

# World Journal of *Hepatology*

*World J Hepatol* 2018 December 27; 10(12): 892-965



**EDITORIAL**

- 892 Unresolved issues in the prophylaxis of bacterial infections in patients with cirrhosis  
*Dirchwolf M, Marciano S, Martinez J, Ruf AE*
- 898 Hepatitis C virus-associated hepatocellular carcinoma after sustained virologic response  
*Sasaki R, Kanda T, Kato N, Yokosuka O, Moriyama M*
- 907 Stem cell transplantation for the treatment of end-stage liver disease  
*Wu DB, Chen EQ, Tang H*

**MINIREVIEWS**

- 911 Autoimmune hepatitis: Appraisal of current treatment guidelines  
*Lowe D, John S*

**ORIGINAL ARTICLE****Basic Study**

- 924 Body mass index and its effects on liver fat content in overweight and obese young adults by proton magnetic resonance spectroscopy technique  
*Pasanta D, Tungjai M, Chancharunee S, Sajomsang W, Kothan S*

**Retrospective Cohort Study**

- 934 Non-invasive prediction of non-alcoholic steatohepatitis in Japanese patients with morbid obesity by artificial intelligence using rule extraction technology  
*Uehara D, Hayashi Y, Seki Y, Kakizaki S, Horiguchi N, Tojima H, Yamazaki Y, Sato K, Yasuda K, Yamada M, Uraoka T, Kasama K*

**Retrospective Study**

- 944 Impact of sepsis and non-communicable diseases on prognostic models to predict the outcome of hospitalized chronic liver disease patients  
*Qazi Arisar FA, Abid S, Shaikh PA, Awan S*

**Observational Study**

- 956 One in five hepatocellular carcinoma patients in the United States are Hispanic while less than 40% were eligible for liver transplantation  
*Robinson A, Ohri A, Liu B, Bhuket T, Wong RJ*

**ABOUT COVER**

Koo Jeong Kang, MD, PhD, Professor, Division of Hepatobiliary Pancreatic Surgery, Department of surgery, Keimyung University Dong-San Medical Center, Daegu 41931, South Korea

**AIMS AND SCOPE**

*World Journal of Hepatology (World J Hepatol, WJH, online ISSN 1948-5182, DOI: 10.4254)*, is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, etc. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, etc.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

**INDEXING/ABSTRACTING**

*World Journal of Hepatology (WJH)* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Wen-Wen Tan*      Proofing Editorial Office Director: *Jin-Lei Wang*

**NAME OF JOURNAL**

*World Journal of Hepatology*

**ISSN**

ISSN 1948-5182 (online)

**LAUNCH DATE**

October 31, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Koo Jeong Kang, Nikolaos Pyrsopoulos

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

**EDITORIAL OFFICE**

Jin-Lei Wang, Director

**PUBLICATION DATE**

December 27, 2018

**COPYRIGHT**

© 2018 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Unresolved issues in the prophylaxis of bacterial infections in patients with cirrhosis

Melisa Dirchwolf, Sebastián Marciano, José Martínez, Andrés Eduardo Ruf

**ORCID number:** Melisa Dirchwolf (0000-0002-9083-3561); Sebastian Marciano (0000-0002-7983-1450); Jose Martinez (0000-0002-7633-3229); Andres Eduardo Ruf (0000-0002-8225-2775).

**Author contributions:** Dirchwolf M, Marciano S, Martínez J and Ruf AE conceived the study and drafted the manuscript; all authors approved the final version of the article.

**Conflict-of-interest statement:** The authors have no conflict of interest to declare.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Received:** August 6, 2018

**Peer-review started:** August 7, 2018

**First decision:** August 24, 2018

**Revised:** September 4, 2018

**Accepted:** October 11, 2018

**Article in press:** October 11, 2018

**Published online:** December 27,

**Melisa Dirchwolf, José Martínez, Andrés Eduardo Ruf,** Unidad de Hígado, Hospital Privado de Rosario, Rosario 2000, Argentina

**Sebastián Marciano,** Unidad de Hígado, and Departamento de Investigación del Hospital Italiano de Buenos Aires, Buenos Aires 1424, Argentina

**Corresponding author:** Melisa Dirchwolf, MD, Attending Doctor, Unidad de Hígado, Hospital Privado de Rosario, Presidente Roca 2440, Rosario 2000, Santa Fe, Argentina. [unidaddehigado.hpr@grupogamma.com.ar](mailto:unidaddehigado.hpr@grupogamma.com.ar)  
**Telephone:** +54-341-4893545

### Abstract

Bacterial infections are highly prevalent and a frequent cause of hospitalization and short-term mortality in patients with cirrhosis. Due to their negative impact on survival, antibiotic prophylaxis for bacterial infections in high-risk subgroups of patients with cirrhosis has been the standard of care for decades. Patients with prophylaxis indications include those at risk for a first episode of spontaneous bacterial peritonitis (SBP) due to a low ascitic fluid protein count and impaired liver and kidney function, patients with a prior episode of SBP and those with an episode of gastrointestinal bleeding. Only prophylaxis due to gastrointestinal bleeding has a known and short-time duration. All other indications imply long-lasting exposure to antibiotics - once the threshold requirement for initiating prophylaxis is met - without standardized criteria for re-assessing antibiotic interruption. Despite the fact that the benefit of antibiotic prophylaxis in reducing bacterial infections episodes and mortality has been thoroughly reported, the extended use of antibiotics in patients with cirrhosis has also had negative consequences, including the emergence of multi-drug resistant bacteria. Currently, it is not clear whether restricting the use of broad and fixed antibiotic regimens, tailoring the choice of antibiotics to local bacterial epidemiology or selecting non-antibiotic strategies will be the preferred antibiotic prophylaxis strategy for patients with cirrhosis in the future.

**Key words:** Cirrhosis; Antibiotic Prophylaxis; Multi-drug resistant bacteria; Spontaneous bacterial peritonitis; Bacterial infections

©The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Antibiotic prophylaxis in patients with cirrhosis has proven to be effective in preventing new episodes of bacterial infections and reducing mortality. However, the

broad and fixed indication of long-term antibiotic therapy in these patients has led to an increase in the emergence of multi-drug resistant bacteria. The development of new strategies for bacterial infection prevention is currently under debate, thus reflecting the need for randomized controlled trials and local epidemiological studies to improve prophylactic antibiotic choice in patients with cirrhosis.

Dirchwolf M, Marciano S, Martínez J, Ruf AE. Unresolved issues in the prophylaxis of bacterial infections in patients with cirrhosis. *World J Hepatol* 2018; 10(12): 892-897  
 URL: <https://www.wjgnet.com/1948-5182/full/v10/i12/892.htm>  
 DOI: <https://dx.doi.org/10.4254/wjh.v10.i12.892>

## INTRODUCTION

During the natural history of cirrhosis, patients may suffer from complications that significantly increase their risk of short-term mortality. One of the main culprits of this outcome is bacterial infections<sup>[1]</sup>, which are highly prevalent. One-third of patients with decompensated cirrhosis will develop an episode of bacterial infection during a one-year period<sup>[2]</sup>, and 24% of patients admitted for an infection will develop a second episode during the same hospital stay<sup>[3]</sup>. Furthermore, bacterial infections are associated with a grim prognosis: patients with end-stage liver disease listed for liver transplantation who suffer an infection have a 42% risk of de-listing or death within 6 mo from admission<sup>[4]</sup>.

For these reasons, antibiotic prophylaxis has been the standard of care in high-risk patients with cirrhosis for decades<sup>[5,6]</sup>. The rationale is accomplishing selective intestinal decontamination to decrease bacterial translocation, which is considered the trigger event for bacterial infections in cirrhosis. There is also evidence of an immunomodulatory effect caused by certain antibiotics such as fluoroquinolones that might have an additional beneficial impact on patients with cirrhosis survival<sup>[7,8]</sup>.

Currently, there are two clinical scenarios for antibiotic prophylaxis in cirrhosis: prevention of spontaneous bacterial peritonitis (SBP) and prevention of bacterial infections after upper gastrointestinal bleeding.

Antibiotic prophylaxis for the prevention of SBP is currently recommended in most practice guidelines<sup>[1,9]</sup>. Primary prophylaxis with fluoroquinolones is indicated in patients with poor liver or renal function and a low ascitic fluid protein count, since these patients showed higher short-term survival under prophylaxis in randomized trials<sup>[10]</sup>. However, a meta-analysis of studies addressing primary prophylaxis in patients with SBP failed to confirm a benefit in survival<sup>[5]</sup>.

The use of norfloxacin after a first episode of SBP to prevent its recurrence is the most robust and widely recognized indication of antibiotic prophylaxis in cirrhosis. Data to sustain secondary prophylaxis for SBP arose from two clinical trials performed in the 1990s and early 2000s. These studies showed that the cumulative incidence of SBP recurrence at one year reached 20%-26% in patients receiving norfloxacin compared to 68% in patients in the placebo group<sup>[11,12]</sup>. Notably, these randomized controlled trials included fluoroquinolones that were effective in treating Gram-negative bacilli, the predominant etiology of SBP at that time. Whether these antibiotics are useful in today's changing bacteria epidemiology has not been re-assessed; to our knowledge, no other studies evaluating secondary prophylaxis for SBP have been published.

Patients with cirrhosis undergoing an episode of acute gastrointestinal bleeding have also proven to benefit from antibiotic prophylaxis. In a robust meta-analysis conducted by Chavez-Tapia *et al*<sup>[13]</sup>, treatment with antibiotics reduced bacterial infections, all-cause mortality, re-bleeding events and hospitalization length in patients with acute gastrointestinal bleeding.

## PITFALLS OF ANTIBIOTIC PROPHYLAXIS IN CIRRHOSIS: EMERGENCE OF RESISTANT BACTERIA AND DRUG TOXICITY

Only prophylaxis due to gastrointestinal bleeding has a known and short-time duration. All other indications imply long-lasting exposure to antibiotics; once the

threshold requirement for initiating prophylaxis is met, without standardized criteria for re-assessing antibiotic interruption, the patient usually maintained antibiotic use until liver transplantation or death. Another usual scenario in clinical practice is the concomitant use of two types of antibiotics as prophylaxis in a single patient (*i.e.*, rifaximin for hepatic encephalopathy and norfloxacin for SBP prevention), with conflicting conclusions as to the efficacy of using only one drug for both objectives<sup>[14-16]</sup>.

Consequences of long-term antibiotic use in patients with cirrhosis are now increasingly being reported. There has been a shift in the type of responsible microorganisms: initially, in the 1990s, Gram-negative bacilli caused two thirds or more of bacterial infections in patients with cirrhosis, whereas in the last 20 years, Gram-positive cocci have been identified in almost one-half of infections in this population<sup>[17-20]</sup>.

Most importantly, the prevalence of resistant and multi-drug resistant bacteria (MDR: bacteria with acquired non-susceptibility to at least one agent in three main antibiotic families<sup>[21]</sup>) has significantly scaled. The prevalence of MDR bacteria increased by 100% when comparing two studies performed in 2002 and 2007-2011 that analyzed bacterial infections in patients with cirrhosis during hospitalization<sup>[19]</sup>. In the latter study, MDR infections accounted for 18%-23% of all identified bacteria<sup>[22]</sup>. Several authors have reported similar or even higher rates of MDR bacteria in different geographies and settings (up to one-half of bacterial infections in health-care acquired settings were caused by MDR bacteria)<sup>[23,24]</sup>. The main risk factors identified for the development of MDR infections were prior contact with the health-care system, a nosocomial or health-associated origin of infection, the use of norfloxacin prophylaxis, recent use of other antibiotics (cephalosporins or beta-lactams) or recent infection by MDR bacteria<sup>[22,23,25]</sup>.

Higher rates of MDR bacterial infections are parallel with higher rates of inadequate initial empirical therapy. Initial empirical therapy has proven to be insufficient in as much as 90% of bacterial infections, but these rates are dependent on the origin of the infection and susceptibility pattern of the responsible bacteria. As expected, the extension of antibiotic resistance and failure of empirical therapy are an independent predictor of morbidity and mortality<sup>[23,26-28]</sup>. Currently, it is suggested that empirical antibiotic therapy should be based on the origin and type of infection, its severity, recent antibiotic use and the prevalence of MDR bacteria<sup>[29]</sup>. Thus, there is a growing need for conducting local studies to identify the epidemiology of MDR bacteria in patients with cirrhosis in each geography (for instance, with microbiological surveillance<sup>[29]</sup>), as well as exploring other prophylactic strategies for bacterial infections other than extended antimicrobial use.

Last but not least, the prolonged use of fluoroquinolones as prophylaxis may cause significant adverse events. This type of antibiotics has had prior warnings issued by the United States Food and Drug Administration referring to disabling and potentially permanent side effects involving tendons, muscles, joints, nerves and the central nervous system. Recently, this agency has strengthened its black box warning for fluoroquinolones, including a separate notice about the drug's potential mental side effects (disturbances in attention, disorientation, agitation, nervousness, memory impairment and delirium) and the risk of coma with hypoglycemia<sup>[30]</sup>.

---

## DIVERGENCE FROM ANTIBIOTIC PROPHYLAXIS TO PREVENT BACTERIAL INFECTIONS

---

Different alternatives to antibiotic prophylaxis have been suggested - whether replacing or complementing the use of antibiotics - such as the use of probiotics, fecal microbiota transplantation, statins, prokinetics and granulocyte colony-stimulating factor. Other suggested measures include restricting or suspending the use of other types of drugs, such as proton pump inhibitors or beta-blockers, that may influence bacterial infection incidence or outcome<sup>[31-39]</sup>. However, data regarding the efficacy of these strategies are contradictory or insufficient at the present time. Thus, non-antibiotic strategies are yet to be included in the standard of care practice guidelines.

---

## UNANSWERED QUESTIONS ABOUT ANTIBIOTIC PROPHYLAXIS

---

The problem that may arise in the near future is the following: if current antibiotic prophylaxis regimens are sustained as the only strategy to prevent infections, and

physicians continue to choose wide-spectrum empiric antibiotics due to the increasing prevalence of MDR bacteria in patients with cirrhosis, what will happen when the available choices for antimicrobials run out? Another concern refers to the maintenance of standard antibiotic prophylaxis in a patient who suffered from an infection caused by quinolone-resistant MDR bacteria. In these cases, whether prophylaxis with the standard antibiotic choice would prevent new episodes of infection is uncertain. Perhaps these patients would benefit from another type of prophylaxis or even with the definite suspension of antibiotic prophylaxis?

## CONCLUSION

Broad use of uninterrupted antibiotic prophylaxis in patients with cirrhosis has contributed to a shift in bacterial epidemiology and antibiotic resistance patterns. The emergence of MDR bacteria has negatively impacted the effectiveness of bacterial infection treatment. The need to conduct regional studies to detect the type and antibiotic susceptibility of bacteria causing infections appears to be clear. Perhaps antibiotic prophylaxis could also be tailored to local bacterial epidemiology in the future, to increase its effectiveness and decrease its deleterious effects. Thus, future studies are needed to better understand the role of antibiotic prophylaxis and to put in perspective the actual risks and benefits of current recommendations. If more rigorous and personalized use of antibiotic prophylaxis is not advocated, there may be a time in the near future when physicians run out of options to treat resistant bacterial infections in cirrhosis.

## REFERENCES

- 1 **Jalan R**, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, Stadlbauer V, Gustot T, Bernardi M, Canton R. 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 **Borzio M**, Salerno F, Piantoni L, Cazzaniga M, Angeli P, Bissoli F, Boccia S, Colloredo-Mels G, Corigliano P, Fornaciari G. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. *Dig Liver Dis* 2001; **33**: 41-48 [PMID: 11303974]
- 3 **Bajaj JS**, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, Brown G, Noble NA, Thacker LR, Kamath PS; NACSELD. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. *Hepatology* 2012; **56**: 2328-2335 [PMID: 22806618 DOI: 10.1002/hep.25947]
- 4 **Reddy KR**, O'Leary JG, Kamath PS, Fallon MB, Biggins SW, Wong F, Patton HM, Garcia-Tsao G, Subramanian RM, Thacker LR. High risk of delisting or death in liver transplant candidates following infections: Results from the North American Consortium for the Study of End-Stage Liver Disease. *Liver Transpl* 2015; **21**: 881-888 [PMID: 25845966 DOI: 10.1002/lt.24139]
- 5 **Saab S**, Hernandez JC, Chi AC, Tong MJ. Oral antibiotic prophylaxis reduces spontaneous bacterial peritonitis occurrence and improves short-term survival in cirrhosis: a meta-analysis. *Am J Gastroenterol* 2009; **104**: 993-1001; quiz 1002 [PMID: 19277033 DOI: 10.1038/ajg.2009.3]
- 6 **Bernard B**, Grangé JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999; **29**: 1655-1661 [PMID: 10347104 DOI: 10.1002/hep.510290608]
- 7 **Zapater P**, González-Navajas JM, Such J, Francés R. Immunomodulating effects of antibiotics used in the prophylaxis of bacterial infections in advanced cirrhosis. *World J Gastroenterol* 2015; **21**: 11493-11501 [PMID: 26556982 DOI: 10.3748/wjg.v21.i41.11493]
- 8 **Juanola O**, Gómez-Hurtado I, Zapater P, Moratalla A, Caparrós E, Piñero P, González-Navajas JM, Giménez P, Such J, Francés R. Selective intestinal decontamination with norfloxacin enhances a regulatory T cell-mediated inflammatory control mechanism in cirrhosis. *Liver Int* 2016; **36**: 1811-1820 [PMID: 27214392 DOI: 10.1111/liv.13172]
- 9 Runyon BA; AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009; **49**: 2087-2107 [PMID: 19475696 DOI: 10.1002/hep.22853]
- 10 **Fernández J**, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, Vila C, Pardo A, Quintero E, Vargas V. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007; **133**: 818-824 [PMID: 17854593 DOI: 10.1053/j.gastro.2007.06.065]
- 11 **Bauer TM**, Follo A, Navasa M, Vila J, Planas R, Clemente G, Vargas V, Bory F, Vaquer P, Rodés J. Daily norfloxacin is more effective than weekly rifloxacin in prevention of spontaneous bacterial peritonitis recurrence. *Dig Dis Sci* 2002; **47**: 1356-1361 [PMID: 12064813]
- 12 **Ginés P**, Rimola A, Planas R, Vargas V, Marco F, Almela M, Forné M, Miranda ML, Llach J, Salmerón JM. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990; **12**: 716-724 [PMID: 2210673]
- 13 **Chavez-Tapia NC**, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, Uribe M. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated Cochrane review. *Aliment Pharmacol Ther* 2011; **34**: 509-518 [PMID: 21707680 DOI: 10.1111/j.1365-2036.2011.04746.x]
- 14 **Elfert A**, Abo Ali L, Soliman S, Ibrahim S, Abd-Elsalam S. Randomized-controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis. *Eur J*

- Gastroenterol Hepatol* 2016; **28**: 1450-1454 [PMID: 27512927 DOI: 10.1097/MEG.0000000000000724]
- 15 **Goel A**, Rahim U, Nguyen LH, Stave C, Nguyen MH. Systematic review with meta-analysis: rifaximin for the prophylaxis of spontaneous bacterial peritonitis. *Aliment Pharmacol Ther* 2017; **46**: 1029-1036 [PMID: 28994123 DOI: 10.1111/apt.14361]
  - 16 **Lutz P**, Parcina M, Bekeredjian-Ding I, Nischalke HD, Nattermann J, Sauerbruch T, Hoerauf A, Strassburg CP, Spengler U. Impact of rifaximin on the frequency and characteristics of spontaneous bacterial peritonitis in patients with liver cirrhosis and ascites. *PLoS One* 2014; **9**: e93909 [PMID: 24714550 DOI: 10.1371/journal.pone.0093909]
  - 17 **Klímová K**, Padilla C, Ávila JC, Clemente G, Ochoa A. Epidemiology of bacterial infections in patients with liver cirrhosis. Experience in a Spanish tertiary health center. *Biomedica* 2016; **36**: 121-132 [PMID: 27622445]
  - 18 **Bartoletti M**, Giannella M, Caraceni P, Domenicali M, Ambretti S, Tedeschi S, Verucchi G, Badia L, Lewis RE, Bernardi M. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. *J Hepatol* 2014; **61**: 51-58 [PMID: 24681345 DOI: 10.1016/j.jhep.2014.03.021]
  - 19 **Fernández J**, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; **35**: 140-148 [PMID: 11786970 DOI: 10.1053/jhep.2002.30082]
  - 20 **Almeida PR**, Camargo NS, Arenz M, Tovo CV, Galperim B, Behar P. [Spontaneous bacterial peritonitis: impact of microbiological changes]. *Arq Gastroenterol* 2007; **44**: 68-72 [PMID: 17639187]
  - 21 **Navasa M**, Rodés J. Bacterial infections in cirrhosis. *Liver Int* 2004; **24**: 277-280 [PMID: 15287849 DOI: 10.1007/s12072-014-9522-z]
  - 22 **Fernández J**, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, Pavesi M, Sola E, Moreira L, Silva A. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012; **55**: 1551-1561 [PMID: 22183941 DOI: 10.1002/hep.25532]
  - 23 **Merli M**, Lucidi C, Di Gregorio V, Falcone M, Giannelli V, Lattanzi B, Giusto M, Ceccarelli G, Farcomeni A, Riggio O. The spread of multi drug resistant infections is leading to an increase in the empirical antibiotic treatment failure in cirrhosis: a prospective survey. *PLoS One* 2015; **10**: e0127448 [PMID: 25996499 DOI: 10.1371/journal.pone.0127448]
  - 24 **Marciano S**, Dirchwolf M, Bermudez CS, Sobenko N, Haddad L, Genre Bert F, Barcán L, Smud A, Posadas-Martínez ML, Giunta D. Spontaneous bacteremia and spontaneous bacterial peritonitis share similar prognosis in patients with cirrhosis: a cohort study. *Hepatol Int* 2018; **12**: 181-190 [PMID: 29224053 DOI: 10.1007/s12072-017-9837-7]
  - 25 **Tandon P**, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012; **10**: 1291-1298 [PMID: 22902776 DOI: 10.1016/j.cgh.2012.08.017]
  - 26 **Ariza X**, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, Ariza J, Xiol X. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. *J Hepatol* 2012; **56**: 825-832 [PMID: 22173153 DOI: 10.1016/j.jhep.2011.11.010]
  - 27 **Cheong HS**, Kang CI, Lee JA, Moon SY, Joung MK, Chung DR, Koh KC, Lee NY, Song JH, Peck KR. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clin Infect Dis* 2009; **48**: 1230-1236 [PMID: 19302016 DOI: 10.1086/597585]
  - 28 **Alexopoulou A**, Vasilieva L, Agiasotelli D, Siranidi K, Pouriki S, Tsiriga A, Toutouza M, Dourakis SP. Extensively drug-resistant bacteria are an independent predictive factor of mortality in 130 patients with spontaneous bacterial peritonitis or spontaneous bacteremia. *World J Gastroenterol* 2016; **22**: 4049-4056 [PMID: 27099449 DOI: 10.3748/wjg.v22.i15.4049]
  - 29 **Fernández J**, Acevedo J. New antibiotic strategies in patients with cirrhosis and bacterial infection. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 1495-1500 [PMID: 26465070 DOI: 10.1586/17474124.2015.1100075]
  - 30 **FDA**. FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. Available from: RUL: <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm612995.htm>
  - 31 **Pande C**, Kumar A, Sarin SK. Addition of probiotics to norfloxacin does not improve efficacy in the prevention of spontaneous bacterial peritonitis: a double-blind placebo-controlled randomized-controlled trial. *Eur J Gastroenterol Hepatol* 2012; **24**: 831-839 [PMID: 22522141 DOI: 10.1097/MEG.0b013e3283537d61]
  - 32 **Yan K**, Garcia-Tsao G. Novel prevention strategies for bacterial infections in cirrhosis. *Expert Opin Pharmacother* 2016; **17**: 689-701 [PMID: 26799197 DOI: 10.1517/14656566.2016.1145663]
  - 33 **Merli M**, Lucidi C, Di Gregorio V, Giannelli V, Giusto M, Ceccarelli G, Riggio O, Venditti M. The chronic use of beta-blockers and proton pump inhibitors may affect the rate of bacterial infections in cirrhosis. *Liver Int* 2015; **35**: 362-369 [PMID: 24836902 DOI: 10.1111/liv.12593]
  - 34 **Galbois A**, Das V, Thabut D, Maury E, Ait-Oufella H, Housset C, Guidet B. Beta-blockers have no effect on outcomes in patients with cirrhosis and severe infections. *Hepatology* 2011; **53**: 1412-1413 [PMID: 21480358 DOI: 10.1002/hep.24053]
  - 35 **Terg R**, Casciato P, Garbe C, Cartier M, Stieben T, Mendizabal M, Niveyro C, Benavides J, Marino M, Colombato L. Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: a multicenter prospective study. *J Hepatol* 2015; **62**: 1056-1060 [PMID: 25481567 DOI: 10.1016/j.jhep.2014.11.036]
  - 36 **Madsen BS**, Havelund T, Krag A. Targeting the gut-liver axis in cirrhosis: antibiotics and non-selective  $\beta$ -blockers. *Adv Ther* 2013; **30**: 659-670 [PMID: 23881723 DOI: 10.1007/s12325-013-0044-1]
  - 37 **Bajaj JS**, Ratliff SM, Heuman DM, Lapane KL. Non-selective beta-blockers are not associated with serious infections in veterans with cirrhosis. *Aliment Pharmacol Ther* 2013; **38**: 407-414 [PMID: 23786291 DOI: 10.1111/apt.12382]
  - 38 **Bajaj JS**, Ratliff SM, Heuman DM, Lapane KL. Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis. *Aliment Pharmacol Ther* 2012; **36**: 866-874 [PMID: 22966967 DOI: 10.1111/apt.12045]
  - 39 **Motzkus-Feagans C**, Pakyz AL, Ratliff SM, Bajaj JS, Lapane KL. Statin use and infections in Veterans with cirrhosis. *Aliment Pharmacol Ther* 2013; **38**: 611-618 [PMID: 23889738 DOI: 10.1111/apt.12045]

10.1111/apt.12430]

**P- Reviewer:** Rezaee-Zavareh MS, Kaya M, Namisaki T, Tijera FHDL

**S- Editor:** Dou Y **L- Editor:** Filipodia **E- Editor:** Tan WW





Published By Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Telephone: +1-925-2238242

Fax: +1-925-2238243

E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

