Title

Outcomes in Patients With Cirrhosis on Primary Compared to Secondary Prophylaxis for Spontaneous Bacterial Peritonitis.

Journal

The American Journal of Gastroenterology, 114(4)

ISSN

0002-9270

Authors

Bajaj, Jasmohan S
Tandon, Puneeta
O'Leary, Jacqueline G
et al.

Publication Date

2019-04-01

DOI

10.14309/ajg.0000000000000044

Peer reviewed

HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Am J Gastroenterol. 2019 April ; 114(4): 599–606. doi:10.14309/ajg.0000000000000044.

Outcomes in Patients with Cirrhosis on Primary Compared to Secondary Prophylaxis for Spontaneous Bacterial Peritonitis

Jasmohan S Bajaj[1], **Puneeta Tandon**[2], **Jacqueline G O'Leary**[3], **Florence Wong**[4], **Scott W Biggins**[5], **Guadalupe Garcia-Tsao**[6], **Patrick S Kamath**[7], **Benedict Maliakkal**[8], **Michael B Fallon**[9], **Jennifer C Lai**[10], **Paul J Thuluvath**[11], **Hugo E Vargas**[12], **Ram M Subramanian**[13], **Leroy R Thacker**[1], **K. Rajender Reddy**[14], and **On behalf of NACSELD (North American Consortium for the Study of End-Stage Liver Disease)**

[1]Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA

[2]University of Alberta, Edmonton, AB, Canada

[3]Dallas VA Medical Center and Baylor University Medical Center, Dallas, TX, USA

[4]University of Toronto, Toronto, ON, Canada

[5]University of Washington, Seattle, WA, USA and University of Denver, Colorado, CO, USA

[6]Yale University Medical Center, West Haven, CT, USA

[7]Mayo Clinic, Rochester, MN, USA

[8]University of Tennessee, Memphis, TN and University of Rochester, Rochester, NY, USA

[9]University of Arizona, Phoenix, AZ, USA and University of Texas, Houston, TX, USA

[10]University of California, San Francisco, CA, USA

[11]Mercy Medical Center, Baltimore, MD, USA

[12]Mayo Clinic, Scottsdale, AZ, USA

[13]Emory University Medical Center, Atlanta, GA, USA

[14]University of Pennsylvania, Philadelphia, PA, USA

Abstract

Background: Antibiotic prophylaxis is recommended for prevention of the first episode of spontaneous bacterial peritonitis (SBP primary prophylaxis 1°) and subsequent episodes (secondary prophylaxis 2°).

Corresponding Author: Jasmohan S Bajaj, MD, Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, 1201 Broad Rock Blvd, Richmond VA 23249, USA, Telephone: +1 (804) 675-5802, Fax: +1 (804) 675-5816, jasmohan.bajaj@vcuhealth.org.

• **Specific author contributions:** All authors were involved in recruitment and drafting the manuscript along with critical revisions. LRT performed the statistical analyses.

AUTHOR CONFLICT OF INTEREST/STUDY SUPPORT:

• Guarantor of the article: JSB is the guarantor

• **Potential competing interests:** none for any author

Aim.—To compare outcomes in cirrhotic inpatients on 1° versus 2° SBP prophylaxis.

Method: NACSELD (North American Consortium for Study of End-Stage Liver Disease) data was evaluated for cirrhosis details, reasons for admission/medications, inpatient course recorded, and outcomes over 90 days. Outcomes [ICU, AKI, inpatient/90-day mortality] were compared between 1° vs. 2° prophylaxis groups after propensity-matching on admission MELD score and serum albumin.

Results: Among 2731 patients enrolled, 305 were on 1° and 187 on 2° SBP prophylaxis. After propensity-matching, 154 patients remained per group. Patients on 1° prophylaxis were more likely to have admission SIRS (p=0.02), with higher ICU admission (31% vs 21%,p=0.05) and inpatient mortality (19% vs 9%,p=0.01) than the 2° prophylaxis group. Patients on 2° prophylaxis had higher total (22% vs 10%,p=0004), readmission (16% vs 9%,p=0.03), and nosocomial SBP rates (6% vs 0.5%,p=0.01) with predominant gram-negative organisms compared to 1° prophylaxis patients. At 90 days, 1° prophylaxis patients had a higher mortality (35% vs 22%,p=0.02) and AKI incidence (48% vs 30%,p=0.04) compared to 2° prophylaxis patients.

Conclusion: In this inpatient cirrhosis study, despite prophylaxis, a high proportion of patients developed SBP, which was associated with mortality. Cirrhotic inpatients on 1° prophylaxis had worse outcomes than those on 2° prophylaxis when propensity-matched for MELD score and serum albumin during the index admission and 90-day follow-up.

Introduction:

Spontaneous bacterial peritonitis (SBP) is one of the most common and dreaded complications of cirrhosis(1). The usual sequelae of unrecognized or untreated SBP are the development of acute kidney injury (AKI), extra-hepatic organ failures, acute-on-chronic liver failure (ACLF) and death(2, 3). Therefore, prevention strategies using antibiotic prophylaxis are important(4). This prophylaxis can be primary (to prevent the first episode of SBP) in patients with low protein ascites or secondary (to prevent recurrent SBP) (5, 6). Whereas primary and secondary SBP prophylaxis are recommended worldwide, most data supported use of norfloxacin with documented improved outcomes over 1-year or less of follow-up(5, 6). With the advent of novel HCV therapies and more advanced cirrhosis care, patients with decompensated cirrhosis may be living longer(7). In addition, the microbiology of SBP has evolved with the emergence of gram-positive bacteria, multi-drug resistant bacteria as well as fungi in recent times(8–10). As a result, re-evaluation of our current SBP prophylactic strategies is warranted, especially in the United States where norfloxacin is not currently available.(6).

The aim of the study was to compare inpatient and 90-day outcomes, including rehospitalization, death and liver transplant, in patients with cirrhosis on primary versus secondary prophylaxis for SBP in a large inpatient cohort.

Methods:

We used the NACSELD (North American Consortium for the Study of End-Stage Liver Disease) database, which collects data on non-electively hospitalized patients with cirrhosis from 14 tertiary hepatology care centers across North America. The focus of this registry is

to evaluate short and longer-term outcomes in such patients. The data were collected between June 2013 and January 2017. All patients were enrolled after informed consent, and we excluded those with an unclear diagnosis of cirrhosis, with prior organ transplant, unwilling to provide consent and those with HIV infection. We also excluded patients with metastatic cancer, those already on palliative/hospice care and those with other pre-existing major organ failures. Admission data regarding demographics, cirrhosis severity, prior admissions, medication use (including SBP prophylaxis) and reason for admission are recorded in a REDCAP database. In addition, the inpatient course, including development of NACSELD-ACLF(11), transfer to intensive care units (ICU) and inpatient mortality are also recorded. NACSELD ACLF is defined by the occurrence of two or more of the following: respiratory failure (use of BiPAP or mechanical ventilation), brain failure (West-Haven grade III/IV hepatic encephalopathy), renal failure (renal replacement therapy) and circulatory failure (shock requiring vasopressors). As is usually diagnosed clinically, SBP was defined as > 250 PMN/mm^3 in the ascites fluid and called culture-negative neutrocytic ascites (CNNA) while culture positive cases with elevated PMN count were also included. For the purposes of this paper, we used both terms interchangeably given the usual low yield of ascites fluid cultures.

The database was created prospectively but analyzed retrospectively for this study. We extracted records of patients who were on SBP prophylaxis at admission and divided them into those on primary (per AASLD guidelines)(6) and secondary (prior SBP episode) prophylaxis. To balance out the predominant confounders in the prediction of death, we performed propensity-matching based on admission MELD score and serum albumin.

Ultimately the propensity-matched cohorts on primary compared to secondary prophylaxis were compared with respect to demographics, cirrhosis severity and other medications on admission. The inpatient course, infection rates and sites and causative organisms were also compared between the 2 groups. For inpatient outcomes we performed a multi-variable analysis using the following independent variables that were significantly different between groups; hospitalized in the past 6 months, lactulose use at admission, rifaximin use at admission, admission SIRS, admission due to infection, and SBP prophylaxis group. We also performed analyses of individual components of the SIRS and the use of first-line vs second-line antibiotics. Second line antibiotics were defined as vancomycin, linezolid, imipenem/meropenem, monobactams, daptomycin, antifungals compared to first line such as fluoroquinolones, cephalosporins, macrolides and metronidazole.

Patients who survived and were not transplanted were followed for 90 days after discharge from the index admission. Specifically, patients who had developed SBP at the index hospitalization were followed. Development of rehospitalization, ACLF, infections, AKI, death and liver transplant were studied between groups at this interval.

Results:

As shown in Figure 1, 2731 patients were in the NACSELD database, of which 2239 were not on SBP prophylaxis at admission. We noted that 305 patients were on primary and 187 were on secondary prophylaxis. After propensity-matching for MELD score and albumin,

154 subjects remained in each group (Figure 1). Almost three-fourths of patients in each group were on fluoroquinolones (n=116 in primary and n=124 in secondary, p=0.17), and the rest were on trimethoprim-sulfamethoxazole. The duration of SBP prophylaxis was statistically similar between the groups (primary median IQR 8 (10) vs. secondary 6.5 (8) months, p=0.42). The last SBP episode in the secondary group was a median (IQR) of 3 (12) months and the median number of prior SBP episodes was 1 (range 1–4). The majority of the SBP episodes that occurred prior to this hospitalization were culture-negative (n=126) with the rest being *E.coli* (n=11), *Klebsiella* (n=3), *Streptococcus* (n=8), *Staphylococcus* (n=4) *Bacteroides* (n=1), and *Veillonella* (n=1). All sites had an equitable distribution of patients on primary and secondary prophylaxis.

Although the groups were similar with respect to demographics, cirrhosis etiology, and diabetes status (table 1), patients on secondary prophylaxis had significantly more cirrhosis-related complications with a higher proportion of patients on therapy for hepatic encephalopathy (HE) including rifaximin and lactulose. There was also a greater proportion of patients who had been hospitalized over the previous 6 months and had refractory ascites, in the secondary prophylaxis group. On the other hand, patients on primary prophylaxis had a greater proportion positive for SIRS criteria on admission. Admission use of non-selective beta-blockers and proton pump inhibitors and serum sodium values were similar between groups.

Of the 308 patients in the entire group, 99 were admitted for infection. Fifty-two patients developed a nosocomial infection; 28 of these patients had it as a second infection while 24 patients developed a nosocomial infection as their first infection.

A greater proportion of secondary prophylaxis patients were admitted with an infection, with a greater proportion admitted with SBP or spontaneous bacteremia and gram-negative isolates, compared to the primary group (Supplementary Tables 1 and 2). The remaining reasons for hospitalization were statistically similar (Table 1). A significantly higher percentage of secondary prophylaxis patients either had SBP on admission or developed it during the hospitalization despite being continued on prophylaxis. There was a statistically similar use of first-line versus second-line antibiotics in the groups (Table 2). The minority of infections had varying isolates, the resistance patterns of which were similar between groups.

The proportion of *de novo* nosocomial infections was significantly higher in the secondary prophylaxis group, regardless of SBP or not (Tables 2 and 3). However, the bacteriology was similar between groups and in the minority that had bacteria identified, the resistance patterns in the bacteria isolated were statistically similar.

Patients on primary prophylaxis had a higher rate of ICU admission and mortality compared to those on secondary prophylaxis despite a statistically similar length of stay and development of ACLF (Table 3). Liver transplant rates were similar between groups. On multi-variable analysis with ICU transfer as the dependent variable, the significant variables that predicted this outcome was rifaximin use (p=0.05), admission infection (p=0.002) and

primary SBP prophylaxis (p=0.004). For inpatient death, the only predictor was primary SBP prophylaxis (p=0.03).

As shown in Figure 1, 116 patients in the primary and 130 in the secondary prophylaxis group were alive and without transplant at 90 days. While there was a similar rate of re-hospitalizations and liver transplant rates between groups, the overall rate of death was lower in those on secondary prophylaxis. In those who were re-hospitalized, infections and ACLF were similar between groups but AKI was significantly higher in the primary prophylaxis groups (Table 4).

Fifteen patients in the primary prophylaxis group had SBP on their index admission compared to 34 of the secondary prophylaxis group (p=0.004, Table 2). These patients were followed and compared to those without SBP, for outcomes during their inpatient and 90-day course. As shown in table 5, patients who developed SBP had a higher rate of liver transplantation compared to those without SBP during their inpatient stay regardless of primary or secondary prophylaxis. AKI and ACLF rates were similar between patients with/without SBP as an inpatient during the index admission. Death rates were statistically similar but trended higher in the primary prophylaxis group who developed SBP compared to the secondary prophylaxis group who developed SBP. There was a higher proportion of patients without SBP who died in the primary prophylaxis group compared to those who were receiving secondary prophylaxis. Similar trends continued at 90 days (Table 6) where there was a significantly higher rate of liver transplant in SBP vs no-SBP patients regardless of the prophylaxis group. Proportion of patients who died at 90 days were again higher in the primary prophylaxis group without SBP compared to the secondary prophylaxis group without SBP, which contributed to an overall lower death/transplant rate at 90 days in this population. The overall rehospitalizations were similar regardless of SBP status.

Discussion

Due to the changing natural history of cirrhosis, infections are a major determinant of outcomes in hospitalized patients(12). There has been a major change in the bacteriology of these infections, and their ability to precipitate ACLF is well-documented worldwide(13–15). The development of ACLF is a harbinger of high mortality and low likelihood of liver transplant; therefore, preventative strategies are important. Antibiotic strategies are aimed at reducing gram-negative infections. However, the effectiveness of these strategies in the evolving era of increasingly prevalent fluoroquinolone resistance, is unclear(9).

Despite efforts over several decades to reduce its impact, SBP remains a major source of infection-related ACLF(11, 16, 17). The use of primary and secondary SBP prophylaxis in patients with cirrhosis is prevalent in clinical practice using fluoroquinolones or trimethoprim-sulfamethoxazole(6). However, a real-world comparison of primary versus secondary SBP prophylaxis strategies is needed to evaluate if prophylaxis can improve outcomes long-term. Patients on secondary prophylaxis were more likely to have had refractory ascites, multiple hospitalizations within the prior 6 months and more difficult to control hepatic encephalopathy, indicated by rifaximin use(18). Almost a quarter of these patients developed or were admitted with SBP, which was higher than in the primary

prophylaxis group despite being on the prophylaxis for a similar duration prior to this index admission. This was compounded by an increase in both SBP and non-SBP nosocomial infections in this group. Moreover, the admission microbes were more likely to be gram-negative in these patients, despite use of prophylaxis targeting these organisms. On the other hand, patients on primary prophylaxis had a higher prevalence of SIRS criteria on admission, were less likely to develop nosocomial infections but were more likely to be transferred to the ICU and experience inpatient mortality. This trend towards higher mortality continued even at 90 days in patients who survived the index hospitalization. Interestingly, the death rate was higher in those without SBP in the index hospitalization in the primary prophylaxis group.

The apparent paradox between subjects who would technically appear more advanced from a cirrhosis status, and their ultimate outcome is intriguing. While cirrhosis is often treated as a liver disease, its effect on the immune system is widespread leading to the determination of cirrhosis-associated acquired immune-deficiency syndrome(19, 20). In cirrhosis, there is an impairment of both SIRS and its opposite response, the compensatory anti-inflammatory response syndrome (CARS) and depending on the individual's genetic and immune make-up, an infection can propel them from one state to the other(20–22). Often this can result in an immune paralysis, which hastens ACLF and death(23). The findings of a greater likelihood of SIRS criteria positivity in patients on primary prophylaxis that was in turn associated with greater mortality could reflect a more robust immune activation in patients without prior SBP. Although most of the primary prophylaxis patients were also hospitalized within the previous 6 months; this rate was still lower than the secondary prophylaxis patients. These observations are in line with those in the CANONIC trial, in which patients without prior decompensation had a higher mortality and development of ACLF compared to the more chronically ill patients, who had overall more advanced liver disease based on the criteria of prior hospitalizations(24). An alternative explanation could be that patients who survive an SBP episode and then qualify for secondary prophylaxis simply selects a group that is more resistant to infectious/inflammatory insults, which could be genetic or other factors(25, 26). This is underlined by the findings that the causative organisms and resistance patterns of infection on admission and nosocomially acquired was similar between primary and secondary prophylaxis groups and the rate of infections was similar between groups at 90 days. Despite this, patients who were on primary prophylaxis and required re-hospitalizations within 90 days, had a greater AKI development than those on secondary prophylaxis. These results could indicate that a patient-specific, individual response to these infections may be a greater determinant of outcomes and the use of primary prophylaxis may select out phenotypes that may not respond well to these infections(27).

Despite the difference in outcomes favoring those with secondary prophylaxis, the higher rate of SBP in this group is bothersome. Further, there was a higher isolation rate of gram-negative organisms, which are the organisms that SBP prophylaxis should prevent. While such prophylaxis could result in selection of resistant organisms, the proportion of infections with isolates was too low to allow sufficient comparisons. One of the HE-related treatments used in greater proportion in the secondary group was rifaximin, which usually indicates worse disease since it is used only in patients who have failed first-line lactulose(18). The

multi-variable analysis demonstrated that rifaximin use, infection on admission and primary prophylaxis were independently associated with ICU transfer. This is likely related to the more advanced disease in patients on rifaximin, which has been associated with better outcomes and lower risk of infections and SBP in prior controlled studies(18, 28, 29). Proton pump inhibitor use has been associated with SBP development in selected studies, but again this was statistically similar between the groups(30, 31). This findings imply that we need to rethink the current strategies for SBP prophylaxis and evaluate potential non-antibiotic approaches for prophylaxis or to recover antibiotic-associated changes. One such strategy to reduce the impact of broad-spectrum antibiotics has been the use of fecal microbial transplantation in cirrhotic and non-cirrhotic studies but further studies are needed(32, 33).

While there was a similar length of stay, rate of ACLF and individual organ failures during hospitalization, there was a higher ICU admission rate and inpatient mortality in the primary prophylaxis group. The reasons for this difference are unclear. A potential reason behind this relatively better prognosis in the secondary prophylaxis group could be that there are protocols in place to rapidly investigate and treat SBP in inpatients, which is not always the case for non-SBP infections(34). Therefore, an earlier diagnosis could hasten antibiotic therapy compared to infections diagnosed later, which could be the case in the primary prophylaxis group. This was again shown in the data comparing patients with and without SBP during the index hospitalization and 90-day outcomes.

The study is limited by the relatively modest number of patients but propensity matching was essential to ensure valid conclusions. We were not able to demonstrate changes in bacterial resistance patterns between groups but this is likely due to the relatively lower proportion of isolates. We did not specifically capture the cause of death given that patients were often discharged to hospice or developed preterminal multi-organ failures, which makes it difficult to pinpoint the specific causes.The division of subjects into receiving primary vs. secondary prophylaxis is not an underlying biological difference but rather an iatrogenic construct, which may be practice driven. A higher rate of inpatient SBP and outpatient refractory ascites also likely meant a higher IV albumin use in the secondary prophylaxis group. This could have contributed to the better outcomes but is unlikely to last for 90 days. In our dataset, there was an equitable distribution of subjects with primary and secondary prophylaxis across sites and moreover, the duration of the prophylaxis and the agents used were also statistically similar. Therefore, this comparison between groups is valid and gives us better insight into future management strategies.

We conclude that despite being on secondary and primary SBP prophylaxis, between a tenth and a quarter of cirrhotic patients still develop SBP. Despite a lower SBP rate on admission and during the hospital, patients on primary prophylaxis had higher inpatient and 90-day mortality, indicating the need for continued monitoring for negative outcomes in all patients on prophylaxis. The response of subjects to prior or current infections could be a major determinant of their outcomes rather than the infections itself and non-antibiotic options tailored to individual subjects are needed in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

• **Financial support:** This was partly supported by an investigator-initiated grant by Grifols Pharmaceuticals. The sponsors had not role in **the study design, collection, analysis, and interpretation of the data and in the writing of the report.**

References:

1. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis 2008;28:26–42. [PubMed: 18293275]
2. Bajaj JS, O'Leary JG, Reddy KR, et al. Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250–6. [PubMed: 24677131]
3. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2011;9:260–5. [PubMed: 21145427]
4. Garcia-Tsao G Bacterial infections in cirrhosis: treatment and prophylaxis. J Hepatol 2005;42 Suppl:S85–92. [PubMed: 15777576]
5. Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24. [PubMed: 17854593]
6. Runyon BA, Aasld. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013;57:1651–3. [PubMed: 23463403]
7. Kanwal F Decreasing mortality in patients hospitalized with cirrhosis. Gastroenterology 2015;148:897–900. [PubMed: 25805421]
8. Bajaj JS, Rajender Reddy K, Tandon P, et al. Prediction of Fungal Infection Development and Their Impact on Survival Using the NACSELD Cohort. Am J Gastroenterol 2018;113:556–563. [PubMed: 29257141]
9. Fernandez J, Tandon P, Mensa J, et al. Antibiotic prophylaxis in cirrhosis: Good and bad. Hepatology 2016;63:2019–31. [PubMed: 26528864]
10. Cholongitas E, Papatheodoridis GV, Lahanas A, et al. Increasing frequency of Gram-positive bacteria in spontaneous bacterial peritonitis. Liver Int 2005;25:57–61. [PubMed: 15698399]
11. O'Leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD Acute-on-Chronic Liver Failure (NACSELD-ACLF) Score Predicts 30-Day Survival in Hospitalized Patients with Cirrhosis. Hepatology 2018.
12. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:1310–24. [PubMed: 24530646]
13. Moreau R Role of Infections in Acute-on-Chronic Liver Failure. Dig Dis 2015;33:577–81. [PubMed: 26159276]
14. Piano S, Morando F, Carretta G, et al. Predictors of Early Readmission in Patients With Cirrhosis After the Resolution of Bacterial Infections. Am J Gastroenterol 2017;112:1575–1583. [PubMed: 28853729]
15. Merli M, Lucidi C, Di Gregorio V, et al. An empirical broad spectrum antibiotic therapy in health-care-associated infections improves survival in patients with cirrhosis: A randomized trial. Hepatology 2016;63:1632–9. [PubMed: 26529126]
16. Fernandez J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2017.
17. Bajaj JS, O'Leary JG, Reddy KR, et al. 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;56:2328–35. [PubMed: 22806618]

18. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071–81. [PubMed: 20335583]
19. Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385–96. [PubMed: 25135860]
20. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:727–38. [PubMed: 21397731]
21. Shawcross DL. Is it time to target gut dysbiosis and immune dysfunction in the therapy of hepatic encephalopathy? Expert Rev Gastroenterol Hepatol 2015;9:539–42. [PubMed: 25846450]
22. Shawcross DL, Sharifi Y, Canavan JB, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. J Hepatol 2011;54:640–9. [PubMed: 21163546]
23. Lin CY, Tsai IF, Ho YP, et al. Endotoxemia contributes to the immune paralysis in patients with cirrhosis. J Hepatol 2007;46:816–26. [PubMed: 17328986]
24. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–37, 1437 e1–9. [PubMed: 23474284]
25. Appenrodt B, Grunhage F, Gentemann MG, et al. Nucleotide-binding oligomerization domain containing 2 (NOD2) variants are genetic risk factors for death and spontaneous bacterial peritonitis in liver cirrhosis. Hepatology 2010;51:1327–33. [PubMed: 20087966]
26. Bruns T, Peter J, Reuken PA, et al. NOD2 gene variants are a risk factor for culture-positive spontaneous bacterial peritonitis and monomicrobial bacterascites in cirrhosis. Liver Int 2012;32:223–30. [PubMed: 21745302]
27. Casper M, Mengel M, Fuhrmann C, et al. The INCA trial (Impact of NOD2 genotype-guided antibiotic prevention on survival in patients with liver Cirrhosis and Ascites): study protocol for a randomized controlled trial. Trials 2015;16:83. [PubMed: 25887140]
28. Kang SH, Lee YB, Lee JH, et al. Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy. Aliment Pharmacol Ther 2017;46:845–855. [PubMed: 28836723]
29. Orr JG, Currie CJ, Berni E, et al. The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-alpha. Liver Int 2016;36:1295–303. [PubMed: 26950766]
30. Goel GA, Deshpande A, Lopez R, et al. Increased rate of spontaneous bacterial peritonitis among cirrhotic patients receiving pharmacologic acid suppression. Clin Gastroenterol Hepatol 2012;10:422–7. [PubMed: 22155557]
31. Bajaj JS, Ratliff SM, Heuman DM, et al. Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis. Aliment Pharmacol Ther 2012;36:866–74. [PubMed: 22966967]
32. Bajaj JS, Kakiyama G, Savidge T, et al. Antibiotic-Associated Disruption of Microbiota Composition and Function in Cirrhosis is Restored by Fecal Transplant. Hepatology 2018.
33. Millan B, Park H, Hotte N, et al. Fecal Microbial Transplants Reduce Antibiotic-resistant Genes in Patients With Recurrent Clostridium difficile Infection. Clin Infect Dis 2016;62:1479–1486. [PubMed: 27025836]
34. Thomson MJ, Tapper EB, Lok ASF. Dos and Don’ts in the Management of Cirrhosis: A View from the 21st Century. Am J Gastroenterol 2018.
35. Wong F, O’Leary JG, Reddy KR, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. Gastroenterology 2013;145:1280–8 e1. [PubMed: 23999172]

Presentations:

Portions of this manuscript were presented at the Plenary Oral Session at the European Association for the Study of Liver Diseases (EASL) Meeting in April 2018 and at the Digestive Disease Week 2018

WHAT IS CURRENTLY KNOWN

- Spontaneous bacterial peritonitis (SBP) is one of the most dreaded complication of cirrhosis
- Antibiotic prophylaxis for SBP focused towards gram-negative organisms can be primary (before any episode) or secondary (after at least one episode)
- With changing bacteriology the short-term and long-term outcomes comparing primary and secondary SBP prophylaxis are unclear

WHAT IS NEW HERE

- Inpatients with cirrhosis on primary SBP prophylaxis patients had a higher ICU admission, acute kidney injury and mortality during the index admission and at 90 days compared to secondary prophylaxis
- Inpatients with cirrhosis on secondary SBP prophylaxis had a higher admission, and nosocomial SBP with gram-negative organisms compared to patients on primary SBP prophylaxis
- Patients on primary SBP prophylaxis had worse outcomes during the index admission and at 90 days, while secondary SBP prophylaxis patients continued to develop SBP.

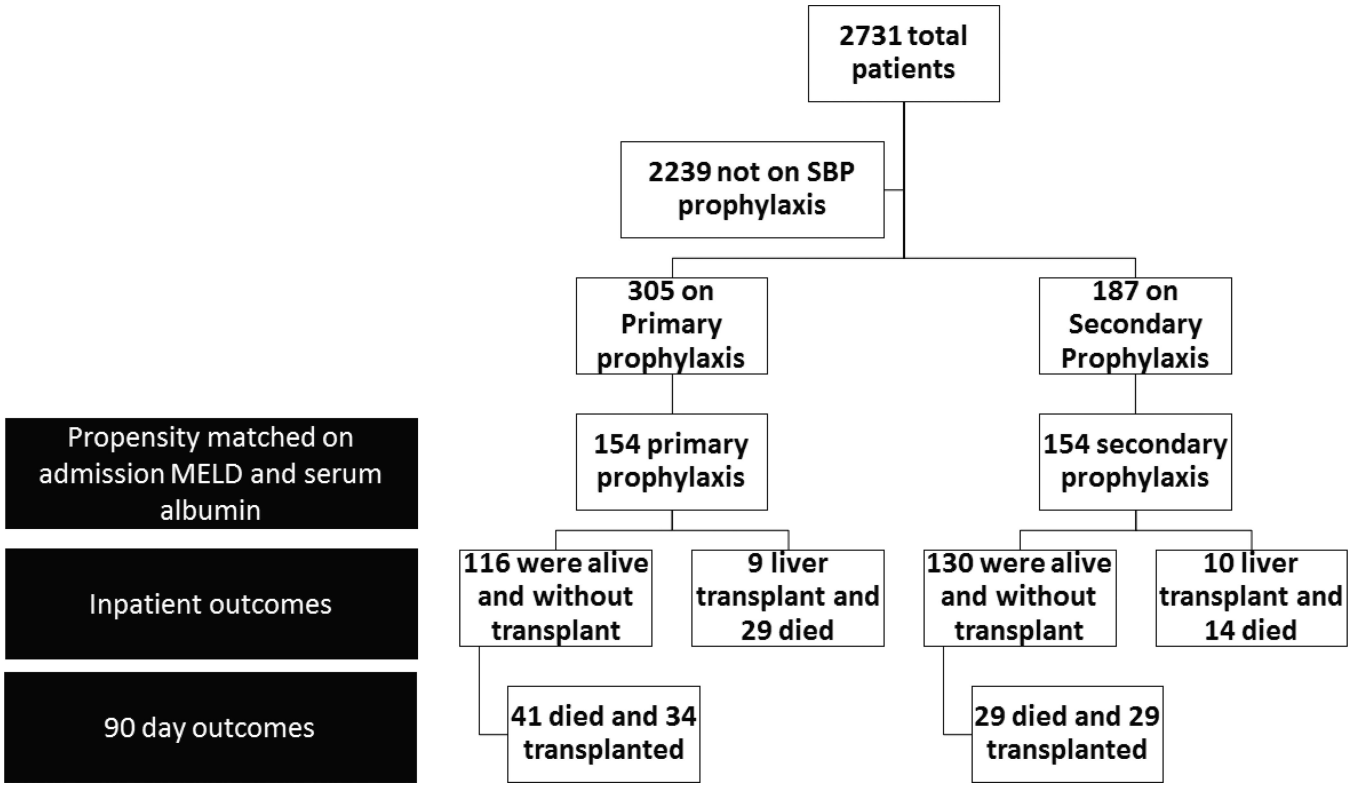

Figure 1:
Flow of patients through the study

Table 1:

Admission features between the propensity-matched cohorts

mean±SD and numbers (%)	Primary prophylaxis (n = 154)	Secondary prophylaxis (n = 154)	p-value
Admission values			
Age (years)	56.7 (10.4)	56.2 (9.9)	0.70
Gender (Male)	92 (60%)	107 (69%)	0.10
Etiology			0.74
Alcohol	50 (32%)	55 (36%)	
Hepatitis C only	30 (19%)	34 (22%)	
Hepatitis C + alcohol	25 (16%)	20 (13%)	
Non-alcoholic fatty liver	31 (20%)	26 (17%)	
Other	18 (12%)	18 (12%)	
Diabetes	45 (30%)	47 (31%)	0.90
Hospitalized prior 6 months	91 (65%)	129 (90%)	<0.0001
Refractory ascites	75 (49%)	106 (69%)	0.0003
Reason for admission			
Admitted with infection	37 (24%)	62 (40%)	0.002
GI Bleed	20 (13%)	11 (7%)	0.10
Hepatic Encephalopathy	29 (19%)	30 (19%)	0.89
Renal Dysfunction	21 (14%)	24 (16%)	0.62
Electrolyte Abnormalities	9 (6%)	7 (5%)	0.62
Anasarca	13 (8%)	20 (13%)	0.19
Alcohol-Related	11 (7%)	6 (4%)	0.20
Urgent Transplant Workup	13 (8%)	12 (8%)	0.84
Other	41 (27%)	32 (21%)	0.21
Cardiac	0 (0%)	3 (2%)	----
Pulmonary	1 (1%)	3 (2%)	0.32
Psychiatric	2 (1%)	0(0%)	----
Other Non-liver Related	7 (5%)	9 (6%)	0.62
Admission laboratory values			
Albumin(g/dl)	2.9 (0.7)	3.0 (0.6)	0.21

mean±SD and numbers (%)	Primary prophylaxis (n = 154)	Secondary prophylaxis (n = 154)	p-value
MELD score	22.7 (7.5)	22.3 (7.2)	0.48
WBC (/mL)	7.5 (5.5)	7.2(4.9)	0.92
Bilirubin (mg/dl)	7.6 (9.9)	6.6 (8.2)	0.81
INR	1.8 (0.6)	1.8 (0.6)	0.85
Serum Sodium (mmol/L)	132.6 (6.8)	132.8 (6.0)	0.66
Serum creatinine (mg/dl)	1.9 (1.7)	1.9 (1.6)	0.66
SIRS and components			
Admission SIRS (n, %)	51 (33%)	35 (23%)	0.02
Temperature criterion	23 (15%)	17 (11%)	0.32
Heart Rate criterion	81 (53%)	62 (41%)	0.03
Respiratory criterion	29 (19%)	17 (11%)	0.04
WBC criterion	54 (36%)	52 (35%)	0.80

Table 2:

Infections and antibiotic use during the index hospitalization

Raw numbers (%)	Primary prophylaxis (n = 154)	Secondary prophylaxis (n = 154)	p-value
Admitted with infection	37 (24%)	62 (40%)	0.002
SBP on/during admission	15 (10%)	34 (22%)	0.004
SBP on admission	14 (9%)	25 (16%)	0.03
Nosocomial SBP	1 (0.5%)	9 (5.8%)	0.01
Second Infection	14 (9%)	14 (9%)	1.0
C.difficile infection	1 (1%)	2 (1%)	0.57
All nosocomial Infection (includes second infections)	22 (14%)	30 (19%)	0.22
First de novo non-SBP nosocomial infection	2 (1.2%)	10 (6.4%)	0.03
Second line antibiotic use	13 (8.4%)	14 (9.1%)	0.78

Second line antibiotics were defined as vancomycin, linezolid, imipenem/meropenem, daptomycin, antifungals compared to first line such as fluoroquinolones, cephalosporins, macrolides and metronidazole.

Table 3:

Inpatient outcomes during the index hospitalization

	Primary prophylaxis (n = 154)	Secondary prophylaxis (n = 154)	p-value
Inpatient AKI	61 (45%)	70 (52%)	0.14
Brain Failure	26 (17%)	31 (20%)	0.46
Respiratory Failure	23 (15%)	20 (13%)	0.62
Renal Replacement	17 (11%)	19 (12%)	0.71
Circulatory Failure	14 (10%)	13 (9%)	0.84
Number of organ failures			0.14
0	104 (68%)	100 (65%)	
1	27 (18%)	36 (23%)	
2	17 (11%)	10 (6%)	
3	5 (3%)	5 (3%)	
4	1 (1%)	3 (2%)	
NACSELD ACLF	23 (15%)	18 (12%)	0.42
Length of stay (days) (mean±SD)	14.4±17.4	16.8±19.7	0.20
ICU admission	48 (31%)	32 (21%)	0.03
Liver transplant	9 (5%)	14 (6%)	0.81
Death	29 (19%)	10 (6%)	0.001
Death/transplant	38 (19%)	24 (15%)	0.05

All data shown as raw numbers and percentage unless mentioned otherwise. ACLF defined according to NACSELD criteria(11). Acute kidney injury (AKI) defined according to consensus criteria(35). Comparisons performed using Mann-Whitney, Fisher's exact or unpaired t-tests as appropriate.

Table 4:

Outcomes at 90 days for the Overall Cohort

	Primary prophylaxis (n = 116)	Secondary prophylaxis (n = 130)	p-value
Re-hospitalization	56 (48%)	73 (56%)	0.22
Inpatient AKI	27 (48% of 56 inpatients)	22 (30% of 73 inpatients)	0.03
Inpatient ACLF	4 (7% of 56 inpatients)	4 (5% of 73 inpatients)	0.72
Inpatient infections	11 (20% of 56 inpatients)	19 (26% of 73 inpatients)	0.40
Liver transplant	34 (29%)	29 (22%)	0.21
Death	41 (35%)	29 (22%)	0.02
Death/transplant	75 (65%)	58 (45%)	0.002

Comparisons performed using Mann-Whitney or Fisher's exact tests as appropriate

Table 5:

Inpatient Outcomes of Patients with and without SBP

	Primary prophylaxis (n = 154)		Secondary prophylaxis (n = 154)	
	No SBP (n=139)	SBP (n=15)	No SBP (n=120)	SBP (n=34)
Inpatient AKI	54 (39%)	7 (47%)	55 (46%)	15 (44%)
Inpatient ACLF	22 (16%)	1 (7%)	15 (12.5%)	3 (9%)
Liver transplant	5 (4%)	4 (20%) *	8 (6%)	6 (18%) *
Death	26 (19%)	3 (20%)	7 (6%) #	3 (9%)
Death/transplant	31 (21%)	7 (27%)	15 (13%) #	9 (26%)

# $p<0.05$ comparing corresponding category in primary vs secondary group,

* $p<0.05$ comparing SBP vs no-SBP within the same group, Comparisons performed using Mann-Whitney or Fisher's exact tests as appropriate

Table 6:

90-day outcomes for patients with or without SBP at the index hospitalization

	Primary prophylaxis (n = 116)		Secondary prophylaxis (n = 130)	
	No SBP (n=105)	**SBP (n=11)**	**No SBP (n=105)**	**SBP (n=25)**
Re-hospitalization	51 (49%)	5 (45%)	60 (57%)	13 (52%)
Liver transplant	27 (26%)	7 (64%) *	20 (19%)	10 (40%) *
Death	38 (36%)	3 (27%)	23 (22%) #	6 (24%)
Death/transplant	65 (61%)	10 (91%) *	43 (41%) #	16 (64%) *

# p<0.05 comparing corresponding category in primary vs secondary group,

* p<0.05 comparing SBP vs no-SBP within the same group, Comparisons performed using Mann-Whitney or Fisher's exact tests as appropriate.