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Original Article

# Use of prokinetic agents or antibiotics is associated with the occurrence of spontaneous bacterial peritonitis in cirrhotic patients

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**Abstract**

*Background*: Prokinetics have been shown to improve intestinal bacterial overgrowth and dysmotility in cirrhotic patients. Antibiotics are suggested for high risk patients for prophylaxis of spontaneous bacterial peritonitis (SBP). However, limited studies have investigated the association of SBP and these medications. We examined the association of prokinetics or antibiotics use and the first episode of SBP development in patients with cirrhosis.
*Methods*: We conducted a case-crossover study using the Taiwanese National Health Insurance Research Database from 2001 to 2010. A total of 129 cirrhotic patients with SBP were identified (defined as International Classification of Disease-Ninth Revision-CM codes: 571.xx for cirrhosis; 567.2, 567.8, and 567.9 for ascites; 789.5 for SBP). We investigated the short term (defined as 14-day period) effect of prokinetic agents or antibiotics use on SBP development using conditional logistic regressions with the adjustment of potential confounders.
*Results*: The results suggested that prokinetic agents or antibiotics use during the 14 days before SBP were associated with an increased risk of SBP [adjusted odds ratio (OR) = 3.2, 95% confidence interval (CI): 1.02–10.04 for prokinetic agents; and adjusted OR = 2.95, 95% CI: 1.05–5.23 for antibiotics]. In dose analysis, the use of prokinetic agents more than 0.5 defined daily dose was more commonly found in the case period without a statistical difference (adjusted OR = 3.637; 95% CI: 0.69–19.13).
*Conclusion*: The results demonstrated an increased risk of primary SBP development among cirrhotic patients with prokinetic agents or antibiotics use. It is important to closely monitor those patients for the occurrence of SBP.


*Keywords:* Antibiotics; Liver cirrhosis; Prokinetic agent; Spontaneous bacterial peritonitis

## 1. Introduction

Spontaneous bacterial peritonitis (SBP) is the most frequent bacterial infection in cirrhotic patients and accounting for 10–30% of bacterial infection in hospitalized patients.[1,2] In-hospital mortality of the first episode of SBP ranges from 10% to 50%.[3,4] In patients who survive an episode of SBP, the cumulative recurrence rate at 1 year is approximately 70%[5] and the probability of survival at 1 year after an episode of SBP is 30–50%. Since the occurrence of SBP markedly worsens the prognosis in cirrhotic patients, numerous researches have studied the risk factors associated with the occurrence of SBP. In addition to the well established risk factors such as advanced liver dysfunction,[6,7] gastrointestinal (GI) bleeding and low ascitic protein,[8,9] medications may also affect the chances of developing SBP. The use of acid suppressive therapy including proton pump inhibitors (PPIs) or H2 receptor antagonist (H2RA) has been found to have a potential association with the occurrence of

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SBP.[10–12] In contrast, non-selective β-blockers may prevent SBP[13] through improvement in chemotaxis and killing capacity in experimental setting.[14] Prophylatic antibiotics, norfloxacin was suggested in patients who recover from an episode of SBP[15] and for high risk patients with low protein ascites and severe liver insufficiency or renal dysfunction[16] to reduce the incidence of primary SBP. However, the use of systemic antibiotics 30 days before SBP diagnosed has been found to be associated with the first episode of SBP caused by gram-positive bacteria,[17] and therefore, the benefit or risk of antibiotics use on SBP in patients without high risk requires further studies to evaluate.

Bacterial translocation (BT), which has been postulated to be the cause of SBP in cirrhosis,[18] is promoted by the presence of intestinal bacterial overgrowth (IBO) and disturbances in bowel motility.[19] Since both IBO and slow orocecal transit occur in cirrhotic patients, it is assumed that the administration of a prokinetic agent might decrease the incidence of IBO by normalizing the delayed small intestinal transit time, and thus reduce the risk of BT in these patients. Cisapride, a serotonin 5-HT4 receptor agonist and intestinal prokinetic drug, has been shown to decrease IBO and BT in experimental cirrhosis,[20,21] and reverse altered small intestinal motility and IBO in cirrhotic patients,[22] but was abandoned due to cardiac side effects. Although prokinetic agent combined with antibiotics has been shown to decrease the incidence of SBP in high risk patients,[23] scant information exists on the protective effect of prokinetic agent alone on SBP. In this study, we performed a case crossover study to investigate the association of prokinetic agents or antibiotics with the risk of first SBP episode in cirrhotic patients with ascites by utilizing the National Health Insurance Research Database (NHIRD) in Taiwan.

## 2. Methods

### 2.1. Database

This study used the National Health Insurance Research Database, which consists of de-identified secondary data derived from the claims and registry data of the Taiwan National Health Insurance (NHI) Program. The Taiwan NHI program began in 1995 and enrolled 99.6% of the inhabitants of the country. Each year, the Taiwan National Health Research Institute (NHRI) collects and publishes the registry and claims data released by the NHI. This study used the cohort datasets containing all the claim and registry data of 1,000,000 randomly sampled beneficiaries who were alive during 2005. These random samples have been confirmed by the NHRI to be representative of population. All the data were de-identified by the National Health Research Institute before publication. This study was exempt from full review by the Institutional Review Board in Taipei Veterans General Hospital since all the data was de-identified and encrypted, and informed consent was waived.

### 2.2. Study population

From 2001 to 2010, we identified all patients admitted with both the diagnosis of ascites (567.2, 567.8, and 567.9 in ICD-9-CM code) and peritonitis (789.5 in ICD-9-CM code) from the cohort database who were 18–80 years in age and have previous diagnosis of liver cirrhosis (571.xx in ICD-9-CM code) at least two times in the outpatient claim data or 1 time in inpatient claim data. We excluded the patients with hepatic cellular carcinoma (155.xx in ICD-9-CM code), GI tract or peritoneal carcinoma (150.xx–154.xx, 156.xx–159.xx), malignant neoplasm of other specified sites (199.xx), inflammatory bowel disease (555.xx–556.xx). Patients with disease and procedures that may cause non-spontaneous bacterial peritonitis were also excluded. In this study, patients having diagnosis of hollow organ perforation (GI tract, biliary, urinary bladder) or vascular insufficiency of bowels or surgery for GI tract anastomosis before the first time admission with diagnosis of both ascites and peritonitis (index admission) were excluded. The actual dosage for the drugs given in the parenteral route is not acquirable in the cohort datasets and those patient using parenteral agents were discarded in case-cross over analyses.

### 2.3. Case-crossover design

The study used case-crossover design to examine the effects of prokinetic agents or antibiotics on the first episode of SBP development in cirrhotic patient. Individual patient serve as control of his or her own in this study. The case period is defined as 1–14 days before the index date. The control period is defined as 29–42 days before the index date, the 15–28 days interval are skipped to avoid carry-over effect. The odds ratio (OR) of SBP in the case period as compared to that in the control period can then be calculated.

### 2.4. Drug exposure

The main exposures of our study are prokinetic agents and antibiotics. According to anatomic therapeutic chemical (ATC) classification system, we identified drug types as alizapride, bromopride, cisapride, domperidone, metoclopramide, and mosapride for prokinetic agents; and A07AA in ATC classification system as antibiotics.

We selected drug types, dosage, route of administration, date of prescriptions, prescribed length of drug usage, and total amount of drug prescribed from the cohort datasets. We calculated drug usage by drug type as total numbers of defined daily dose (TDDD), total usage days (total prescribed length of drug usage in days), averaged daily DDD (ADDD, TDDD divided by the total usage day).

### 2.5. Covariates

We also identified the usage of drugs that may modify the risk of SBP including antifungal drugs (D01B), antimycobacterials (J04), antivirals (J05), PPI (A02BC), H2RA (A02BA), β-blockers (C07), and antacids (A02A) of each patient from the cohort datasets. The diagnosis that associated the SBP including GI bleeding (456.0, 456.20, 530.7, 530.82, 531.0x, 531.4x, 532.0x, 532.2x, 532.4x, 533.0x, 533.2x,533.4x, 534.0x, 534.4x, 535.0x, 535.1x, 535.2x, 535.x1, 537.83, 562.02, 562.03, 562.12,

5652.13, 569.3, 569.85, 578.9 in ICD-9-CM codes), common infections including upper respiratory tract infection (465.x), pneumonia (480–487.0), urinary tract infection (599.0), GI tract infection (008–009.3, 574.0, 574.3, 574.6, 574.8, 576.1, 577.0–1, 572.0), biliary tract infection (574.0, 574.3, 574.8, 576.1), pancreatitis (577.0–1), liver abscess (572.0) and the date was identified and was determined as in the case period or control period accordingly.

### 2.6. Comorbid conditions

We identified comorbidities for each patient when they had a specific diagnosis at two or more outpatient visits or at one or more inpatient admissions including ischemic heart disease (410.xx–414.xx in ICD-9-CM codes), stroke (430.xx–438.xx), diabetes mellitus (250.xx), atrial fibrillation (427.3x), chronic obstructive pulmonary disease (493.2x), hyponatremia (276.1), chronic renal failure (585), hepatic coma (572.2), variceal bleeding (456.0 and 456.20), peptic ulcer bleeding (531.0x, 531.4x, 532.0x, 532.2x, 532.4x, 533.0x, 533.2x, 533.4x), and previous abdominal surgeries. The Charlson comorbidity index was calculated for baseline comorbid condition severity and divided as having an index score of 0, 1–2, 3–4, and ≥5.[24,25]

### 2.7. Statistical analysis

Statistical analysis was performed with R 2.15.2 (R foundation for Statistical Computing, Vienna, Austria). Conditional logistic regression was used to calculate the OR. The OR of exposure of prokinetics agent or antibiotics between the case and control periods was expressed at 95% confidence intervals (CI), and a p value less than 0.05 was considered as significant. We adjusted the prokinetics, antibiotics, PPIs, H2RAs, β-blockers, GI tract bleeding, and infections for adjusted OR in multivariate analysis. We also performed a potential dose–response relationship study between SBP and prokinetic agents exposure by using average defined daily dose (ADDD) as a continuous variable in conditional logistic regression. Adjusted OR was calculated after adjusting comorbidities and covariates.

Sensitivity analyses were performed by (1) Comparing the different control period. (2) Since there are possible incubation period for the peritonitis, we also performed sensitivity test by using the interval at 15–28 days before index date as case period comparing with multiple respective control periods.

## 3. Results

### 3.1. Demographics

We identified 243 cirrhosis patients with ascites, aged 18–80 years, hospitalized for SBP from 2001 to 2010. After excluding those who met the exclusion criteria, a total of 129 patients were included in the final analysis (Fig. 1). The demographics of enrolled patients were shown in Table 1. There were 75% male with average age 54 ± 11 years. About 37% of the patients (n = 48) had used prokinetic agents within 12 months of SBP (Table 2) and antibiotics were prescribed in 69% of the patients (n = 90). PPIs, H2RA, antacids, β-blockers and antiviral drugs were used in 33%, 42%, 54%, 28% and 6% of the patients, respectively.

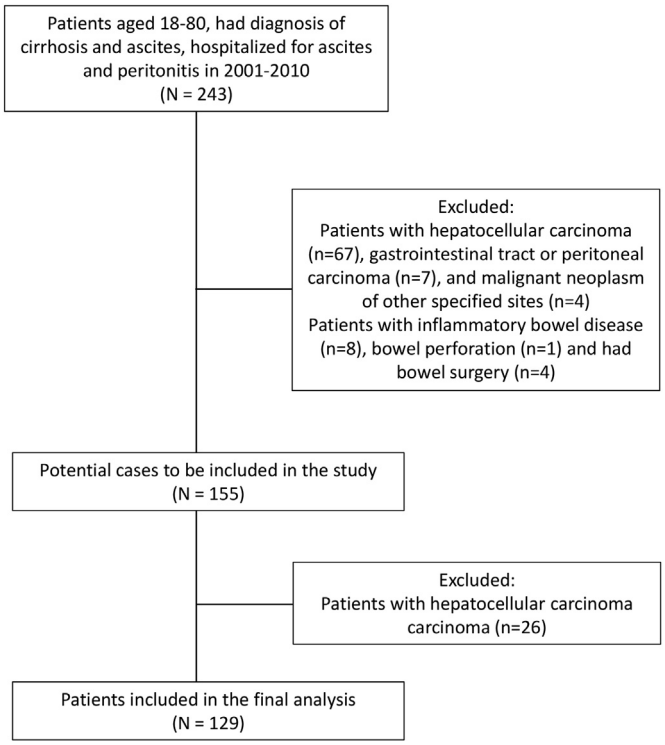


Fig. 1. Flow of the study cohort.

Among patients who received antibiotics, 14 had episodes of infections and 57 had GI tract bleeding due to variceal or peptic ulcer hemorrhage. For patients who used antibiotics, there was no difference in demographics (including gender, age, cormobidities, encephalopathy, variceal bleeding, hyponatremia, and peptic ulcer bleeding) between patients with and those without infections (Supplementary Table 1).

Table 1
Patient demographics.

| Characteristics | N (%) | |
|---|---|---|
| Male gender, | 97 | (75.2) |
| Age, mean (SD) | 54 | (11.3) |
| Ischemic heart disease | 25 | (19.4) |
| Myocardial infarction | 1 | (0.8) |
| Stroke | 14 | (10.9) |
| Diabetes mellitus | 40 | (31.0) |
| Atrial fibrillation/flutter | 4 | (3.1) |
| Chronic obstructive pulmonary disease | 2 | (1.6) |
| Chronic renal failure | 11 | (8.5) |
| Hepatic encephalopathy | 42 | (32.6) |
| Variceal bleeding | 39 | (30.2) |
| Hyponatremia | 6 | (4.7) |
| Peptic ulcer bleeding | 32 | (24.8) |
| Charlson comorbidity index score | | |
| 1–2 | 58 | (45.0) |
| 3–4 | 63 | (48.8) |
| ≥5 | 8 | (6.2) |

SD = standard deviation.

Table 2
Use of medications and presence of confounding factors within 12 months of first episode of spontaneous bacterial peritonitis.

| Drugs Type | N (%) | |
|---|---|---|
| Prokinetic agents | 48 | (37.2) |
| Antibiotics | 90 | (69.0) |
| Proton pump inhibitors | 43 | (33.3) |
| H2-receptor antagonist | 54 | (41.9) |
| Antacids | 70 | (54.3) |
| β-blockers | 36 | (27.9) |
| Antiviral drugs | 8 | (6.2) |
| Urinary tract infection | 5 | (3.9) |
| Respiratory tract infection | 4 | (3.1) |
| Hepato-pancreatico-biliary infection | 6 | (4.7) |
| Biliary or urinary tract infection | 11 | (8.5) |
| Any infection | 14 | (10.9) |

### 3.2. Risk analysis

Prokinetic agents were more likely to be used in the case period than the control period with an OR of 1.38 (95% CI: 0.55−3.42, $p = 0.493$) and antibiotics were also used more often in the case period (OR:1.67, 95% CI:0.88−3.16, $p = 0.118$) (Table 3).

Multivariate analysis have shown that after adjusting medications, GI bleeding and infections, there was no significant difference in prokinetic agents or antibiotics use between the case period and control period. No single drug (prokinetics, antibiotics, PPIs, H2RA, β-blockers or antiviral drugs) or character was an independent risk factor for SBP (Table 3 and Supplementary Table 2).

### 3.3. Sensitivity analysis

However, in sensitivity analysis by using different control period intervals, antibiotics were used significantly more frequently in the case period than in the control period in using 43−56 days, and 57−70 days, with the adjusted OR being 2.31 (95% CI: 1.01−5.29, $p = 0.048$) and 2.35 (95% CI: 1.05−5.23, $p = 0.037$), respectively (Table 4). Prokinetic agents were used more frequently in the case period of 1−14 days than in the control period of 57−70 days (adjusted OR = 3.20, 95% CI: 1.02−10.04, $p = 0.046$). The difference was not significant when comparing 1−14 days to 43−56 days.

When using 15−28 days as the case period, the prokinetic agents and antibiotics were still used more frequently in the case period, but did not reach statistical significant difference as compared with control periods. PPI, H2RA, or antacids use, GI tract bleeding and infection events showed variable odds ratio of more or less than 1.00 in the case period and control period, the difference was not significant.

### 3.4. Dose analysis

In dose analysis, the use of prokinetic agents more than 0.5 DDD is more commonly found as compared with those less than 0.5 DDD in the case period than control period in most of the interval settings (OR = 0.15−3.664), no statistical difference ($p = 0.127$−$0.992$) can be found (Table 5). The impacts of TDDD and total usage days of prokinetic agents were also analyzed and the results showed that neither the TDDD or the total usage day was associated with the risk of SBP development (Supplementary Tables 3 and 4).

## 4. Discussion

This study demonstrated that short-term use of prokinetic agents or antibiotics was associated with an increased risk of first episode SBP development in cirrhotic patients with ascites. Prokinetic agents and antibiotics were more likely to be used in the case period than the control period in sensitivity analysis using different time widows. The effects of PPIs, H2RA, β-blockers or antiviral drugs administration on SBP could not be proved in our study.

Previous studies have investigated the effects of prokinetic agents on IBO in experimental cirrhosis and cirrhotic patients.[20−22] However, limited studies have conducted an evaluation of the effects on SBP of prokinetic agent use. Though the short-term use of cisapride for 1 week was found to decrease IBO in cirrhotic patients,[20] we found an association of an increased risk of SBP with prokinetic agents use in the present study. Besides, the use of prokinetics more than 0.5

Table 3
Conditional logistic regression of drug risk for spontaneous bacterial peritonitis.

| Drug Types | Period | | | | Crude OR | 95% CI | p | Adjusted OR | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | Only in case period | Only in control period | Both in case and control period | Neither in case nor control period | | | | | | |
| 1−14 days (case period) vs. 29−42 days (control period) | | | | | | | | | | |
| Prokinetic agents | 11 | 8 | 6 | 104 | 1.38 | (0.55−3.42) | 0.493 | 1.54 | (0.58−4.11) | 0.385 |
| Antibiotics | 25 | 15 | 6 | 83 | 1.67 | (0.88−3.16) | 0.118 | 1.81 | (0.88−3.70) | 0.104 |
| Proton pump inhibitors | 9 | 5 | 13 | 102 | 1.80 | (0.60−5.37) | 0.292 | 0.77 | (0.02−26.80) | 0.887 |
| H2-receptor antagonists | 7 | 9 | 3 | 110 | 0.78 | (0.29−2.09) | 0.618 | 0.36 | (0.01−10.06) | 0.549 |
| Antacids | 12 | 10 | 18 | 89 | 1.20 | (0.52−2.78) | 0.670 | 1.81 | (0.05−62.28) | 0.742 |
| β -blockers | 6 | 6 | 10 | 107 | 1.00 | (0.32−3.10) | 1.000 | 0.92 | (0.27−3.07) | 0.887 |
| GI tract bleeding | 2 | 1 | 0 | 126 | 2.00 | (0.18−22.06) | 0.571 | 1.79 | (0.09−34.06) | 0.698 |
| Infection | 2 | 4 | 0 | 123 | 0.50 | (0.09−2.73) | 0.423 | 0.35 | (0.05−2.24) | 0.281 |

OR = odds ratio; CI = confidence intervals.

Table 4
Sensitivity analysis.

| Drug Types | Period | | | | Crude OR | 95% CI | p | Adjusted OR | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | Only in case period | Only in control period | Both in case and control period | Neither in case nor control period | | | | | | |
| 1–14 days (case period) vs. 43–56 days (control period) | | | | | | | | | | |
| Prokinetic agents | 12 | 7 | 5 | 105 | 1.71 | (0.67–4.35) | 0.257 | 1.76 | (0.65–4.81) | 0.269 |
| Antibiotics | 22 | 12 | 9 | 86 | 1.83 | (0.91–3.70) | 0.606 | 2.31 | (1.01–5.29) | 0.048 |
| Proton pump inhibitors | 9 | 7 | 13 | 100 | 1.29 | (0.48–3.45) | 0.618 | 0.18 | (0.01–3.10) | 0.239 |
| H2-receptor antagonists | 6 | 10 | 4 | 109 | 0.60 | (0.22–1.65) | 0.323 | 0.11 | (0.01–2.03) | 0.138 |
| Antacids | 12 | 12 | 18 | 87 | 1.00 | (0.45–2.23) | 1.000 | 4.21 | (0.22–78.91) | 0.336 |
| β-blockers | 8 | 4 | 8 | 109 | 2.00 | (0.60–6.64) | 0.258 | 2.36 | (0.62–8.95) | 0.205 |
| GI tract bleeding | 2 | 1 | 0 | 126 | 2.00 | (0.18–22.06) | 0.571 | 5.35 | (0.31–92.80) | 0.249 |
| Infection | 2 | 3 | 0 | 124 | 0.67 | (0.11–3.99) | 0.657 | 0.40 | (0.05–3.36) | 0.398 |
| 1–14 days (case period) vs. 57–70 days (control period) | | | | | | | | | | |
| Prokinetic agents | 14 | 4 | 3 | 108 | 3.50 | (1.15–10.63) | 0.027 | 3.20 | (1.02–10.04) | 0.046 |
| Antibiotics | 26 | 13 | 5 | 85 | 2.00 | (1.03–3.89) | 0.041 | 2.35 | (1.05–5.23) | 0.037 |
| Proton pump inhibitors | 13 | 6 | 9 | 101 | 2.17 | (0.82–5.70) | 0.117 | 0.90 | (0.09–9.26) | 0.927 |
| H2-receptor antagonists | 7 | 8 | 3 | 111 | 0.88 | (0.32–2.41) | 0.796 | 0.50 | (0.04–6.80) | 0.600 |
| Antacids | 15 | 9 | 15 | 90 | 1.67 | (0.73–3.81) | 0.226 | 2.01 | (0.14–29.63) | 0.610 |
| β-blockers | 8 | 5 | 8 | 108 | 1.60 | (0.52–4.89) | 0.410 | 1.07 | (0.31–3.71) | 0.912 |
| GI tract bleeding | 2 | 4 | 0 | 123 | 0.50 | (0.09–2.73) | 0.423 | 0.35 | (0.04–2.85) | 0.329 |
| Infection | 1 | 2 | 1 | 125 | 0.50 | (0.05–5.51) | 0.571 | 0.45 | (0.03–9.56) | 0.607 |
| 15–28 days (case period) vs. 43–56 days (control period) | | | | | | | | | | |
| Prokinetic agents | 8 | 6 | 6 | 109 | 1.33 | (0.46–3.84) | 0.594 | 1.33 | (0.42–4.26) | 0.630 |
| Antibiotics | 15 | 16 | 5 | 93 | 0.94 | (0.46–1.90) | 0.857 | 1.00 | (0.44–2.26) | 0.994 |
| Proton pump inhibitors | 4 | 4 | 16 | 105 | 1.00 | (0.25–4.00) | 1.000 | 0.53 | (0.03–8.28) | 0.654 |
| H2-receptor antagonist | 2 | 9 | 5 | 113 | 0.22 | (0.05–1.03) | 0.054 | 0.11 | (0.00–2.59) | 0.169 |
| Antacids | 4 | 9 | 21 | 95 | 0.44 | (0.14–1.44) | 0.177 | 1.75 | (0.07–42.53) | 0.732 |
| β-blockers | 6 | 4 | 8 | 111 | 1.50 | (0.42–5.32) | 0.530 | 2.49 | (0.51–12.27) | 0.261 |
| GI tract bleeding | 2 | 1 | 0 | 126 | 2.00 | (0.18–22.06) | 0.571 | 3.65 | (0.13–102.35) | 0.446 |
| Infection | 3 | 3 | 0 | 123 | 1.00 | (0.20–4.96) | 1.000 | 1.07 | (0.18–6.51) | 0.939 |
| 15–28 days (case period) vs. 57–70 days (control period) | | | | | | | | | | |
| Prokinetic agents | 11 | 4 | 3 | 111 | 2.75 | (0.88–8.64) | 0.083 | 2.61 | (0.79–8.55) | 0.114 |
| Antibiotics | 16 | 14 | 4 | 95 | 1.14 | (0.56–2.34) | 0.715 | 1.11 | (0.45–2.76) | 0.817 |
| Proton pump inhibitors | 9 | 4 | 11 | 105 | 2.25 | (0.69–7.31) | 0.177 | 2.10 | (0.19–23.78) | 0.548 |
| H2-receptor antagonists | 3 | 7 | 4 | 115 | 0.43 | (0.11–1.66) | 0.220 | 0.36 | (0.02–5.67) | 0.465 |
| Antacids | 8 | 7 | 17 | 97 | 1.14 | (0.41–3.15) | 0.796 | 1.23 | (0.06–24.58) | 0.890 |
| β-blockers | 7 | 6 | 7 | 109 | 1.17 | (0.39–3.47) | 0.782 | 1.31 | (0.39–4.43) | 0.661 |
| GI tract bleeding | 2 | 4 | 0 | 123 | 0.50 | (0.09–2.73) | 0.423 | 0.45 | (0.06–3.18) | 0.424 |
| Infection | 2 | 2 | 1 | 124 | 1.00 | (0.14–7.10) | 1.000 | 0.93 | (0.07–11.65) | 0.953 |

OR = odds ratio; CI = confidence intervals.

DDD is more commonly found as compared with those less than 0.5 DDD in the case period in dose analysis. Several plausible factors might explain the observed finding. First, some patients have atypical symptoms of SBP instead of fever or abdominal pain, and 30% patients have ileus as the presentation at the time diagnosis of SBP.[26] Thus the usage of prokinetic agents would be biased toward case period, and the result would be biased toward non-difference, since the hypothesis of our study is that prokinetics are more commonly seen in the control period that case period. Second, in addition to IBO, there are other factors related to the development of SBP in cirrhotic patients including increased intestinal permeability and impaired immunity[18] those cannot be reversed by prokinetic agents. Third, it is known that underlying indications of prokinetic agents are those disorders related to reduced GI motility and the use of prokinetics may reflect GI dysmotility in enrolled patients. We have applied a case-crossover study design, which means each study subject

Table 5
Analysis for dose for prokinetics more than 0.5 DDD compared with less than 0.5 DDD in different interval.

| Interval | Crude OR | 95% CI | p | Adjusted OR | 95% CI | p |
|---|---|---|---|---|---|---|
| 1–14 days vs. 29–42 days | 1.667 | (0.40–6.97) | 0.484 | 1.944 | (0.42–8.98) | 0.395 |
| 1–14 days vs. 43–56 days | 1.400 | (0.44–4.41) | 0.566 | 1.608 | (0.48–5.41) | 0.443 |
| 1–14 days vs. 57–70 days | 3.500 | (0.73–16.85) | 0.118 | 3.637 | (0.69–19.13) | 0.127 |
| 15–28 days vs. 43–56 days | 1.250 | (0.34–4.66) | 0.739 | 0.993 | (0.25–4.01) | 0.992 |
| 15–28 days vs. 57–70 days | 5.000 | (0.58–42.80) | 0.142 | 5.442 | (0.52–56.94) | 0.157 |
| 15–28 days vs. 71–84 days | 1.333 | (0.30–5.96) | 0.706 | 0.915 | (0.19–4.44) | 0.912 |

DDD = defined daily dose; OR = odds ratio; CI = confidence intervals.

serves as his/her own control and the bowel motility has low variability during the study period (1−70 days). However, it is likely that the observed increased risk of SBP might be still partially explained by potential confounding factors by reduced GI motility.

In addition to prokinetic agents, we also analyzed the association between the uses of antibiotics and the risk of SBP. Notably, the use of antibiotics is associated with an increased risk of first episode of SBP development in our sensitivity analysis. Innate and adaptive immunity dysfunction is a major component of decompensated cirrhosis.[27] Bacterial infections are more common in cirrhotic patients compared to healthy controls and continue to be a leading cause of acute on chronic liver failure and mortality.[28] Liver-related complications including GI bleeding, hepatic encephalopathy, hypervolemic hyponatremia and acute kidney injury could be triggered by bacterial infections[29] and thus early diagnosis and initiation of antibiotic therapy is essential in cirrhotic patients with bacterial infections. As a result, patients with cirrhosis consume more antibiotics than the general population. In our study, 69% patients had taken antibiotics within 12 months of the first episode of SBP. The main indications of antibiotics prescription were infection and prophylaxis of GI bleeding. The use of antibiotics may reflect the higher frequency of bacterial infection and GI bleeding caused by impaired underlying immune status or poor liver function. Taken together, the associations between the prokinetic agents or antibiotics and the risk of SBP may result from the underlying GI dysmotility or impaired immune status in enrolled cirrhotic patients. Therefore, the prescription of prokinetic agents or antibiotics may be considered as a warning sign and the physician should pay more attention to those high risk patients for the occurrence of SBP.

The use of PPI has been proposed to facilitate IBO and thus to contribute to pathological BT. Besides, it has been suggested that acid-suppressive drugs may inhibit neutrophil function and natural killer cell activity based on experimental data.[30] Previous studies have found the association between PPI use or acid-suppressive therapy (including PPI and H2RA) and the development of SBP in cirrhotic patients with ascites.[10−12,31] In our study, cirrhotic patients with short-term PPI or antacid use had a higher risk of SBP, even though the results were not statistically significant. In addition, we did not find an increased risk of SBP in patients with H2RA use. Those findings may be related to the small sample size of enrolled patients. Therefore, physicians still should be careful in prescribing acid-suppressive drugs including PPI and H2RA in patients with cirrhosis and ascites.

Several limitations should be noted in this study. First, we acknowledge that a causal relationship between prokinetics or antibiotics use and the risk of SBP cannot be inferred based on an observational study, so a prospective study may be needed to further determine the causal relationship. Second, since this is the secondary database analysis, there may be coding error or under coding of covariate condition, which would result in misclassification; however, this issue is most like to occur in equal probability both in the case period and control period, thus the relationship between the case period and control period and the variables such as the odds ratio of comorbidities between case and control period were not be affected. Third, several potential confounding factors that might affect the risk of SBP development, such as ascetic protein level, severity of liver dysfunction and genetic risk factors, are not available in the NHIRD. However, since we used a case-crossover design in this study, these confounding factors were unlikely to have changed during such a relatively short study period.

In conclusion, we observed the association between short-term prokinetic agents or antibiotics use and an increased risk of first episode SBP development in cirrhotic patients with ascites. The prescription of prokinetic agents or antibiotics may be considered as a warning sign and physicians need to closely monitor those patients for the occurrence of SBP. Future prospective studies are needed to assess the role of prokinetic agents or antibiotics in SBP development.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jcma.2018.01.013.

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