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文献综述 REVIEW

肝硬化合并细菌感染易感性机制的研究进展

李 莹, 韩 涛

背景资料
肝硬化特别是终末期肝硬化患者对感染极为易感, 是普通人群的4-5倍, 将近25%-30%的肝硬化患者在入院或住院期间存在感染. 而感染是导致肝硬化患者出现各种并发症及器官衰竭、甚至死亡的常见原因, 病死率极高.

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Mechanisms of susceptibility to bacterial infections in cirrhotic patients

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Abstract
Bacterial infections are very common in cirrhotic patients, and the incidence is 4-5 times higher than that in the general population. The mechanisms of susceptibility to bacterial infections in cirrhotic patients include intestinal bacterial overgrowth, bacterial translocation, increased number of potentially pathogenic bacteria accompanied by reduced number of beneficial bacteria; small bowel motility disturbances and delayed gut transit, increased intestinal permeability; genetic predisposition to bacterial infections; immunodeficiency accompanied by persistent activation of the immune cells with production of pro-inflammatory cytokines. In this paper, we will discuss the mechanisms of susceptibility to bacterial infections in cirrhotic patients.

Key Words: Cirrhosis; Bacterial infections; Translocation; Immune dysfunction

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摘要
肝硬化患者合并细菌感染的风险是普通人群的4-5倍, 对细菌感染易感性的机制主要是由于肝硬化患者肠道微生物群特点即肠道细菌过度生长、细菌异位、致病菌比例增加、有益菌比例降低, 肠道功能障碍即肠道运动转运功能障碍、肠道渗透性增加, 基因易感性, 和免疫功能紊乱等.

关键词: 肝硬化; 感染; 细菌异位; 免疫紊乱

核心提示: 肝硬化对细菌感染易感性主要是由于肝硬化肠道微生物群特点(质与量的改变)、肠道功能障碍(肠道转运功能障碍及渗透性增

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加)、基因易感性和免疫功能紊乱.

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0 引言

细菌感染、消化道出血、肝性脑病和肝肾综合征是肝硬化患者的四大常见, 其中合并细菌感染最为常见, 是代偿期肝硬化患者进展至失代偿期、出现肝功能衰竭、肝外脏器衰竭、甚至死亡的常见原因, 也是导致肝硬化患者无法正常接受肝移植治疗及移植后失败的常见原因[1,2]. 将近25%-30%的肝硬化患者在入院或住院期间存在感染[1], 是普通人群的4-5倍, 肝硬化患者一旦合并感染病死率将升高近4倍[1,3], 因此正确理解肝硬化患者合并细菌感染的易感性机制, 及时防治细菌感染对肝硬化的救治非常关键. 目前肝硬化患者合并细菌感染易感性的主要机制有于肝硬化患者肠道微生物群特点、肠道功能障碍、宿主基因易感性和免疫功能紊乱等方面, 现就这一专题进行综述.

1 肝硬化患者肠道微生物特点

宿主与肠道微生物之间精确平衡被打乱则导致疾病发生[4,5]. 微生物改变包括量的改变(肠道细菌过度生长)和质的改变(微生物种群失调). 肝硬化患者常出现肠道细菌过度生长, 特别是小肠[6]. 导致肠道微生物过度生长的原因包括胃酸分泌改变、肠道动力降低、胆汁流量降低、IgA分泌改变、抗微生物分子缺乏和门脉高压[7,8]. 研究显示给小鼠喂食3 wk乙醇, 抗微生物分子Reg3b和Reg3g明显降低[8], 致对肠杆菌属抗菌活性降低. 胆汁酸可通过直接抑制和间接调节宿主细胞抗菌肽基因表达而抑制细菌增殖[9]. 肝硬化患者机体存在一系列胆汁酸改变, 总粪胆酸减少可导致肠道菌群过度生长[10]. 肝硬化患者最突出微生物种群改变为潜在致病菌增加、有益菌比例降低, 不同病因肝硬化有着相似粪便菌群分布[11-13]. 终末期肝硬化机体特征如胆汁流量降低等均影响肠道微生物种群的构成.

肝硬化患者合并肠道微生物过度生长易发生自发性细菌性腹膜炎(spontaneous bacterial peritonitis, SBP), 肠道微生物数量改变起到关键性作用. 实验显示单纯肠道微生物过度生长即可导致细菌易位和肝脏炎症, 如应用抗生素减轻肠道细菌负荷, 可改善肝脏疾病状况, 且临床应用中可降低终末期肝硬化患者肝病严重程度、减少内毒素血症和感染并发症发生[14]. 肠道菌群亦参与肝硬化肝性脑病的发生[15], 合并轻微肝性脑病的肝硬化患者较未合并者更易存在肠道细菌过度生长, 特别是致病性大肠杆菌和葡萄球菌的过度生长[16]. 应用肠道不吸收的抗生素如利福昔明对肠道进行去污染对于亚临床和显性肝性脑病是有效的治疗手段[17]. 近期的一项Meta分析显示应用益生菌、益生元和牛初乳可以影响肠道菌群, 显著改善肝性脑病[18].

肝硬化腹水小鼠合并细菌易位使得潘氏细胞产生防御素和Reg3分子水平降低, 从而导致对肠杆菌属的抗菌活性降低[7]. 肝硬化患者发生细菌易位可导致炎症、血液动力学紊乱[19]和严重感染, 病死率接近40%[3]. 细菌易位产物导致非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)和酒精性肝病的进展. 终末期肝病患者肠道细菌迁移至腹腔和循环可导致SBP和菌血症, 易位的活菌及微生物产物导致临床并发症的发生, 细菌易位是肝硬化患者病死率的主要决定因素.

2 肝硬化患者肠道功能障碍

肝硬化患者肠道动力紊乱, 特别是门脉高压患者存在异常的肠道压力波传播模式, 表现为大量长串和高频波逆向传播, 肝移植后小肠测压异常得到改善[20]. 肝硬化患者小肠转运时间延长[21,22], 约35%患者存在小肠滞留时间延长, 与腹泻、腹痛增加密切相关, 给予服用西沙比利加速结肠转运, 可去除80%患者肠道细菌过度生长, 因此小肠转运延迟可致肠道细菌过度生长, 进一步导致腹泻、腹痛、细菌易位及感染并发症(如SBP)[20].

肝硬化患者肠道渗透性增加, 疾病终末期、并发脓毒血症、合并腹水、存在SBP病史、合并细菌感染的肝硬化患者肠道渗透性显著增加. 细菌感染特别是SBP与肠道渗透性增加密切相关[3], 细菌反复从肠腔进入肠系膜淋巴结(细菌易位), 进而进入腹水导致SBP. 入院时肠道渗透性增加可以作为肝硬化患者细菌感染的预测因子, 与肝硬化并发症密切相关[23].

研发前沿

正确理解肝硬化患者合并细菌感染的易感性机制, 对开发肝硬化患者感染早期诊断新方法、制定规范化细菌感染预防及治疗策略非常关键.

相关报道
Jalan等对肝硬化合并细菌感染的早期诊断、预防和治疗提出了规范化指南.

此外肠道对细菌产物的渗透, 如内毒素、细菌DNA等可以导致免疫系统激活、循环状态紊乱并诱发肾功能衰竭及肝性脑病[18]. 肝硬化患者肝脏对内毒素清除减少和/或肠道细胞因子产生增加, 内毒素致敏的巨噬细胞释放一氧化氮和促炎因子, 进一步破坏肠道屏障功能[24], 导致免疫和血流动力学紊乱、心功能障碍[25]及肝脏疾病进展[26]. 肝病患者摄入酒精可导致肠道渗透性增加和内毒素血症, 且先于脂肪性肝炎发生[27], 通过刺激肝纤维化导致肝脏损伤, 进一步提示肠道渗透性增加在慢性肝损伤中发挥了重要作用.

肝硬化患者肠道屏障功能障碍发病机制复杂[20]. (1)酒精及其代谢产物通过一氧化氮介导的氧化应激、产生反应氧、细胞骨架改变及对细胞直接损伤导致紧密连接异常[28]; (2)门脉高压可影响肠道屏障完整性, 引起肠壁水肿、细胞间隙扩大、肠道渗透性增加, 应用非选择性β受体阻滞剂可降低肠道渗透性、减少细菌易位[29]; (3)肠道细菌改变特别是小肠细菌过度生长影响肠道屏障功能、增加肠道渗透性. 潘氏细胞防御功能受损, 黏膜对入侵细菌的杀伤能力降低[8]易出现细菌易位[29]; (4)肝硬化特别是失代偿期, 肠上皮细胞紧密连接蛋白表达改变[30], 与血内毒素水平相关[7], 成孔蛋白-封闭蛋白2增加[24], 紧密连接蛋白-闭合蛋白和封闭蛋白-1表达显著降低[31]; (5)针对入侵细菌宿主胞吞作用受损. 肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)是紧密连接和胞吞作用关键调节因子, 终末期肝硬化肠道淋巴组织中TNF-α[32]; (6)分泌介质可限制细菌与上皮表面直接接触, 肝硬化此分泌功能缺乏, 包括IgA、胆汁脂质和抗微生物肽[7].

3 肝硬化患者细菌感染的基因易感性

细胞外的细菌通过膜结合Toll样受体(Toll-like receptors, TLR)和细胞内Nod受体(Nod-like receptors, NLR)(包括NOD2和NLRP3)被宿主识别, 进一步激活核因子NFKβ和释放抗微生物肽. Nischalke等[33]研究显示*TLR2*基因多态性与SBP特别是革兰氏阳性菌导致的SBP相关. *TLR2*基因内含子2串联GT重复序列数量增加的患者具有SBP高风险性, 纯合子*TLR2*启动子序列突变[-16934A>T(rs4696480)]亦与SBP高风险相关. 研究亦发现发生TLR2 Arg753Gln(rs5743708)变异的患者SBP风险增加, 亦与其他感染性疾病相关, 包括心内膜炎、泌尿系感染、儿童复发性细菌感染、ICU危重患者入院已存感染和肝移植后革兰氏阳性菌感染复发[34]. 携带TLR2 Arg753Gln变异的SBP患者培养均为阴性, 且腹水蛋白浓度较高, 中位生存期低于GG基因型患者[34]. 一项回顾性研究阐述了TLR4多态性与肝硬化患者感染率增加及强烈刺激细胞因子表达的相关性[35]. NOD2对革兰氏阴性菌细胞壁组成成分胞壁酰二肽敏感, 已证实*NOD2*、*NLRP3*和*TLR4*基因变异可增加脓毒血症患者的病死率. 肝硬化携带NOD2变异的患者, 发生SBP和死亡风险更高、发生静脉曲张出血和原发性肝癌频率更高[36,37]. 多变量分析显示如*NOD*和*TLR2*基因变异同时存在则发生SBP风险极高, 同时可以作为肠道屏障功能异常和细菌易位的替代标志. 亦有研究显示单核细胞趋化蛋白(monocyte chemotactic protein, MCP)1的-2518位AA基因型是肝硬化患者SBP的高危因素, 合并SBP患者血清和腹水中MCP-1蛋白水平要高于未合并者, 且治疗后MCP-1蛋白水平下降. MCP-1蛋白亦与无症状菌尿相关[38].

4 肝硬化患者免疫状态紊乱

肝硬化相关免疫紊乱(cirrhosis associated immune dysfunction, CAID)包括免疫缺陷状态和免疫系统持续激活炎症状态[39].

4.1 肝硬化相关免疫缺陷 免疫监控功能受损. 肝窦纤维化、肝窦毛细血管化、间隔纤维化、门脉系统分流和Kuffer细胞缺失或受损共同导致免疫监控功能受损, 对血液中内毒素和细菌清除能力降低, 导致菌血症、组织器官感染和对免疫系统持续刺激. 实验中Kuffer细胞或其补体受体缺乏将导致难以控制的菌血症及宿主死亡, 临床肝硬化患者网状内皮组织功能降低与细菌感染高风险性和低生存率密切相关[40].

肝硬化患者先天免疫蛋白和识别受体合成减少, 导致吞噬细胞杀菌能力降低. 腹水可增加肝硬化患者细菌感染风险, 患者血清、腹水中补体C3、C4和CH50浓度降低导致免疫调节素活性下降. 肝硬化患者基因多态性致甘露糖结合凝集素识别分子和转运受体血清水平降低, 导致细菌感染风险增加[41].

循环免疫细胞受损: (1)中性粒细胞数量减少、吞噬功能受损、过氧化物阴离子O_2^-产生缺乏、过氧化物酶活性降低、对肽聚糖识别蛋白反应性降低致其杀菌能力受损, 微血管内皮黏附能力和游出能力降低致其对感染部位的趋化能力受损[42]; (2)循环中单核细胞数量、分布和功能均发生改变, 促炎$CD14^+CD16^+$亚组单核细胞增多, 存在嗜菌能力有限的单核细胞扩增[43]. 循环中单核细胞Fc-γ受体功能障碍, 此为清除IgG包被细菌所必须[44]; (3)B细胞外周血绝对计数减少、记忆性B细胞功能障碍、$CD27^+$记忆性B细胞缺乏, 导致对CD40/TLR9应答不足、对共刺激标志物上调功能受损、TNFβ和IgG生成受损及T细胞异种刺激受损[45]; (4)T细胞池受损, T淋巴细胞减少并影响辅助T细胞(T helper cells, Th)和细胞毒T细胞(cytotoxic T cells, Tc)、天然T细胞损耗、T细胞池回缩、循环中T淋巴细胞体内激活增殖减少[46,47]; (5)循环和肝脏中NK细胞受损, 对细胞因子刺激反应性较差[48].

肠道淋巴组织损伤. 肠道渗透性增加、肠道细菌过度生长使得肠道淋巴组织始终处于细菌易位和细菌产物增加的微环境, 持续刺激致肠道和肠系膜淋巴结内活化的单核细胞、树突状细胞和T淋巴细胞增多[32,49], 引起固有层、黏膜上皮和肠系膜淋巴结促炎/抗炎因子扩增表达、肠道树突状细胞吞噬作用增强[32,49], 导致全身性炎症[32,50]及肠道屏障功能衰竭.

4.2 免疫系统持续激活炎症状态 肝硬化循环免疫细胞活化表现: (1)中性粒细胞: 呼吸爆发增加和CD11b表达增加[51]; (2)单核细胞: 表面人类白细胞抗原(human leukocyte antigen, HLA)-DR、活化/共刺激分子CD80和CD86表达增加、通路上调并增加促炎因子的产生, 如[TNF-α、白介素-6(interleukin-6, IL-6)][32,50,52]; (3)T淋巴细胞: T细胞表面活化抗原表达增加, 进一步增加TNF-α、干扰素-γ(interferon-γ, IFN-γ)、IL-17的生成[32,50,53]; (4)B淋巴细胞: 激活/共刺激标志物、HLA-DR和CD86的上调、对细胞因子反应性增加和高球蛋白血症[54]. 活化的循环免疫细胞成为促炎因子如TNF-α、TNF-α受体Ⅰ和Ⅱ、IL-1β、IL-6、IFNγ、IL-17、细胞间黏附分子-1(intercellular adhesion molecule 1, ICAM-1)和血管细胞黏附分子(vascular celladhesion molecule, VCAM)-1血清浓度增加的主要原因, 其中单核细胞是循环TNF-α的主要来源, 血清TNF-α水平与单核细胞产生TNF-α能力成正相关[50]. 这种全身性炎症的严重程度与肝硬化程度相平行, 特别是肝硬化合并腹水患者[32,50,55], 可应用Child-Pugh评分进行评估[56,57].

全身性炎症病理性机制. 终末期肝硬化患者免疫应答所致全身性炎症起始于肠道细菌进入机体内环境. 来自肠道细菌的病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)和/或损伤相关分子模式(damage-associated molecular patterns, DAMPs)可识别先天免疫细胞表达的模式识别受体(pattern recognition receptors, PRRs), 活菌和肝-内脏循环中的PAMPs(包括LPS、脂肽、含糖聚合物、鞭毛蛋白和细菌DNA)均可导致全身性炎症反应[55,58], 肠道淋巴组织和肠系膜淋巴结中已活化的免疫细胞进入外周血并传播全身性炎症[32,59]. PRRs触发基因转录、表达并合成一系列广谱分子, 包括多种促炎、抗炎细胞因子、趋化因子、细胞黏附分子和免疫受体, 驱动获得性免疫. 此外PRRs介导免疫细胞活化还包括加强吞噬细胞活性[51]、损伤血管内皮[50,57,60]、肝脏合成急性期蛋白[50,57,61]、趋化白细胞到炎症部位, 肝硬化合并腹水患者先天性免疫系统细胞PRRs表达(主要是TLRs和NLRs)上调[51,62].

创新盘点
本文详细剖析、综述了肝硬化细菌感染易感性机制. 从肝硬化肠道微生物群特点、肠道功能障碍、基因易感性和免疫功能紊乱几方面进行详细阐述, 深刻地揭示了肝硬化患者易感机制.

5 结论

肝硬化患者肠道微生物种群量和质的改变、肠道功能异常、基因易感性和肝硬化相关的免疫紊乱共同导致肝硬化患者对感染的易感性, 通过对感染易感性的深入剖析可帮助临床医生从各易感环节入手, 对肝硬化患者感染采取积极有效的预防措施, 有效降低患者病死率.

6 参考文献

1 Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, Stadlbauer V, Gustot T, Bernardi M, Canton R, Albillos A, Lammert F, Wilmer A, Mookerjee R, Vila J, Garcia-Martinez R, Wendon J, Such J, Cordoba J, Sanyal A, Garcia-Tsao G, Arroyo V, Burroughs A, Ginès P. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014; 60: 1310-1324 [PMID: 24530646 DOI: 10.1016/j.jhep.2014.01.024]
2 Bajaj JS, O'Leary JG, Wong F, Reddy KR, Kamath

应用要点
通过对易感性机制的剖析, 有助于研发肝硬化细菌感染早期诊断方法及制定有效防治策略.

PS. Bacterial infections in end-stage liver disease: current challenges and future directions. *Gut* 2012; 61: 1219-1225 [PMID: 22661495 DOI: 10.1136/gutjnl-2012-302339]
3 Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010; 139: 1246-1256, 1256.e1-e5 [PMID: 20558165 DOI: 10.1053/j.gastro.2010.06.019]
4 Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012; 336: 1268-1273 [PMID: 22674334 DOI: 10.1126/science.1223490]
5 Littman DR, Pamer EG. Role of the commensal microbiota in normal and pathogenic host immune responses. *Cell Host Microbe* 2011; 10: 311-323 [PMID: 22018232 DOI: 10.1016/j.chom.2011.10.004]
6 Pande C, Kumar A, Sarin SK. Small-intestinal bacterial overgrowth in cirrhosis is related to the severity of liver disease. *Aliment Pharmacol Ther* 2009; 29: 1273-1281 [PMID: 19302262 DOI: 10.1111/j.1365-2036.2009.03994.x]
7 Teltschik Z, Wiest R, Beisner J, Nuding S, Hofmann C, Schoelmerich J, Bevins CL, Stange EF, Wehkamp J. Intestinal bacterial translocation in rats with cirrhosis is related to compromised Paneth cell antimicrobial host defense. *Hepatology* 2012; 55: 1154-1163 [PMID: 22095436 DOI: 10.1002/hep.24789]
8 Yan AW, Fouts DE, Brandl J, Stärkel P, Torralba M, Schott E, Tsukamoto H, Nelson KE, Brenner DA, Schnabl B. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 2011; 53: 96-105 [PMID: 21254165 DOI: 10.1002/hep.24018]
9 Kakiyama G, Pandak WM, Gillevet PM, Hylemon PB, Heuman DM, Daita K, Takei H, Muto A, Nittono H, Ridlon JM, White MB, Noble NA, Monteith P, Fuchs M, Thacker LR, Sikaroodi M, Bajaj JS. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. *J Hepatol* 2013; 58: 949-955 [PMID: 23333527 DOI: 10.1016/j.jhep.2013.01.003]
10 Lorenzo-Zúñiga V, Bartolí R, Planas R, Hofmann AF, Viñado B, Hagey LR, Hernández JM, Mañé J, Alvarez MA, Ausina V, Gassull MA. Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. *Hepatology* 2003; 37: 551-557 [PMID: 12601352]
11 Bajaj JS, Hylemon PB, Ridlon JM, Heuman DM, Daita K, White MB, Monteith P, Noble NA, Sikaroodi M, Gillevet PM. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. *Am J Physiol Gastrointest Liver Physiol* 2012; 303: G675-G685 [PMID: 22821944 DOI: 10.1152/ajpgi.00152.2012]
12 Wu ZW, Lu HF, Wu J, Zuo J, Chen P, Sheng JF, Zheng SS, Li LJ. Assessment of the fecal lactobacilli population in patients with hepatitis B virus-related decompensated cirrhosis and hepatitis B cirrhosis treated with liver transplant. *Microb Ecol* 2012; 63: 929-937 [PMID: 21965156 DOI: 10.1007/s00248-011-9945-1]
13 Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology* 2014; 146: 1513-1524 [PMID: 24440671 DOI: 10.1053/j.gastro.2014.01.020]
14 Kalambokis GN, Tsianos EV. Rifaximin reduces endotoxemia and improves liver function and disease severity in patients with decompensated cirrhosis. *Hepatology* 2012; 55: 655-656 [PMID: 22030839 DOI: 10.1002/hep.24751]
15 Tranah TH, Vijay GK, Ryan JM, Shawcross DL. Systemic inflammation and ammonia in hepatic encephalopathy. *Metab Brain Dis* 2013; 28: 1-5 [PMID: 23224356 DOI: 10.1007/s11011-012-9370-2]
16 Gupta A, Dhiman RK, Kumari S, Rana S, Agarwal R, Duseja A, Chawla Y. Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy. *J Hepatol* 2010; 53: 849-855 [PMID: 20675008 DOI: 10.1016/j.jhep.2010.05.017]
17 Sidhu SS, Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). *Am J Gastroenterol* 2011; 106: 307-316 [PMID: 21157444 DOI: 10.1038/ajg.2010.455]
18 Shukla S, Shukla A, Mehboob S, Guha S. Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. *Aliment Pharmacol Ther* 2011; 33: 662-671 [PMID: 21251030 DOI: 10.1111/j.1365-2036.2010.04574.x]
19 Bellot P, Francés R, Such J. Pathological bacterial translocation in cirrhosis: pathophysiology, diagnosis and clinical implications. *Liver Int* 2013; 33: 31-39 [PMID: 23121656 DOI: 10.1111/liv.12021]
20 Kalaitzakis E. Gastrointestinal dysfunction in liver cirrhosis. *World J Gastroenterol* 2014; 20: 14686-14695 [PMID: 25356031 DOI: 10.3748/wjg.v20.i40.14686]
21 Sadik R, Abrahamsson H, Björnsson E, Gunnarsdottir A, Stotzer PO. Etiology of portal hypertension may influence gastrointestinal transit. *Scand J Gastroenterol* 2003; 38: 1039-1044 [PMID: 14621277]
22 Chander Roland B, Garcia-Tsao G, Ciarleglio MM, Deng Y, Sheth A. Decompensated cirrhotics have slower intestinal transit times as compared with compensated cirrhotics and healthy controls. *J Clin Gastroenterol* 2013; 47: 888-893 [PMID: 23632359 DOI: 10.1097/MCG.0b013e31829006bb]
23 Pijls KE, Jonkers DM, Elamin EE, Masclee AA, Koek GH. Intestinal epithelial barrier function in liver cirrhosis: an extensive review of the literature. *Liver Int* 2013; 33: 1457-1469 [PMID: 23879434 DOI: 10.1111/liv.12271]
24 Du Plessis J, Vanheel H, Janssen CE, Roos L, Slavik T, Stivaktas PI, Nieuwoudt M, van Wyk SG, Vieira W, Pretorius E, Beukes M, Farré R, Tack J, Laleman W, Fevery J, Nevens F, Roskams T, Van der Merwe SW. Activated intestinal macrophages in patients with cirrhosis release

NO and IL-6 that may disrupt intestinal barrier function. *J Hepatol* 2013; 58: 1125-1132 [PMID: 23402745 DOI: 10.1016/j.jhep.2013.01.038]
25 Karagiannakis DS, Vlachogiannakos J, Anastasiadis G, Vafiadis-Zouboulis I, Ladas SD. Frequency and severity of cirrhotic cardiomyopathy and its possible relationship with bacterial endotoxemia. *Dig Dis Sci* 2013; 58: 3029-3036 [PMID: 23907333 DOI: 10.1007/s10620-013-2693-y]
26 Sandler NG, Koh C, Roque A, Eccleston JL, Siegel RB, Demino M, Kleiner DE, Deeks SG, Liang TJ, Heller T, Douek DC. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. *Gastroenterology* 2011; 141: 1220-1230, 1230. e1-e3 [PMID: 21726511 DOI: 10.1053/j.gastro.2011.06.063]
27 Keshavarzian A, Farhadi A, Forsyth CB, Rangan J, Jakate S, Shaikh M, Banan A, Fields JZ. Evidence that chronic alcohol exposure promotes intestinal oxidative stress, intestinal hyperpermeability and endotoxemia prior to development of alcoholic steatohepatitis in rats. *J Hepatol* 2009; 50: 538-547 [PMID: 19155080 DOI: 10.1016/j.jhep.2008.10.028]
28 Elamin EE, Masclee AA, Dekker J, Jonkers DM. Ethanol metabolism and its effects on the intestinal epithelial barrier. *Nutr Rev* 2013; 71: 483-499 [PMID: 23815146 DOI: 10.1111/nure.12027]
29 Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, Lammert F, Trauner M, Peck-Radosavljevic M, Vogelsang H. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. *J Hepatol* 2013; 58: 911-921 [PMID: 23262249 DOI: 10.1016/j.jhep.2012.12.011]
30 Assimakopoulos SF, Charonis AS. Uncovering the molecular events associated with increased intestinal permeability in liver cirrhosis: the pivotal role of enterocyte tight junctions and future perspectives. *J Hepatol* 2013; 59: 1144-1146 [PMID: 23928410 DOI: 10.1016/j.jhep.2013.06.031]
31 Assimakopoulos SF, Tsamandas AC, Tsiaoussis GI, Karatza E, Triantos C, Vagianos CE, Spiliopoulou I, Kaltezioti V, Charonis A, Nikolopoulou VN, Scopa CD, Thomopoulos KC. Altered intestinal tight junctions' expression in patients with liver cirrhosis: a pathogenetic mechanism of intestinal hyperpermeability. *Eur J Clin Invest* 2012; 42: 439-446 [PMID: 22023490 DOI: 10.1111/j.1365-2362.2011.02609.x]
32 Muñoz L, Albillos A, Nieto M, Reyes E, Lledó L, Monserrat J, Sanz E, de la Hera A, Alvarez-Mon M. Mesenteric Th1 polarization and monocyte TNF-alpha production: first steps to systemic inflammation in rats with cirrhosis. *Hepatology* 2005; 42: 411-419 [PMID: 16025514]
33 Nischalke HD, Berger C, Aldenhoff K, Thyssen L, Gentemann M, Grünhage F, Lammert F, Nattermann J, Sauerbruch T, Spengler U, Appenrodt B. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. *J Hepatol* 2011; 55: 1010-1016 [PMID: 21356257 DOI: 10.1016/j.jhep.2011.02.022]
34 Bruns T, Reuken PA, Fischer J, Berg T, Stallmach A. Further evidence for the relevance of TLR2 gene variants in spontaneous bacterial peritonitis. *J Hepatol* 2012; 56: 1207-1208; author reply 1208-1209 [PMID: 22019578 DOI: 10.1016/j.jhep.2011.09.010]
35 Soriano G, Sánchez E, Nieto JC, Román E, Vidal S, Oliva L, Guarner-Argente C, Poca M, Torras X, Juárez C, Guarner C. Cytokine production in patients with cirrhosis and D299G and/or T399I Toll-like receptor 4 polymorphisms. *J Hepatol* 2013; 58(Suppl 1): S247-S248 [DOI: 10.1016/S0168-8278(13)60608-X]
36 Appenrodt B, Grünhage F, Gentemann MG, Thyssen L, Sauerbruch T, Lammert F. Nucleotide-binding oligomerization domain containing 2 (NOD2) variants are genetic risk factors for death and spontaneous bacterial peritonitis in liver cirrhosis. *Hepatology* 2010; 51: 1327-1333 [PMID: 20087966 DOI: 10.1002/hep.23440]
37 Bruns T, Peter J, Reuken PA, Grabe DH, Schuldes SR, Brenmoehl J, Schölmerich J, Wiest R, Stallmach A. NOD2 gene variants are a risk factor for culture-positive spontaneous bacterial peritonitis and monomicrobial bacterascites in cirrhosis. *Liver Int* 2012; 32: 223-230 [PMID: 21745302 DOI: 10.1111/j.1478-3231.2011.02561.x]
38 Filik L. Monocyte chemotactic protein-1 gene polymorphism and spontaneous bacterial peritonitis. *World J Gastroenterol* 2010; 16: 914 [PMID: 20143473]
39 Albillos A, Lario M, álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol* 2014; 61: 1385-1396 [PMID: 25135860 DOI: 10.1016/j.jhep.2014.08.010]
40 Jenne CN, Kubes P. Immune surveillance by the liver. *Nat Immunol* 2013; 14: 996-1006 [PMID: 24048121 DOI: 10.1038/ni.2691]
41 Altorjay I, Vitalis Z, Tornai I, Palatka K, Kacska S, Farkas G, Udvardy M, Harsfalvi J, Dinya T, Orosz P, Lombay B, Par G, Par A, Csak T, Osztovits J, Szalay F, Csepregi A, Lakatos PL, Papp M. Mannose-binding lectin deficiency confers risk for bacterial infections in a large Hungarian cohort of patients with liver cirrhosis. *J Hepatol* 2010; 53: 484-491 [PMID: 20605050 DOI: 10.1016/j.jhep.2010.03.028]
42 Rolas L, Makhezer N, Hadjoudj S, El-Benna J, Djerdjouri B, Elkrief L, Moreau R, Périanin A. Inhibition of mammalian target of rapamycin aggravates the respiratory burst defect of neutrophils from decompensated patients with cirrhosis. *Hepatology* 2013; 57: 1163-1171 [PMID: 23080369 DOI: 10.1002/hep.26109]
43 Seidler S, Zimmermann HW, Weiskirchen R, Trautwein C, Tacke F. Elevated circulating soluble interleukin-2 receptor in patients with chronic liver diseases is associated with non-classical monocytes. *BMC Gastroenterol* 2012; 12: 38 [PMID: 22530792 DOI: 10.1186/1471-230X-12-38]
44 Gomez F, Ruiz P, Schreiber AD. Impaired function of macrophage Fc gamma receptors and bacterial infection in alcoholic cirrhosis. *N Engl J Med* 1994; 331: 1122-1128 [PMID: 7935636]
45 Doi H, Iyer TK, Carpenter E, Li H, Chang KM,

名词解释

肝硬化相关免疫紊乱: 包括免疫缺陷状态和免疫系统持续激活炎症状态共存, 肝硬化初期全身炎症状态占主导地位, 进展至终末期免疫缺陷状态占主导地位.

同行评价

文章内容写出了新意, 总结了肝硬化合并细菌感染易感性的机制, 对感染采取积极有效的预防措施大有帮助.

Vonderheide RH, Kaplan DE. Dysfunctional B-cell activation in cirrhosis resulting from hepatitis C infection associated with disappearance of CD27-positive B-cell population. *Hepatology* 2012; 55: 709-719 [PMID: 21932384 DOI: 10.1002/hep.24689]

46 Lario M, Muñoz L, Ubeda M, Borrero MJ, Martínez J, Monserrat J, Díaz D, Alvarez-Mon M, Albillos A. Defective thymopoiesis and poor peripheral homeostatic replenishment of T-helper cells cause T-cell lymphopenia in cirrhosis. *J Hepatol* 2013; 59: 723-730 [PMID: 23742913 DOI: 10.1016/j.jhep.2013.05.042]

47 Morishima C, Di Bisceglie AM, Rothman AL, Bonkovsky HL, Lindsay KL, Lee WM, Koziel MJ, Fontana RJ, Kim HY, Wright EC. Antigen-specific T lymphocyte proliferation decreases over time in advanced chronic hepatitis C. *J Viral Hepat* 2012; 19: 404-413 [PMID: 22571902 DOI: 10.1111/j.1365-2893.2011.01562.x]

48 Laso FJ, Madruga JI, Girón JA, López A, Ciudad J, San Miguel JF, Alvarez-Mon M, Orfao A. Decreased natural killer cytotoxic activity in chronic alcoholism is associated with alcohol liver disease but not active ethanol consumption. *Hepatology* 1997; 25: 1096-1100 [PMID: 9141423]

49 Muñoz L, José Borrero M, Ubeda M, Lario M, Díaz D, Francés R, Monserrat J, Pastor O, Aguado-Fraile E, Such J, Alvarez-Mon M, Albillos A. Interaction between intestinal dendritic cells and bacteria translocated from the gut in rats with cirrhosis. *Hepatology* 2012; 56: 1861-1869 [PMID: 22611024 DOI: 10.1002/hep.25854]

50 Albillos A, Hera Ad Ade L, Reyes E, Monserrat J, Muñoz L, Nieto M, Prieto A, Sanz E, Alvarez-Mon M. Tumour necrosis factor-alpha expression by activated monocytes and altered T-cell homeostasis in ascitic alcoholic cirrhosis: amelioration with norfloxacin. *J Hepatol* 2004; 40: 624-631 [PMID: 15030978]

51 Tritto G, Bechlis Z, Stadlbauer V, Davies N, Francés R, Shah N, Mookerjee RP, Such J, Jalan R. Evidence of neutrophil functional defect despite inflammation in stable cirrhosis. *J Hepatol* 2011; 55: 574-581 [PMID: 21236309 DOI: 10.1016/j.jhep.2010.11.034]

52 Gandoura S, Weiss E, Rautou PE, Fasseu M, Gustot T, Lemoine F, Hurtado-Nedelec M, Hego C, Vadrot N, Elkrief L, Lettéron P, Tellier Z, Pocidalo MA, Valla D, Lebrec D, Groyer A, Monteiro RC, de la Grange P, Moreau R. Gene- and exon-expression profiling reveals an extensive LPS-induced response in immune cells in patients with cirrhosis. *J Hepatol* 2013; 58: 936-948 [PMID: 23321315 DOI: 10.1016/j.jhep.2012.12.025]

53 Sun HQ, Zhang JY, Zhang H, Zou ZS, Wang FS, Jia JH. Increased Th17 cells contribute to disease progression in patients with HBV-associated liver cirrhosis. *J Viral Hepat* 2012; 19: 396-403 [PMID: 22571901 DOI: 10.1111/j.1365-2893.2011.01561.x]

54 Girón JA, Alvarez-Mon M, Menéndez-Caro JL, Abreu L, Albillos A, Manzano L, Durántez A. Increased spontaneous and lymphokine-conditioned IgA and IgG synthesis by B cells from alcoholic cirrhotic patients. *Hepatology* 1992; 16: 664-670 [PMID: 1505909]

55 Albillos A, de la Hera A, González M, Moya JL, Calleja JL, Monserrat J, Ruiz-del-Arbol L, Alvarez-Mon M. Increased lipopolysaccharide binding protein in cirrhotic patients with marked immune and hemodynamic derangement. *Hepatology* 2003; 37: 208-217 [PMID: 12500206]

56 Trebicka J, Krag A, Gansweid S, Schiedermaier P, Strunk HM, Fimmers R, Strassburg CP, Bendtsen F, Møller S, Sauerbruch T, Spengler U. Soluble TNF-alpha-receptors I are prognostic markers in TIPS-treated patients with cirrhosis and portal hypertension. *PLoS One* 2013; 8: e83341 [PMID: 24386183 DOI: 10.1371/journal.pone.0083341]

57 Wiese S, Mortensen C, Gøtze JP, Christensen E, Andersen O, Bendtsen F, Møller S. Cardiac and proinflammatory markers predict prognosis in cirrhosis. *Liver Int* 2014; 34: e19-e30 [PMID: 24313898 DOI: 10.1111/liv.12428]

58 González-Navajas JM, Bellot P, Francés R, Zapater P, Muñoz C, García-Pagán JC, Pascual S, Pérez-Mateo M, Bosch J, Such J. Presence of bacterial-DNA in cirrhosis identifies a subgroup of patients with marked inflammatory response not related to endotoxin. *J Hepatol* 2008; 48: 61-67 [PMID: 17998145]

59 Úbeda M, Muñoz L, Borrero MJ, Díaz D, Francés R, Monserrat J, Lario M, Lledó L, Such J, álvarez-Mon M, Albillos A. Critical role of the liver in the induction of systemic inflammation in rats with preascitic cirrhosis. *Hepatology* 2010; 52: 2086-2095 [PMID: 21105108 DOI: 10.1002/hep.23961]

60 Buck M, Garcia-Tsao G, Groszmann RJ, Stalling C, Grace ND, Burroughs AK, Patch D, Matloff DS, Clopton P, Chojkier M. Novel inflammatory biomarkers of portal pressure in compensated cirrhosis patients. *Hepatology* 2014; 59: 1052-1059 [PMID: 24115225 DOI: 10.1002/hep.26755]

61 Kaser A, Ludwiczek O, Waldenberger P, Jaschke W, Vogel W, Tilg H. Endotoxin and its binding proteins in chronic liver disease: the effect of transjugular intrahepatic portosystemic shunting. *Liver* 2002; 22: 380-387 [PMID: 12390473]

62 Riordan SM, Skinner N, Nagree A, McCallum H, McIver CJ, Kurtovic J, Hamilton JA, Bengmark S, Williams R, Visvanathan K. Peripheral blood mononuclear cell expression of toll-like receptors and relation to cytokine levels in cirrhosis. *Hepatology* 2003; 37: 1154-1164 [PMID: 12717397]

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