeutic Advances in Chronic Disease*, **6**, 124-137. https://doi.org/10.1177/2040622315580069

[53] Lv, X.Y., Ding, H.G., Zheng, J.F., Fan, C.L. and Li, L. (2020) Rifaximin Improves Survival in Cirrhotic Patients with Refractory Ascites: A Real-World Study. *World Journal of Gastroenterology*, **26**, 199-218. https://doi.org/10.3748/wjg.v26.i2.199

[54] Hanafy, A.S. and Hassaneen, A.M. (2016) Rifaximin and Midodrine Improve Clinical Outcome in Refractory Ascites Including Renal Function, Weight Loss, and Short-Term Survival. *European Journal of Gastroenterology & Hepatology*, **28**, 1455-1461. https://doi.org/10.1097/MEG.0000000000000743

[55] Yokoyama, K., Fukuda, H., Yamauchi, R., Higashi, M., Miyayama, T., Higashi, T., *et al*. (2022) Long-Term Effects of Rifaximin on Patients with Hepatic Encephalopathy: Its Possible Effects on the Improvement in the Blood Ammonia Concentration Levels, Hepatic Spare Ability and Refractory Ascites. *Medicina* (*Kaunas*), **58**, Article No. 1276. https://doi.org/10.3390/medicina58091276

[56] Dong, T., Aronsohn, A., Gautham, R.K. and Te, H.S. (2016) Rifaximin Decreases the Incidence and Severity of Acute Kidney Injury and Hepatorenal Syndrome in Cirrhosis. *Digestive Diseases and Sciences*, **61**, 3621-3626. https://doi.org/10.1007/s10620-016-4313-0

[57] Mostafa, T., Badra, G. and Abdallah, M. (2015) The Efficacy and the Immunomodulatory Effect of Rifaximin in Prophylaxis of Spontaneous Bacterial Peritonitis in Cirrhotic Egyptian Patients. *Turkish Journal of Gastroenterology*, **26**, 163-169. https://doi.org/10.5152/tjg.2015.7782

[58] Ponziani, F.R., Gerardi, V., Pecere, S., D'Aversa, F., Lopetuso, L., *et al*. (2015) Effect of Rifaximin on Gut Microbiota Composition in Advanced Liver Disease and Its Complications. *World Journal of Gastroenterology*, **21**, 12322-12333. https://doi.org/10.3748/wjg.v21.i43.12322

[59] Praharaj, D.L., Premkumar, M., Roy, A., Verma, N., Taneja, S., Duseja, A. and Dhiman, R.K. (2022) Rifaximin vs. Norfloxacin for Spontaneous Bacterial Peritonitis Prophylaxis: A Randomized Controlled Trial. *Journal of Clinical and Experimental Hepatology*, **12**, 336-342. https://doi.org/10.1016/j.jceh.2021.08.010

[60] Hasan, I., Rashid, T., Chirila, R.M., Ghali, P. and Wadei, H.M. (2021) Hepatorenal Syndrome: Pathophysiology and Evidence-Based Management Update. *Romanian Journal of Internal Medicine*, **59**, 227-261. https://doi.org/10.2478/rjim-2021-0006

[61] Francoz, C., Durand, F., Kahn, J.A., Genyk, Y.S. and Nadim, M.K. (2019) Hepatorenal Syndrome. *Clinical Journal of the American Society of Nephrology*, **14**, 774-781. https://doi.org/10.2215/CJN.12451018

[62] Schrier, R.W., Arroyo, V., Bernardi, M., Epstein, M., Henriksen, J.H. and Rodés, J. (1988) Peripheral Arterial Vasodilation Hypothesis: A Proposal for the Initiation of Renal Sodium and Water Retention in Cirrhosis. *Hepatology*, **8**, 1151-1157. https://doi.org/10.1002/hep.1840080532

[63] Wilde, B., Canbay, A. and Katsounas, A. (2023) Clinical and Pathophysiological Understanding of the Hepatorenal Syndrome: Still Wrong or Still Not Exactly Right? *World Journal of Clinical Cases*, **11**, 1261-1266. https://doi.org/10.12998/wjcc.v11.i6.1261

[64] Wang, M., Qin, T., Zhang, Y., Zhang, T., Zhuang, Z., Wang, Y., Ding, Y. and Peng, Y. (2022) Toll-Like Receptor 4 Signaling Pathway Mediates Both Liver and Kidney Injuries in Mice with Hepatorenal Syndrome. *The American Journal of Physiology-Gastrointestinal and Liver Physiology*, **323**, G461-G476. https://doi.org/10.1152/ajpgi.00048.2022

[65] Luo, M., Xie, P., Deng, X., Fan, J. and Xiong, L. (2023) Rifaximin Ameliorates Loperamide-Induced Constipation in Rats through the Regulation of Gut Microbiota and Serum Metabolites. *Nutrients*, **15**, Article No. 4502. https://doi.org/10.3390/nu15214502

[66] Hari, A. (2021) Muscular Abnormalities in Liver Cirrhosis. *World Journal of Gastroenterology*, **27**, 4862-4878. https://doi.org/10.3748/wjg.v27.i29.4862

[67] Tantai, X., Liu, Y., Yeo, Y.H., Praktiknjo, M., Mauro, E., Hamaguchi, Y., *et al*. (2022) Effect of Sarcopenia on Survival in Patients with Cirrhosis: A Meta-Analysis. *Journal of Hepatology*, **76**, 588-599. https://doi.org/10.1016/j.jhep.2021.11.006

[68] Sato, S., Namisaki, T., Murata, K., Fujimoto, Y., Takeda, S., Enomoto, M., *et al*. (2021) The Association between Sarcopenia and Endotoxin in Patients with Alcoholic Cirrhosis. *Medicine* (*Baltimore*), **100**, e27212. https://doi.org/10.1097/MD.0000000000027212

[69] Jindal, A. and Jagdish, R.K. (2019) Sarcopenia: Ammonia Metabolism and Hepatic Encephalopathy. *Clinical and Molecular Hepatology*, **25**, 270-279. https://doi.org/10.3350/cmh.2019.0015

[70] Qiu, J., Thapaliya, S., Runkana, A., Yang, Y., Tsien, C., Mohan, M.L., *et al*. (2013) Hyperammonemia in Cirrhosis Induces Transcriptional Regulation of Myostatin by an NF-*κ*B-Mediated Mechanism. *Proceedings of the National Academy of Sciences of the United States of America*, **110**, 18162-18167. https://doi.org/10.1073/pnas.1317049110

[71] Yao, J., Chang, L., Yuan, L. and Duan, Z. (2016) Nutrition Status and Small Intestinal Bacterial Overgrowth in Patients with Virus-Related Cirrhosis. *Asia Pacific Journal of Clinical Nutrition*, **25**, 283-291.

[72] Maslennikov, R., Alieva, A., Poluektova, E., Zharikov, Y., Suslov, A., Letyagina, Y., *et al*. (2023) Sarcopenia in Cirrhosis: Prospects for Therapy Targeted to Gut Microbiota. *World Journal of Gastroenterology*, **29**, 4236-4251. https://doi.org/10.3748/wjg.v29.i27.4236