LIVER

Higher Rate of Spontaneous Bacterial Peritonitis Recurrence With Secondary Spontaneous Bacterial Peritonitis Prophylaxis Compared With No Prophylaxis in 2 National Cirrhosis Cohorts

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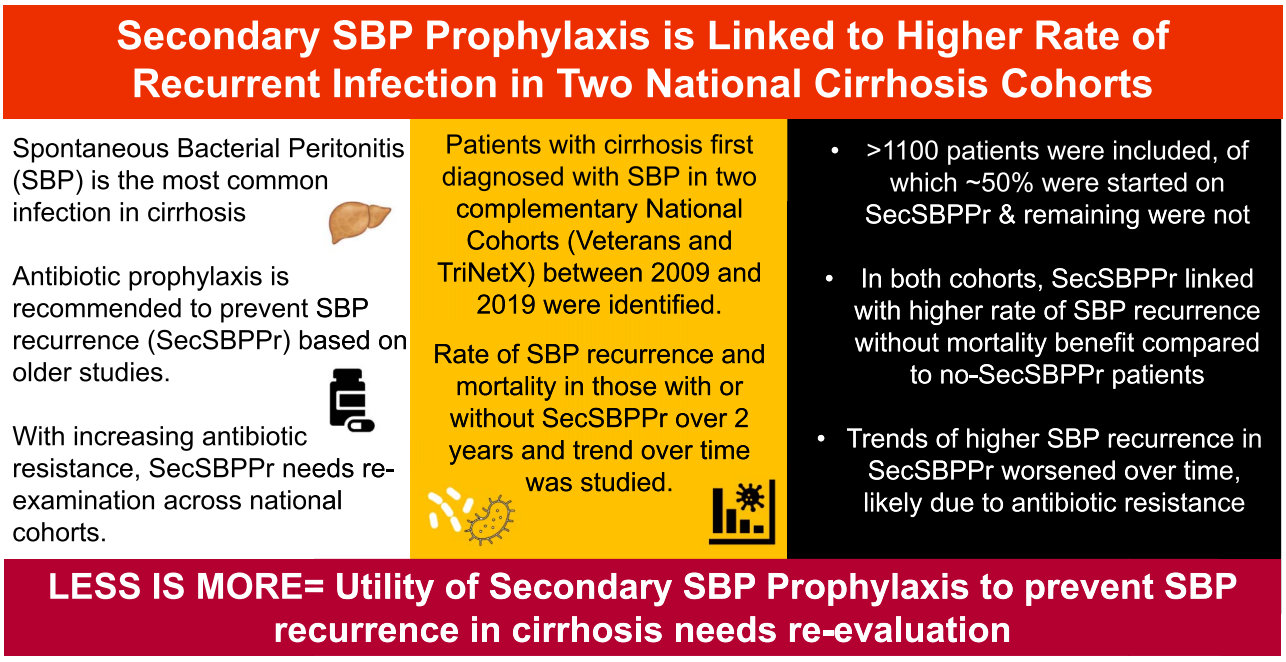
INTRODUCTION: **Spontaneous bacterial peritonitis (SBP) bacteriology has changed over time. Reappraisal of primary SBP prophylaxis showed an increased rate of resistance in patients on primary prophylaxis with resultant discontinuation of this prophylaxis throughout the Veterans Affairs (VA). We aimed to re-evaluate the risk-benefit ratio of secondary SBP prophylaxis (SecSBPPr).**



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METHODS: **Using validated *International Classification of Diseases-9/10* codes, we used the VA Corporate Data Warehouse and the Non-VA National TriNetX database to identify patients in 2 different large US systems who survived their first SBP diagnosis (with chart review from 2 VA centers) between 2009 and 2019. We evaluated the prevalence of SecSBPPr and compared outcomes between those who started on SecSBPPr vs not.**

RESULTS: **We identified 4,673 veterans who survived their index SBP episode; 54.3% of whom were prescribed SecSBPPr. Multivariable analysis showed higher SBP recurrence risk in those on vs off SecSBPPr (hazards ratio 1.63 [1.40–1.91], $P < 0.001$). This was accompanied by higher fluoroquinolone resistance odds in SecSBPPr patients (odds ratio = 4.32 [1.36–15.83], $P = 0.03$). In TriNetX, we identified 6,708 patients who survived their index SBP episode; 48.6% were on SecSBPPr. Multivariable analysis similarly showed SecSBPPr increased SBP recurrence risk (hazards ratio 1.68 [1.33–1.80], $P < 0.001$). Both data sets showed higher SBP recurrence trends over time in SecSBPPr patients. Results remained consistent at 6-month and 2-year timepoints.**

DISCUSSION: **In 2 national data sets of >11,000 patients with SBP, we found that SecSBPPr was prescribed in roughly half of patients. When initiated, SecSBPPr, compared with no prophylaxis after SBP, increased the risk of SBP recurrence in multivariable analysis by 63%–68%, and this trend worsened over time. SecSBPPr should be reconsidered in cirrhosis.**

KEYWORDS: infections; antibiotic resistance; liver transplant; fluoroquinolones; trimethoprim-sulfamethoxazole

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D404

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INTRODUCTION

With advancing cirrhosis and development of ascites, there is a risk of spontaneous bacterial peritonitis (SBP) (1). Delays in or absence of SBP treatment is associated with acute kidney injury, organ failure(s), acute-on-chronic liver failure, and death, and once SBP occurs, there is a high rate of recurrence (2–4). The microbiome in patients with cirrhosis changes as liver disease progresses, with etiology of liver disease, and with medications given. Patients with decompensated cirrhosis have high rates of bacterial, fungal, and viral dysbiosis, which is worsened by antibiotic use, such as SBP prophylaxis, and leads to further enrichment of antibiotic resistance genes (5–8). The current preventive strategies for recurrence include daily antibiotic use, usually with fluoroquinolones or trimethoprim-sulfamethoxazole (TMP-SMX) (1). However, with the increasing prevalence of antibiotic resistance, as well as the shift in SBP causative organisms from Gram-negative to Gram-positive organisms, the real-world efficacy of SBP prophylaxis needs to be re-examined (9,10). This re-evaluation is particularly relevant now because recent data documented the risk-benefit ratio of primary SBP prophylaxis has changed, likely secondary to the increasing prevalence of resistant organisms (11–13).

Therefore, it is time to re-evaluate the risks and benefits of secondary SBP prophylaxis (SecSBPPr). This reappraisal of SecSBPPr needs analysis of large nationally representative cohorts to ensure that differences in practice patterns do not dictate results. To address this gap in knowledge, 2 cohorts were studied: the Corporate Data Warehouse (CDW) of US veterans and the nonveteran TriNetX cohort. We hypothesized the rate of SBP recurrence is higher and is worsening over time in patients with cirrhosis and previous SBP who were initiated on SecSBPPr compared with those who were not initiated on SecSBPPr after an episode of SBP in 2 large national US cohorts.

METHODS

We used the Veterans Affairs (VA)-CDW with chart review from 2 centers to further validate the codes for SBP and the TriNetX database from 2009 to 2019.

VA-CDW

Cohort creation. We obtained the first (index) inpatient or outpatient diagnosis of SBP between 2009 and 2019 using validated *International Classification of Diseases* (*ICD-9/10)* codes (*ICD-9*: 567.23; *ICD-10*: K65.2) in each cohort among those with a previous cirrhosis diagnosis (*ICD* codes included in supplementary). Index SBP diagnosis was defined by the first instance of an *ICD-9/10* code and was then filtered to the years 2009–2019, excluding those where the index diagnosis date was outside of this range. Patients were observed starting 30 days after the SBP diagnosis for 2 years. The latest index SBP diagnosis date considered was December 1, 2017, so that each patient received a full 2-year window of follow-up time. Patients who died or received a liver transplant up to 30 days after their index SBP infection were not included in the cohort because these outcomes were likely caused by the index SBP event and not from the presence or absence of prophylactic medication. SecSBPPr was defined as continuous use (≥2 refills) of fluoroquinolones or TMP-SMX up to 120 days after the index diagnosis date. We also collected additional information on demographics, admission medications, MELD-Na, platelet count (10^9/L), albumin (g/dL), white blood cell count (10^9/L), Charlson Comorbidity Index (CCI), and outcomes. A full description of definitions can be found in the Supplementary section. Cohort characteristics were summarized and compared between the groups: no SecSBPPr vs SecSBPPr (Table 1). Continuous variables were presented as the mean (±SD) or median (inter quartile range), and categorical variables were presented as counts and percentages of the total. Variables were compared between the groups using 2-sample *t* test, Wilcoxon rank-sum tests, or Pearson χ^2 tests, as appropriate.

Table 1. All patients with SBP in the VA-CDW database

n = 4,673 patients with first SBP episode	Not started on secondary prophylaxis (n = 2,134, 45.7%)	Started on secondary prophylaxis (n = 2,539, 54.3%)	*P* value
Variable			
Laboratory test results/demographics			
Age	61.49 (±9.13)	61.55 (±8.11)	0.80
Male sex	2045 (97.7%)	2,430 (96.7%)	0.07
White race	1,533 (77.7%)	1912 (81.1%)	**0.005**
Hispanic ethnicity	194 (9.4%)	252 (10.3%)	0.36
Alcohol etiology	812 (38.1%)	999 (39.3%)	0.38
Charlson Comorbidity Index	5.02 (±2.65)	5.52 (±2.69)	**<0.001**
MELD-Na	17.87 (±6.78)	18.34 (±6.24)	**0.02**
Platelet count (10^9/L)	134.00 (81.00–221.00)	101.00 (66.00–170.00)	**<0.001**
Albumin (g/dL)	2.72 (±0.67)	2.81 (±0.65)	**<0.001**
White blood cell count (10^9/L)	6.80 (4.80–9.30)	5.87 (4.10–8.20)	**<0.001**
VA complexity, level 1	1969 (92.3%)	2,428 (95.6%)	**<0.001**
North Atlantic region	424 (19.8%)	436 (17.2%)	**0.020**
Medications			
Proton pump inhibitors	772 (36.2%)	1,028 (40.5%)	**0.003**
Statins	200 (9.4%)	245 (9.6%)	0.79
Lactulose	622 (29.1%)	948 (37.3%)	**<0.001**
Rifaximin	191 (9.0%)	364 (14.3%)	**<0.001**
Propranolol	348 (16.3%)	501 (19.7%)	**0.003**
Nadolol	41 (1.9%)	83 (3.3%)	**0.006**
Carvedilol	80 (3.7%)	107 (4.2%)	0.46
Selective β-blocker	208 (9.7%)	245 (9.6%)	0.95
Outcomes			
2-year SBP recurrence	293 (13.7%)	611 (24.1%)	**<0.001**
2-year all-cause mortality	1,261 (59.1%)	1,564 (61.6%)	0.08
2-year liver transplant	33 (1.5%)	87 (3.5%)	**<0.001**

Bold entries indicate statistically significant.
CDW, Corporate Data Warehouse; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; VA, Veterans Affairs.

Analysis of outcomes. The primary outcome of interest was the time (in days) to SBP recurrence during the 2-year follow-up period that was >30 days after the index episode. All-cause mortality and liver transplant rates were examined as potential competing risks. We included this 1-month buffer period between the index date and the beginning of the follow-up period to ensure that the second SBP episode was truly a new instance of the disease.

The analysis of time-to-event data with competing risks is often approached through either Fine and Gray's competing risks regression (CRR) or Cox proportional hazards modeling of the cause-specific hazard, which is simply a standard Cox model with the competing events censored. In this study, we used Cox proportional hazards rather than CRR to maximize interpretability and clarity. Specifically, the interpretation of the subdistribution hazard obtained from CRR is not intuitive—representing the instantaneous rate of the outcome given that the patient has not yet experienced the outcome, or the patient has already experienced a competing event. This can become confusing, especially in our study, when both competing events were absorbing (one cannot become infected with SBP after death, and liver transplant is curative). However, the interpretation of the cause-specific hazard is more natural—since we censor the competing risks, the coefficient estimate is simply the instantaneous rate of SBP recurrence among those actually still at risk (i.e., alive and with active cirrhosis). For this reason, it has been shown that—although both methods are valid–use of the cause-specific hazard is preferable over Fine and Gray's competing risk regression in etiological studies, such as ours, whereas CRR is preferred in predictive modeling (14).

All-cause mortality and liver transplant rates were examined as secondary outcomes; these were examined using logistic regression models. Proportional hazards assumptions for Cox models were assessed visually by examining plots of the Schoenfeld residuals over time.

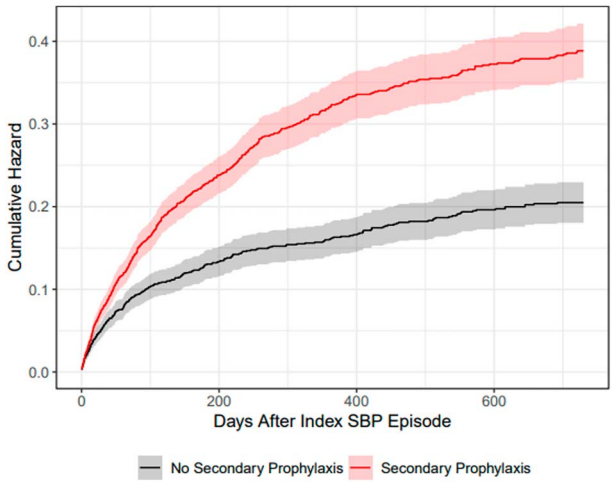

Figure 1. Cumulative incidences of SBP recurrence in Veterans Affairs Corporate Data Warehouse. Data are presented as cumulative hazards for SBP recurrence with solid curves and 95% CI shading. Patients on secondary prophylaxis (red) had an unadjusted hazard ratio of 1.82 (95% CI: [1.59–2.10], $P < 0.001$) for SBP recurrence vs those who were not on secondary prophylaxis (gray). CI, confidence interval; SBP, spontaneous bacterial peritonitis.

Change over time. For all models, we also adjusted for covariates that were significantly different between the no-SecSBPPr vs SecSBPPr groups. Finally, in the SBP recurrence model, we hypothesized that the potential effect of secondary SBPPr on SBP recurrence would become worse over time. Thus, an additional interaction between the time from index diagnosis (defined numerically as the number of days after January 1, 2009, of the patient's index date, divided by 365) and secondary prophylaxis was tested.

Antibiotic resistance. We examined the proportion of fluoroquinolone-resistant infections among those on fluoroquinolone-specific SecSBPPr (vs no SecSBPPr), as well as the proportion of trimethoprim sulfomethoxazole-resistant infections among those on TMP-SMX SecSBPPr (vs no SecSBPPr). Antibiotic resistance data were collected within the date of recurrence ±14 days to capture all potential susceptibility results within the infection date. Logistic regression models were used to examine associations, and further multivariable modeling was performed, again adjusting for all covariates that were significantly different between the secondary prophylaxis groups.

Sensitivity analysis. Multiple sensitivity analyses were performed to ensure results were consistent over various conditions. First, we examined the treatment effect on SBP recurrence within those only taking ciprofloxacin (which was a majority of those on SecSBPPr) compared with either ciprofloxacin or TMP-SMX/Bactrim.

Secondly, in this study, we considered a 2-year follow-up time to measure SBP recurrence. However, to assess a more immediate outcome, we considered a 6-month follow-up time (180 days) as an alternative endpoint. Statistical analyses were identical to those performed in the main analysis.

RStudio version 4.3.1 was used for all statistical analysis. All hypothesis tests were 2-sided with statistical significance considered $P < 0.05$.

Validation of results in 2 VA centers. Charts from the patients included in the CDW from the Richmond and Dallas VA were reviewed to confirm the presence of SBP and whether fluoroquinolone or TMP-SMX use was indeed started for SecSBPPr.

Validation of results in a TriNetX national nonveteran cohort

TriNetX is a national database of insured, non-VA patients (trinetx.com) sourced from healthcare organizations participating in the TriNetX Research Network. These healthcare organizations are usually large academic medical institutions with both inpatient and outpatient facilities within the United States. TriNetX contains information regarding patient demographics, diagnoses, and procedures through *ICD* or Current Procedural Terminology codes, laboratory values, prescription data, transplant, and death records. This cohort was assembled using similar methods as described above but with some differences. First, some covariates were not available (or very sparse) in TriNetX, including hospital complexity, region, international normalized ration (INR) laboratory test results, CCI, and information on antibiotic resistance. Because INR was not available to calculate MELD-Na score, we used the MELD-XI score instead, which excludes INR. We also adjusted for individual laboratory results (if statistically significantly different between the SecSBPPr groups) (15). Second, the death records on TriNetX only provide the month of death, rather than an exact date; to counteract this, we used the middle (15th) of each month as the day of death-based analyses. Finally, prescription refill data were not available, so we only considered a single instance of ciprofloxacin/TMP-SMX at the time of index diagnosis (up to 120-day postindex episode) to be indicative of SecSBPPr. Identical statistical analyses were performed on TriNetX as the VA-CDW cohort, and the results were compared.

Institutional Review Board (IRB) approval was obtained from the Richmond and Dallas VA (for the VA records) and Virginia Commonwealth University (for TriNetX) Institutional Review Boards before the study was initiated. The IRB approvals included a waiver of individual informed consent.

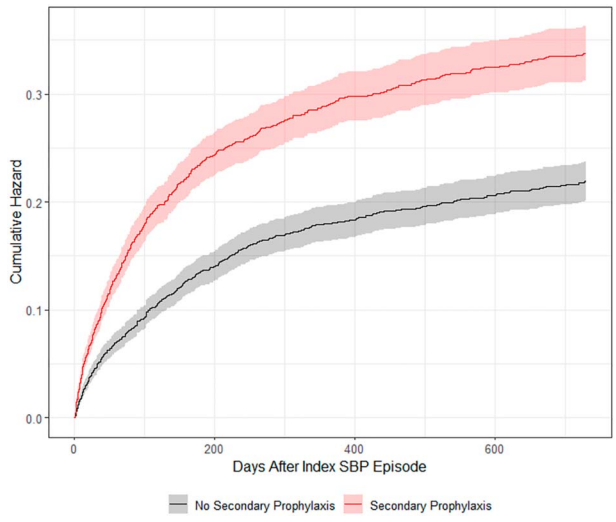

Figure 2. Cumulative incidences of SBP recurrence in the TriNetX cohort. Data are presented as cumulative hazards for SBP recurrence with solid curves and 95% CI shading. Patients on secondary prophylaxis (red) had an unadjusted hazard ratio of 1.61 (95% CI: [1.44–1.80] $P < 0.001$) for SBP recurrence vs those who were not on secondary prophylaxis (gray). CI, confidence interval; SBP, spontaneous bacterial peritonitis.

Table 2: Univariable and multivariable analyses for outcomes in VA-CDW

	Univariable analysis	
Outcome	**Hazard or odds ratio (95% CI)**	***P* value**
SBP recurrence	1.82 (1.59–2.10)	**<0.001**
All-cause mortality	1.11 (0.98–1.25)	0.081
Liver transplant	2.13 (1.52–3.43)	**<0.001**
	Multivariable analysis	
Outcomes	**Hazard or odds ratio (95% CI)**	***P* value**
SBP recurrence		
Secondary prophylaxis	1.63 (1.40–1.91)	**<0.001**
Platelet count	0.99 (0.99–1.00)	**<0.001**
MELD-Na	1.03 (1.02–1.04)	**<0.001**
All-cause mortality		
Secondary prophylaxis	0.93 (0.81–1.06)	0.28
Platelet count	1.00 (0.99–1.00)	**<0.001**
Proton pump inhibitors	1.21 (1.05–1.40)	**0.009**
Lactulose	1.20 (1.03–1.40)	**0.02**
North Atlantic region	0.82 (0.69–0.98)	**0.03**
Charlson Comorbidity Index	1.20 (1.17–1.24)	**<0.001**
WBC count	1.02 (1.00–1.04)	**0.03**
MELD-Na	1.06 (1.05–1.07)	**<0.001**
Albumin	0.62 (0.56–0.69)	**<0.001**
Liver transplant		
Secondary prophylaxis	1.85 (1.20–2.94)	**0.007**
Platelets	1.00 (0.99–1.00)	**0.03**
North Atlantic region	1.70 (1.06–2.65)	**0.02**
Rifaximin	1.88 (1.17–2.96)	**0.007**
MELD-Na	1.06 (1.03–1.09)	**<0.001**
WBC count	0.89 (0.81–0.97)	**0.008**

Death/transplant was odds ratios, and time to recurrence was hazard ratio.
Bold entries indicate statistically significant.
CDW, Corporate Data Warehouse; CI, confidence interval; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; VA, Veterans Affairs; WBC, white blood cell.

RESULTS

VA-CDW cohort creation and description

From 2009 to 2019, we identified 4,673 patients who survived their index SBP episode, with 2,539 (54.3%) started on SecSBPPr after the index episode. Among these, 2,144 (84.4%) were on fluoroquinolones (ciprofloxacin: 1985, 92.6%, other: 159, 7.4%), and 395 (14.6%) were on TMP-SMX. Cohort characteristics can be found in Table 1. Patients who were put on SecSBPPr were significantly more likely to be on lactulose (37.3% vs 29.1%, $P < 0.001$), rifaximin (14.3% vs 9.0%, $P < 0.0001$), propranolol (19.7% vs 16.3%, $P < 0.001$), nadolol (3.3% vs 1.9%, $P = 0.006$), and proton pump inhibitors (PPI) (40.5% vs 36.2%, $P = 0.003$). These patients also had higher mean CCI (5.52 vs 5.02, $P < 0.001$), serum albumin (2.81 vs 2.72, $P < 0.001$), and MELD-Na scores (18.34 vs 17.87, $P = 0.017$); lower median white blood cell (WBC) counts (5.87 vs 6.80, $P < 0.001$) and median platelet counts (101.00 vs 134.00, $P < 0.001$); and were more likely to be White (81.1% vs 77.7%, $P = 0.005$), in VA complexity level 1 centers (95.6% vs 92.3%, $P < 0.001$), and less likely to be admitted in the North Atlantic VA Region (17.2% vs 19.9%, $P = 0.020$).

VA-CDW multivariable analysis. Among the 4,673 veterans who survived their index SBP episode, 904 (19.3%) had a second SBP episode within the 2-year follow-up period. The crude rates of recurrence (24.1% vs 13.7%, $P < 0.001$) and liver transplant rate (3.5% vs 1.5%, $P < 0.001$) were higher in those on vs off SecSBPPr (Table 1). On univariable analysis, the rates of SBP recurrence in the SecSBPPr group were significantly higher (Figure 1, hazards ratio (HR): 1.82, 95% confidence interval [CI: 1.59–2.10], $P < 0.001$), as were the odds of liver transplant (odds ratio [OR]: 2.13, 95% CI: [1.52–3.43], $P < 0.001$). Visual evidence of this trend is shown by splitting the index year into 3 timepoints and observing the increasing difference in hazard ratios between the treatment groups (see Supplementary Figure S1, http://links.lww.com/AJG/D404). The odds of all-cause mortality in the SecSBPPr group were numerically higher but not statistically significant (OR: 1.11, 95% CI: [0.98–1.25], $P = 0.081$).

After adjusting for all covariates that were significantly different between the treatment groups, the rates of SBP recurrence remained statistically significantly higher in patients on SecSBPPr ($P < 0.001$, Adj. HR: 1.63, 95% CI: [1.40–1.91]). Other variables associated with a higher risk of a second SBP episode were lower platelet counts ($P < 0.001$) and higher MELD-Na score ($P < 0.001$). The Schoenfeld residual plot was generally flat, indicating no major deviations from the proportional hazards assumption (see Supplementary Figure S3a, http://links.lww.com/AJG/D404).

Analysis of period. When the interaction between continuous time and SecSBPPr was added to the adjusted Cox proportional hazards model for SBP recurrence, we found that patients receiving SecSBPPr were 1.07 times more likely to have a second SBP episode for every additional year after 2009 (95% CI: [1.01–1.13], $P = 0.026$). Visual evidence of this trend can be seen in Figure 2.

Other outcomes. For all-cause mortality, adjusting for covariates did not change the results; death rates were not altered by the presence or absence of SecSBPPr on multivariable analysis (Table 2, $P = 0.28$). Other variables associated with higher rates of death were PPI use ($P = 0.008$), lactulose use ($P = 0.021$), regions other than North Atlantic ($P = 0.025$), higher MELD-Na ($P < 0.001$), higher CCI ($P < 0.001$), lower platelet counts ($P < 0.001$), higher WBC ($P < 0.001$), and lower albumin ($P < 0.001$).

For liver transplant, after adjusting for covariates, the positive association between secondary prophylaxis and this outcome remained consistent (adj. OR: 1.85, 95% CI: [1.20–2.94], $P = 0.007$). Other variables associated with higher transplant rates were North Atlantic Region ($P = 0.023$), rifaximin use ($P = 0.007$), higher MELD-Na ($P < 0.001$), lower platelets ($P = 0.032$), and lower WBC counts ($P = 0.008$). For all adjusted models, specific hazard/odds ratios and 95% CIs can be found in Table 2.

Antibiotic resistance. Only 100 (2.2%) patients were culture-positive with antibiotic resistance data available. Of these patients, all had sensitivity data for fluoroquinolones and 16 for TMP-SMX sensitivity. Within those on fluoroquinolone SecSBPPr, 67.9% (38/56) had evidence of fluoroquinolone-resistant isolates vs 45.5% in those not on SecSBPPr (OR: 2.53, 95% CI: [1.13–5.82], $P = 0.026$). Multivariable analysis of fluoroquinolone resistance documented SecSBPPr to be statistically significantly associated with this outcome after adjusting for all

Table 3. All patients with SBP in the TriNetX database

n = 6,708 patients with first SBP episode	Not started on secondary prophylaxis (n = 3,447, 51.4%)	Started on secondary prophylaxis (n = 3,261, 48.6%)	*P* value
Laboratory test results/demographics			
Age	56.66 (±11.47)	56.17 (±10.96)	0.07
Male sex	2,191 (63.6%)	2,116 (64.9%)	0.27
White race	2,260 (76.7%)	2,356 (79.7%)	**0.005**
Hispanic ethnicity	598 (22.7%)	495 (19.2%)	**0.002**
Alcohol etiology	1739 (50.4%)	1829 (56.1%)	**<0.001**
MELD-XI score	16.84 (±6.34)	16.93 (±5.79)	0.62
Bilirubin (g/dL)	1.8 (0.9–3.8)	2.4 (1.2–4.6)	**<0.001**
Creatinine (mg/dL)	1.00 (0.72–1.60)	0.93 (0.70–1.31)	**<0.001**
Sodium (mEq/L)	135.03 (±5.39)	134.73 (±5.38)	**0.04**
Albumin (g/dL)	2.83 (±0.70)	2.77 (±0.66)	**0.006**
White blood cell count (10^9/L)	6.50 (4.40–9.61)	6.20 (4.20–9.00)	**0.01**
Platelet count (10^9/L)	116.00 (73.00–187.00)	100.00 (65.00–159.00)	**<0.001**
Medications			
Proton pump inhibitor	1,331 (38.6%)	1,734 (53.2%)	**<0.001**
Statins	262 (7.6%)	263 (8.1%)	0.51
Lactulose	1,154 (33.5%)	1,605 (49.2%)	**<0.001**
Rifaximin	600 (17.4%)	937 (28.7%)	**<0.001**
Propranolol	281 (8.2%)	389 (11.9%)	**<0.001**
Nadolol	201 (5.8%)	376 (11.5%)	**<0.001**
Carvedilol	145 (4.2%)	128 (3.9%)	0.60
Selective β-blocker	299 (8.7%)	325 (10.0%)	0.08
Outcomes			
2-year SBP recurrence	551 (16.0%)	734 (22.5%)	**<0.001**
2-year all-cause mortality	1,157 (33.6%)	1,207 (37.0%)	**0.003**
2-year liver transplant	191 (5.5%)	468 (14.4%)	**<0.001**

Bold entries indicate statistically significant.
MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis.

covariates previously discussed (adj. OR: 4.32, 95% CI: [1.36–15.83], $P = 0.018$). There was only one patient on TMP-SMX SecSBPPr within the subset with sensitivity data; this patient did have a TMP-SMX-resistant infection (N = 1, 100.0%) vs 46.6% (7 of 15) resistance in those not on TMP-SMX SecSBPPr, but this sample size was insufficient for further statistical analysis.

Sensitivity analysis. In the multivariable model, the effect of secondary prophylaxis on SBP recurrence within those taking ciprofloxacin prophylaxis was similar to that obtain with both antibiotic types (adj. HR: 1.65 [1.41–1.93], $P < 0.001$).

On examination of a 6-month endpoint, the effect of secondary prophylaxis on SBP recurrence remained statistically significant (adj. HR: 1.56 [1.31–1.87], $P < 0.001$), as did the time-based trend (adj. HR, 2012–2015 vs 2009–2011: 1.24 [0.77–2.00], $P = 0.364$, 2016+ vs 2009–2011: 1.60 [1.04–2.44], $P = 0.031$). SecSBPPr was associated with lower odds of death (adj. OR: 0.78 [0.68–0.90], $P < 0.001$) in the immediate 6 months—although as seen in the main analysis, this short-term decrease in risk eventually disappeared. Liver transplant rates (adj. OR: 1.50 [0.78–3.03], $P = 0.238$) were higher but not significantly different between the groups at 6 months, likely because of low overall numbers at this early endpoint, which inflated the standard error of the coefficient estimate.

Chart review. The Dallas VA cohort had 90 patients and Richmond VA had 45 patients who were included in the CDW with a computer diagnosis of SBP. Within the Dallas VA, the mean age was 61.7 ± 7.6 years, and all patients except 2 were male. Documented SBP was seen in 78% (70/90) of patients, 7% (6/90) of patients were treated empirically for undocumented SBP, and the other patients had other types of infections during their admission. Of these patients with SBP, 67% were started on SecSBPPr (n = 41 on fluoroquinolone, n = 3 on TMP-SMX, and n = 3 on cefpodoxime).

In the Richmond VA cohort, the mean age was 60.4 ± 9.6 years, and only one patient was a woman. Eighty percent (36 of 45) had SBP; the rest were unclear (n = 5) or had secondary SBP because of umbilical hernia incarceration or hepatic abscesses (n = 4). Of the 36 patients with SBP, 26 were started on SecSBPPr

Table 4. Univariable and multivariable analyses for outcomes in TriNetX

	Univariable analysis	
Outcome	**Hazard or odds ratio (95% CI)**	***P* value**
SBP recurrence	1.61 (1.44–1.80)	**<0.001**
All-cause mortality	1.16 (1.05–1.29)	**0.003**
Liver transplant	2.86 (2.40–3.41)	**<0.001**
	Multivariable analysis	
Outcomes	**Hazard or odds ratio (HR/OR) (95% CI)**	***P* value**
SBP recurrence		
Secondary prophylaxis	1.68 (1.33–1.80)	**<0.001**
White race	1.28 (1.02–1.62)	**0.03**
Hispanic ethnicity	1.28 (1.05–1.57)	**0.02**
Creatinine	1.08 (1.04–1.12)	**<0.001**
All-cause mortality		
Secondary prophylaxis	1.02 (0.87–1.20)	0.80
White race	1.24 (1.01–1.52)	**0.04**
Hispanic ethnicity	0.44 (0.35–0.54)	**<0.001**
Bilirubin	0.97 (0.95–1.00)	**0.02**
Proton pump inhibitors	1.27 (1.07–1.51)	**0.008**
Liver transplant		
Secondary prophylaxis	2.53 (1.89–3.44)	**<0.001**
Platelet count	0.99 (0.99–1.00)	**<0.001**
Bilirubin	1.07 (1.04–1.10)	**<0.001**
Proton pump inhibitors	0.74 (0.56–0.99)	**0.05**
Rifaximin	1.65 (1.20–2.28)	**0.002**

Death/transplant was odds ratios, and time to recurrence was hazard ratio.
CI, confidence interval; HR, hazards ratio; OR, odds ratio; SBP, spontaneous bacterial peritonitis.

(n = 21 on fluoroquinolones and n = 5 on TMP-SMX). Ascites fluid organisms were isolated in 36% (n = 13) of the patients with SBP (9 Gram-negative, 3 Gram-positive, and one fungus).

TriNetX cohort. This cohort contained 6,708 patients with SBP (age 56.42 ± 11.23, 64.2% male, and 48.6% on SecSBPPr). Patients on SecSBPPr had similar trends in cohort characteristics, namely greater severity of cirrhosis and higher rates of admission medications (rifaximin, lactulose, and PPI; Table 3). SecSBPPr patients were also more likely to be White, of non-Hispanic ethnicity, and have an alcohol-related etiology of cirrhosis. On univariable analysis (Table 4), SecSBPPr patients again had higher rates of 2-year SBP recurrence (HR: 1.61 [1.44–1.80], $P < 0.001$), LT (OR: 2.86 [2.40–3.41], $P < 0.001$), and death (OR: 1.16 [1.05–1.29], $P = 0.003$). Similar to VA-CDW, TriNetX also showed visual evidence of this (see Supplementary Figure S2, http://links.lww.com/AJG/D404).

Multivariable adjustment. After covariate adjustment, the rate of 2-yr SBP recurrence remained significantly higher in SecSBPPr (HR: 1.68 [1.33–1.80], $P < 0.001$), as did the odds of liver transplant (OR: 2.53 [1.89–3.44], $P < 0.001$). Mortality was no longer statistically significant ($P = 0.795$). The Schoenfeld residual plot was generally flat, indicating no major deviations from the proportional hazards assumption (see Supplementary Figure S3b, http://links.lww.com/AJG/D404).

Change over time. When the interaction between continuous time and SecSBPPr was added to the adjusted Cox proportional hazards model for SBP recurrence, we found that patients receiving SecSBPPr were 1.11 times more likely to have a recurrent SBP episode for every additional year after 2009 (95% CI: [1.03–1.21], $P = 0.011$).

Sensitivity analysis. In the multivariable model, the effect of secondary prophylaxis on SBP recurrence within those taking ciprofloxacin prophylaxis was similar to that obtained with both antibiotic types (adj. HR: 1.75 [1.45–2.11], $P < 0.001$).

On examination of a 6-month endpoint, the effect of secondary prophylaxis on SBP recurrence remained statistically significant (adj. HR: 1.81 [1.45–2.26], $P < 0.001$), as did the time-based trend (adj. HR, 2012–2015 vs 2009–2011: 2.00 [0.90–4.47], $P = 0.09$, 2016+ vs 2009–2011: 2.36 [1.17–5.00], $P = 0.025$). For death (adj. OR: 1.09 [0.91–1.32], $P = 0.346$) and liver transplant (adj. OR: 3.82 [2.55–5.93], $P < 0.001$), trends were similar to those observed at 2 years.

DISCUSSION

In 2 large US-based cohorts of patients, both veterans and non-veterans with cirrhosis and SBP, study data demonstrated that those who were initiated on SecSBPPr after the index case of SBP had a higher rate of SBP recurrence compared with those who did not receive prophylaxis. Moreover, this higher rate of SBP recurrence increased in those who received SecSBPPr over time, with the highest separation being in the latter periods.

These 2 cohorts of patients demonstrated that only roughly half of patients after SBP diagnosis are placed on SecSBPPr per American Association for the Study of Liver Disease guidance and European Association for the Study of Liver guidelines (1,16). Likely patient, provider, and systems problems are at play in this relatively low rate of utilization of what is believed to be an important quality metric. Patient-based reasons may include non-adherence with follow-up, low health literacy, fear of side effects, or cost of the medication. System-level problems may include but are not limited to lack of education on the importance of prophylaxis to midlevel or primary care providers and lack of records availability or communication if a patient was diagnosed at an outside hospital.

Because SBP prophylaxis is considered current standard of care, only database studies can challenge this ingrained dogma. Because of the marked changes in etiology of liver disease, access to liver transplant, microbiology resistance rates, and SBP causative organisms since original studies of primary and SecSBPPr in the 1980s and 1990s, we sought to re-evaluate the risk-benefit ratio of these prophylactic therapies (17). Our first step was a reappraisal of primary SBP prophylaxis. This undertaking first revealed that outcomes of prospectively enrolled inpatients in the North American Consortium for the Study of End-Stage Liver Disease admitted on primary SBP prophylaxis vs SecSBPPr were worse, even after propensity score matching (12). In fact, patients on primary SBP prophylaxis had a higher rate of systemic inflammatory response syndrome, need for intensive care unit care, nosocomial SBP rate, readmission rate, and inpatient and 90-day mortality rate. We then evaluated the national VA-CDW data to evaluate outcomes of patients with SBP who were on vs off primary SBP prophylaxis. Patients taking primary SBP prophylaxis who developed SBP had a much higher rate of Gram-negative resistance. European data have also documented a declining benefit of primary SBP

prophylaxis with norfloxacin no longer having a survival advantage in a randomized controlled trial (18). Given the changing risk-benefit ratio of primary prophylaxis combined with the high rate of *Escherichia coli* resistance across the United States to ciprofloxacin, the National VA Health Care System decided to no longer recommend primary SBP prophylaxis (11).

Therefore, the next step was to re-evaluate the utility of SecSBPPr. Interestingly, those initiated on SecSBPPr had a higher rate of SBP recurrence compared with those not receiving SecSBPPr. Moreover, this higher SBP recurrence numerically increased in those who received SecSBPPr over time. This database appraisal provided an opportunity to assess the impact of SecSBPPr on important clinical outcomes such as SBP recurrence, death, and liver transplant. Our major finding was that despite controlling for clinical, patient-based, and system-based factors, SecSBPPr use emerged as a significant contributor to SBP recurrence without any mortality benefit. This is striking because the initial randomized clinical trials and guidelines cite prevention of SBP recurrence as the primary reason for SecSBPPr initiation (1,10,17).

Reasons for this higher rate of SBP recurrence in SecSBPPr are likely related to diminishing coverage of causative organisms over time because of increased prevalence of resistance and/or change in microbiology (13,19–22). With recent studies in patients on SecSBPPr, there was a higher relative abundance of Gram-positive pathobionts, increase in microbial virulence, and changes in bacteriophage linkages that could affect effectiveness of antibiotics (13,23,24). In the VA-CDW database, this was found in those who had culture data available. The results are also consistent with the VA-CDW experience in primary SBP prophylaxis, which showed up to 50% fluoroquinolone resistance to *E. coli* and *Klebsiella pneumoniae* that are main targets for SBP prophylaxis (11). Another indirect piece of evidence is the widening of the gap in SBP recurrence rate over time, with a higher rate in SecSBPPr over time. There is ample evidence of the worsening resistance profile and shift from Gram-negative to Gram-positive organisms in outpatients and inpatients with cirrhosis, which is consistent with this widening of the gap over time. The sparse culture results diminish the ability of practitioners to tailor SecSBPPr strategies and instead force them to use the same regimen for all patients. It is unclear from our data how often culture bottles were inoculated at the bedside to optimize culture results because a higher rate of culture-positive patients with SBP could help guide which antibiotic agent(s) to use for SecSBPPr (25).

The higher rate of SBP recurrence with SecSBPPr was consistent across 2 different healthcare systems, which adds to the reliability of the results. Veterans included in CDW tend to be older and male, and less likely to be minorities, compared with the general US population, whereas TriNetX is more reflective of the US patient population (26). Regardless of these differences, the low rate of SecSBPPr and the pattern of consequences were similar. This included higher SBP recurrence but no significant impact on overall mortality when adjusted for baseline severity of liver disease and system-based factors. Although LT was higher in the SecSBPPr group, less than 5% of patients underwent this procedure, and this small number of patients, surely followed by transplant hepatologists, may simply have been more likely to have received guideline-based care (27). Mortality, on the other hand, was higher in the SecSBPPr group on crude comparisons, but not on multivariable analysis. This is likely due to factors other than SBP that affect risk of death that are not modifiable by SecSBPPr use (28). Patients with cirrhosis are prone to several complications that affect mortality, and these findings show the limitations of focusing on prevention of one complication (29). Regardless, as mentioned above, the primary aim of SecSBPPr is to prevent SBP recurrence, the opposite of which was seen in our results. SBP recurrence leads to more hospitalizations, interventions, and further antibiotic use, which need to be avoided.

The question that now arises is how to decrease the rate of SBP recurrence considering this data. Until nonantibiotic strategies that are not disruptive to the microbiome and immune system are available, reflexive initiation of SecSBPPr should be reconsidered potentially with a randomized controlled clinical trial (30). Especially in areas of high baseline resistance to the major causative organisms, initiation of SecSBPPr should be guided by antimicrobial stewardship programs. In the VA, SBP primary prophylaxis is now discouraged because of the high prevalence of resistance to the same antibiotics used for SecSBPPr. In addition to potential lack of efficacy and negative impact on the microbiome, fluoroquinolones and TMP-SMX are associated with neurologic and hematologic adverse events, as well as drug-induced liver injury, and Achilles tendon injury (31–33). These adverse events are especially poorly tolerated in decompensated patients and add to the reasons to re-evaluate the use of SecSBPPr (33,34). However, ultimately nonantibiotic strategies either through lowering portal pressure or modulating the microbiome are needed to decrease the primary and secondary risk of SBP (5,35).

Our data are limited by database restrictions, which do not allow for specific in-depth analysis. For example, we were not able to identify whether a patient died because of liver-related reasons vs other causes or whether SBP was acquired in-hospital vs present on admission. We have adjusted for these limitations by either performing chart review or by using 2 very large and different cohorts with consistent results. Because this is not an randomized controlled trial, it is possible that patients in our cohort who were initiated on SecSBPPr had unmeasured risk factors for additional episodes of SBP; however, we adjusted for the most associated risk factors available and the difference between the 2 groups remained.

In the chart reviews, the appropriateness of SBP diagnoses and SecSBPPr initiation were largely validated. The culture data are sparse and likely reflect clinical practice (VA-CDW) and database limitations (TriNetX). We only used a 2-year window to determine pattern changes over time and only have data through 2019 because of the COVID-19 pandemic. The use of *ICD* codes alone to capture SBP, while having high positive predictive values as demonstrated from our chart review, may suffer from low sensitivity. This implies that there could be many patients not included in our analysis who did have SBP. Again, this is a limitation of the database and retrospective nature of the study that may have lowered our sample size. However, because all patients included in the analysis had these codes, the high positive predictive values demonstrate that the subset of patients that were analyzed was very likely to truly have SBP.

Finally, there was the potential for misclassification among the exposure and the outcome because of patients receiving prophylaxis measures or SBP diagnoses outside of the VA and TriNetX networks. However, misclassification in the exposure would theoretically lower the observed effect size of prophylaxis on SBP recurrence because the "no-prophylaxis" group would contain a mixture of patients who were actually receiving treatment and those who were truly not on SecSBPPr. Thus, the fact that we observed strong and significant effects, even in the presence of this misclassification, is a strength.

Misclassification in the outcome because of patients receiving an SBP diagnosis out-of-network would lower the observed SBP

recurrence rates. We hypothesize that this bias would occur in both treatment groups—but may be more prominent in the no-prophylaxis group because these patients were more likely to be receiving SecSBPPr out-of-network as well.

We conclude that in patients newly diagnosed with SBP, initiation of SecSBPPr is associated with a 63%–68% higher rate of SBP recurrence in multivariable analysis compared with those who were not started on prophylaxis in 2 large multicenter cohorts. The higher rate of SBP recurrence with SecSBPPr increased over time, likely because of increasing prevalence of resistant organisms. Careful reconsideration of SecSBPPr in patients with SBP in areas of high baseline resistance to fluoroquinolones and TMP-SMX is needed.

CONFLICTS OF INTEREST

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Specific author contributions: J.S.B.: conceptualized and was involved in all aspects. N.R.P., S.Y.T., M.N., S.S., and E.F.: were involved in data extraction and analysis. J.D.M., J.G.O., and R.K.S.: were involved in critical revisions. All authors approved the final version.

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Study Highlights

WHAT IS KNOWN

- ✓ Secondary prophylaxis to prevent recurrence of spontaneous bacterial peritonitis (SBP) has been recommended in several guidelines.
- ✓ Changing demographics and bacteriology could impact the effectiveness of secondary SBP prophylaxis, but a national perspective is needed.
- ✓ In a national veterans cohort, primary SBP prophylaxis was associated with worse outcomes because of antibiotic resistance, which led to the VA discouraging this practice systemwide. However, the data regarding secondary SBP prophylaxis are unclear.

WHAT IS NEW HERE

- ✓ Almost 50% of patients with cirrhosis with SBP across 2 large US-based national cohorts (veterans and TriNetX) evaluated from 2009 to 2019 were not initiated on secondary SBP prophylaxis, which gave us an opportunity to analyze the effectiveness over time in preventing recurrence.
- ✓ In >11,000 patients regardless of veterans or nonveterans, the use of secondary SBP prophylaxis worsened the rate of SBP recurrence without changes in mortality compared with those who were not on it over a 2-year and 6-month timepoint after the SBP episode.
- ✓ The SBP recurrence rate with secondary SBP prophylaxis worsened as time progressed in both cohorts and could be linked with worsening antibiotic resistance, and the utility of this practice should be reconsidered.

REFERENCES

1. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74(2):1014–48.
2. Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-chronic liver failure clinical guidelines. Am J Gastroenterol 2022;117(2):225–52.
3. Karvellas CJ, Bajaj JS, Kamath PS, et al. AASLD Practice Guidance on acute-on-chronic liver failure and the management of critically ill patients with cirrhosis. Hepatology. 2024;79(6):1463–502.
4. Patel N, Silvey S, O'Leary JG, et al. Early paracentesis is associated with better prognosis compared with late or no-paracentesis in hospitalized veterans with cirrhosis and ascites. Liver Transpl 2023;29(9):919–27.
5. Shamsaddini A, Gillevet PM, Acharya C, et al. Impact of antibiotic resistance genes in gut microbiome of patients with cirrhosis. Gastroenterology 2021;161(2):508–21.e7.
6. Patel VC, Lee S, McPhail MJW, et al. Rifaximin-α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. J Hepatol 2022;76(2):332–42.
7. Bajaj JS, Pena-Rodriguez M, La Reau A, et al. Longitudinal transkingdom gut microbial approach towards decompensation in outpatients with cirrhosis. Gut 2023;72(4):759–71.
8. Bajaj JS, Liu EJ, Kheradman R, et al. Fungal dysbiosis in cirrhosis. Gut 2018;67(6):1146–54.
9. https://www.jointcommission.org/resources/patient-safety-topics/infection-prevention-and-control/antibiotic-stewardship/. Accessed June 17, 2024.
10. Komolafe O, Roberts D, Freeman SC, et al. Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis in people with liver cirrhosis: A network meta-analysis. Cochrane Database Syst Rev 2020;1:CD013125.
11. Badal BD, Silvey S, Dragilev L, et al. Primary prophylaxis for spontaneous bacterial peritonitis is linked to antibiotic resistance in the Veterans Health Administration. Hepatology 2023;77(6):2030–40.
12. Bajaj JS, Tandon P, O'Leary JG, et al. Outcomes in patients with cirrhosis on primary compared to secondary prophylaxis for spontaneous bacterial peritonitis. Am J Gastroenterol 2019;114(4):599–606.
13. Mucke MM, Mayer A, Kessel J, et al. Quinolone and multidrug resistance predicts failure of antibiotic prophylaxis of spontaneous bacterial peritonitis. Clin Infect Dis 2020;70(9):1916–24.
14. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol 2009;170(2):244–56.
15. Heuman DM, Mihas AA, Habib A, et al. MELD-XI: A rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl 2007;13(1):30–7.
16. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406–60.
17. Gines P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: Results of a double-blind, placebo-controlled trial. Hepatology 1990;12(4 Pt 1):716–24.
18. Moreau R, Elkrief L, Bureau C, et al. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology. 2018;155(6):1816–27 e9.
19. Fernandez J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2019;70(3):398–411.
20. Piano S, Tonon M, Angeli P. Changes in the epidemiology and management of bacterial infections in cirrhosis. Clin Mol Hepatol 2021;27(3):437–45.
21. Prado V, Hernandez-Tejero M, Mucke MM, et al. Rectal colonization by resistant bacteria increases the risk of infection by the colonizing strain in critically ill patients with cirrhosis. J Hepatol 2022;76(5):1079–89.
22. Bajaj JS, Kamath PS, Reddy KR. The evolving challenge of infections in cirrhosis. N Engl J Med 2021;384(24):2317–30.
23. Bajaj JS, Rodriguez MP, Fagan A, et al. Impact of bacterial infections and spontaneous bacterial peritonitis prophylaxis on phage-bacterial dynamics in cirrhosis. Hepatology 2022;76(6):1723–34.
24. Bajaj JS, Shamsaddini A, Acharya C, et al. Multiple bacterial virulence factors focused on adherence and biofilm formation associate with outcomes in cirrhosis. Gut Microbes 2021;13(1):1993584.
25. Runyon BA, AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: An update. Hepatology 2009;49(6):2087–107.

26. National Healthcare Quality and Disparities Report: Chartbook on Healthcare for Veterans. Rockville, MD: Agency for Healthcare Research and Quality (US); 2020.
27. Mellinger JL, Moser S, Welsh DE, et al. Access to subspecialty care and survival among patients with liver disease. Am J Gastroenterol 2016; 111(6):838–44.
28. Piano S, Bunchorntavakul C, Marciano S, et al. Infections in cirrhosis. Lancet Gastroenterol Hepatol 2024;9(8):745–57.
29. de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII–renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–74.
30. Munoz KA, Ulrich RJ, Vasan AK, et al. A Gram-negative-selective antibiotic that spares the gut microbiome. Nature 2024;630(8016):429–36.
31. Baggio D, Ananda-Rajah MR. Fluoroquinolone antibiotics and adverse events. Aust Prescr 2021;44(5):161–4.
32. Kemnic TR, Coleman M. Trimethoprim Sulfamethoxazole. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513232/. Accessed July 1, 2024.
33. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases. Sulfamethoxazole-Trimethoprim. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547937/. Accessed July 1, 2024.
34. Chirapongsathorn S, Sukeepaisarnjaroen W, Treeprasertsuk S, et al. Characteristics of drug-induced liver injury in chronic liver disease: Results from the Thai Association for the Study of the Liver (THASL) DILI registry. J Clin Transl Hepatol 2023;11(1):88–96.
35. Trebicka J, Hernaez R, Shawcross DL, et al. Recent advances in the prevention and treatment of decompensated cirrhosis and acute-on-chronic liver failure (ACLF) and the role of biomarkers. Gut 2024;73(6): 1015–24.