Alternative Therapy for Spontaneous Bacterial Peritonitis Prevention: Does RI-faximin Work, Work, Work?

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Learning Objectives

1. Describe the pathophysiology of spontaneous bacterial peritonitis (SBP)
2. Identify risk factors for developing SBP
3. Select guideline recommended treatment and preventative therapies for SBP
4. Determine appropriate clinical situations to use rifaximin for SBP prevention
Background Information

I. Cirrhosis
   a. Progressive replacement of normal hepatic cells with fibrous scar tissue
   b. Irreversible loss of hepatocytes (see appendix A for pathophysiology)
II. Eighth leading cause of death in the United States and 13th leading cause of death worldwide
   a. Risk of death is 4.7 to 9.7 times higher than the general population
   b. Mortality associated with degree of hepatic impairment and severity
III. Associated with an annual direct cost exceeding $2 billion and indirect costs exceeding $10 billion
IV. Etiologies of cirrhosis
   a. Most common
      i. Alcohol
         a. Duration and amount dependent
         b. Typically develops after 10 or more years of daily ingestion of 6-8 drinks daily
      ii. Viral infections
         a. Hepatitis C and B viruses cause inflammation
         b. Contracted via intravenous (IV) drug use, sexual contact or may be idiopathic
   b. Less common
      i. Non-alcoholic steatohepatitis (NASH)
      ii. Genetic/congenital
      iii. Idiopathic
V. Common complications of cirrhosis
   a. Portal hypertension: hepatic venous pressure gradient (HVPG) exceeding 10 to 12 mmHg
   b. Hepatic encephalopathy (HE): characterized by impaired cognition, confusion, and changes in behavior
   c. Ascites: accumulation of fluid in the peritoneal space
   d. Varices: development of collateral vessels in the esophagus, stomach and rectum
   e. Hepatorenal syndrome (HRS): renal failure due to reduced renal perfusion secondary to systemic vasodilation and intravascular depletion
   f. Spontaneous bacterial peritonitis (SBP): infection of the ascitic fluid that occurs in the absence of bowel or peritoneal perforation and in the presence of cirrhosis

Epidemiology of SBP

I. Accounts for 10-30% of infections in hospitalized cirrhotic patients
II. In-hospital mortality ranges from 10-50%
   a. In hospital mortality in cirrhosis with septic shock exceeds 70%
III. SBP occurrence is an important prognosis factor as the overall 1 year mortality rate after the first episode is 30-93%
IV. High probability of recurrence and increases with time in patients not receiving appropriate preventative therapy

![Figure 1: Probability of SBP Recurrence without Prophylaxis](image-url)
Pathophysiology\textsuperscript{1,4-5,8,10,12}

I. Factors enhancing bacterial translocation
   a. Decreased bile acid concentration
   b. Decreased small-bowel motility
   c. Increased intestinal mucosal permeability

II. Impaired immunological defense mechanisms
    a. Defective neutrophil functions and decreased phagocytic activity
    b. Decreased opsonic and complement activity
    c. Patient factors
       i. Malnutrition
       ii. Excessive alcohol intake

III. Pathogens\textsuperscript{8}
    a. Most Common
       i. Escherichia coli (E.coli)
       ii. Klebsiella pneumoniae
       iii. Streptococcus species
    b. Less Common
       i. Pseudomonas species
       ii. Staphylococcus species
       iii. Enterococcus species
       iv. Acinetobacter baumanii

IV. Factors associated with SBP\textsuperscript{4-5}
    a. Elevated bilirubin
    b. Low ascitic fluid protein
    c. Thrombocytopenia
    d. Renal impairment
    e. Hyponatremia
    f. Low levels of 25-hydroxy vitamin D
    g. Variceal hemorrhaging
    h. Previous SBP

Diagnosis and Clinical Manifestations\textsuperscript{1,4-8,11-13}

I. Clinical manifestations
   a. Asymptomatic
   b. Worsening encephalopathy
   c. Worsening renal failure
   d. Abdominal pain and tenderness
   e. Nausea and diarrhea
   f. Ileus
   g. Leukocytosis
   h. Fever

II. Diagnosis
    a. Paracentesis: collection of ascitic fluid for analysis
       i. Polymorphonuclear (PMN) cell count $\geq$ 250/mm\textsuperscript{3}
       ii. Culture and sensitivity: positive in approximately 40% of SBP infections
Table 1: Guideline recommendations for treatment of SBP

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommended Antibiotics</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association for the Study of Liver Diseases (AASLD) Practice Guideline</td>
<td>Empiric antibiotic therapy with an intravenous third-generation cephalosporin, preferably cefotaxime 2 g every 8 hours. (Level A) Oral ofloxacin (400 mg twice per day) can be considered a substitute for intravenous cefotaxime in inpatients without prior exposure to quinolones, vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dL. (Level BIIa)</td>
<td>Minimum of 5 days</td>
</tr>
<tr>
<td>European Association For The Study Of The Liver (EASL) Guideline</td>
<td>First line antibiotic treatment are the third-generation cephalosporins (Level AI). Alternative options include amoxicillin/clavulanic acid and quinolones such as ciprofloxacin or ofloxacin. (Level BI).</td>
<td>Minimum of 5 days</td>
</tr>
<tr>
<td>British Society of Gastroenterology (BSG) Guideline</td>
<td>Third generation cephalosporins such as cefotaxime have been most extensively studied in the treatment of SBP and have been shown to be effective. (Level AIIa)</td>
<td>Minimum of 5 days</td>
</tr>
</tbody>
</table>

I. Community-acquired SBP
   a. Historically caused by gram negative pathogens, specifically enterobacteriaceae
   b. 3rd generation cephalosporins, are preferred for empiric therapy
   c. Quinolone therapy may be administered depending on susceptibility and decreased severity of illness

II. Hospital-acquired SBP and patients at high risk for multidrug resistant pathogens
   a. The following factors are associated with resistant infections
      i. Infection acquired during hospitalization
      ii. SBP prophylaxis therapy
      iii. Exposure to broad spectrum antibiotics
      iv. Frequent hospitalizations
      v. Previous infections with multi-resistant pathogens
   b. To ensure adequate coverage of potential pathogens, broader spectrum agents may be preferable:
      i. Cefepime
      ii. Piperacillin-tazobactam
      iii. Carbapenems

III. Albumin administration
   a. Reduces development of irreversible renal impairment and mortality
   b. Recommended in SBP if patients have one of the following:
      i. Serum creatinine > 1 mg/dL
      ii. Blood urea nitrogen > 30 mg/dL
      iii. Total bilirubin > 4 mg/dL
   c. Dosed as 1.5 g of albumin/kg within 6 hours of detection and 1 g/kg on the third day

SBP Prevention

I. Reduces incidences of SBP and mortality
   a. Relative risk reduction (RRR) of 51% in the overall incidence of SBP
   b. RRR of 35% in mortality for patients receiving prophylactic antibiotics
II. Patient populations\textsuperscript{13}
   a. Hospitalized patients with variceal hemorrhage receive a 7 day course of antibiotics therapy
   b. History of SBP
   c. Patients with low-protein status with renal dysfunction or severe liver dysfunction

   Severe liver dysfunction
   i. Child-Pugh score of $> 9$ (see appendix B)
   ii. Serum bilirubin of $> 3$mg/dL

   Renal dysfunction
   iii. Serum creatinine $> 1.2$mg/dL
   iv. Blood urea nitrogen $> 25$mg/dL
   v. Serum sodium $< 130$mEq/L

III. Guideline recommended antibiotics for SBP prevention (see appendix C for studies)
   a. Norfloxacin
      i. Drug of choice
      ii. 400 mg by mouth daily
      iii. No longer available in the United States
   b. Ciprofloxacin
      i. Used in lieu of norfloxacin
      ii. 500 mg by mouth daily
         a. Weekly dose studied, however, this is not recommended due to potential shortened time to resistance development
   c. Sulfamethoxazole/trimethoprim
      i. Recommended alternative to ciprofloxacin therapy
      ii. 800 mg/160 mg by mouth 5 days during the week

<p>| Table 2: Guideline recommended agents for prevention\textsuperscript{13-15} |
|----------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th><strong>Agent</strong></th>
<th>AASLD</th>
<th>EASL</th>
<th>BSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>(Level AI)</td>
<td>(Level AI)</td>
<td>(Level Blb)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>---</td>
<td>(Level All)</td>
<td>(Level Blb)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>(Level AI)</td>
<td>(Level All)</td>
<td>---</td>
</tr>
<tr>
<td>-trimethoprim</td>
<td></td>
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</table>

| Table 3: Disadvantages to current preventative therapy\textsuperscript{9,19-20,34} |
|---------------------------------|-----------------|
| Warnings and Precautions        |                  |
| Fluoroquinolones (FQN)          |                  |
| Tendon rupture, central nervous system effects, QTc prolongation, hepatotoxicity photosensitivity and hemolytic anemia | Hematological adverse effects, dermatological reactions, hepatic necrosis, hyperkalemia, and sulfonamide allergy reaction |
| Interactions                    |                  |
| Theophylline, cation containing products (i.e. antacids, milk, supplements), QTc prolonging agents and phosphate binders | CYP2C9 and CYP3A4 inducers and inhibitors, concomitant QTc prolonging agents, methotrexate, phenytoin and warfarin |
| Supra-Infections                |                  |
| ▪ Associated with development of *clostridium difficile* associated diarrhea (CDAD) and fungal infections |                  |
| ▪ Associated with high mortality and increased hospital costs in the setting of cirrhosis |                  |
| Resistance and Pathogen Selection |                  |
| ▪ Prophylaxis (specifically FQN) is risk factor for multi-drug resistance pathogens |                  |
| ▪ Approximately 30 percent of gram negative pathogens are resistant to FQN therapy and sulfamethoxazole-trimethoprim |                  |
| ▪ Associated with decreased response to empiric antibiotic therapy for SBP treatment |                  |
| ▪ Emergence of gram positive SBP infections |                  |

IV. Proposed solutions for disadvantages to antibiotic prophylaxis\textsuperscript{9}
   a. Continue to improve risk stratification to ensure antibiotics are appropriately prescribed
      a. Rotating antibiotics to prevent resistance development
      b. Use of alternative broad spectrum antibiotics with minimal systemic absorption, such as rifaximin
Background for Rifaximin\textsuperscript{9,22-31}

I. History
   a. Discovered and patented by Alfa Wassermann in the 1980s
   b. Structural analog of rifampin and belongs to the rifamycin antimicrobial family
   c. First approved in Italy in 1987 for treatment of gastrointestinal diseases and received US FDA approval in 2004 for traveler’s diarrhea
   d. Approved for the reduction of overt hepatic encephalopathy recurrence and irritable bowel syndrome by the FDA in 2010 and 2015, respectively

II. Mechanism of action
   a. Elicits bacterial killing activity by binding to the beta subunit of bacterial DNA-dependent RNA polymerase to inhibit bacterial RNA synthesis

III. Spectrum of activity
   a. In vitro activity demonstrated against gram-positive, gram-negative, aerobic and anaerobic bacteria to include \textit{E.coli}
   b. Minimum inhibitory concentration (MIC) for 90% killing ranges from 16-128 mcg/mL as demonstrated in bacterial isolates from traveler’s diarrhea\textsuperscript{22,24-25}
   c. High fecal concentrations of up to 8000 mcg/g in human hosts\textsuperscript{24-25}
   d. Ramos, et al. compared MICs of rifaximin to norfloxacin in patients with advanced cirrhosis admitted to a hospital in Spain
      i. MIC\textsubscript{90} for rifaximin was lower for the majority of the tested organisms, including multidrug resistant pathogens (see appendix D)\textsuperscript{26}

IV. Pharmacokinetics(PK)/pharmacodynamics(PD)
   a. Absorption
      i. Minimal gastrointestinal absorption, but absorption increases with severity of hepatic impairment
         a. Child-Pugh Class C had 20-fold higher area under the curve compared to a healthy subject in PK studies
   b. Metabolism and Excretion
      i. Absorbed medication undergoes CYP3A4 metabolism
      ii. Approximately 96% of the medication is excreted unchanged in the feces
      iii. Negligible renal excretion

V. Potential advantages for SBP prevention with rifaximin\textsuperscript{4,22-23}
   a. Possibly reduced resistance
      i. Reduced expression of virulence factors
      ii. Negligible bioavailability
   b. More favorable adverse effect profile and minimal interactions

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Indication} & \textbf{Dosing} \\
\hline
Traveler’s diarrhea & 200 mg three times daily (TID) for 3 days \\
\hline
Reduction of overt HE occurrence & 550 mg twice daily (BID) \\
\hline
Irritable bowel syndrome & 550 mg TID for 14 days \\
\hline
Non FDA Approved Indications and Dosing & \\
\hline
CDAD & 200 to 400 mg 2 to 3 times daily for 14 days \\
\hline
Treatment of HE & 400 mg TID for 5 to 10 days \\
\hline
\end{tabular}
\caption{Current FDA approved indications and dosing\textsuperscript{22}}
\end{table}
c. Vlachogiannakos, et al. demonstrated improved outcomes with rifaximin. 
   i. Investigated the effect of rifaximin on the long-term prognosis of patients with alcohol-related hepatic cirrhosis and ascites
   ii. Prospective cohort continuation trial of patients assigned to decontamination with rifaximin or no therapy
      a. Patients included from a prospective trial that evaluated rifaximin in intestinal decontamination and liver hemodynamics
      b. Included patients who had an adequate hemodynamic response (decrease in HVPG)
   iii. Patient cohorts were matched by age, sex, and Child-Pugh grade and followed for up to 5 years
   iv. Included 69 patients, 23 receiving rifaximin and 46 not on rifaximin
   v. Results
      a. 5-year survival: 61% with rifaximin versus 13.5% with controls (p=0.012)
      b. Variceal bleeding: 35% with rifaximin versus 59.5% with controls (p=0.011)
      c. Free of HE: 68.5% with rifaximin versus 53% with controls (p=0.034)
      d. Free of HRS: 95.5% with rifaximin versus 49% with controls (p=0.037)
      e. SBP occurrence: 4.5% with rifaximin versus 46% with controls (p=0.027)

VI. Disadvantages to rifaximin use
   a. Cost: Average Wholesale Pricing
      i. $3665.16 for 30 day supply of 400 mg TID
      ii. $2328.76 for 30 day supply of 550 mg BID
   a. Currently dosed 400mg three times daily, which may reduce compliance
   b. Limited clinical information regarding long-term rifaximin and resistance development in cirrhosis patients

Clinical Controversy: Can rifaximin be prescribed to prevent SBP?

Literature Review

Table 6: Rifaximin Studies in SBP

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Patient population</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanouneh et al.</td>
<td>Retrospective</td>
<td>404 patients for primary prevention</td>
<td>Rifaximin versus no therapy</td>
</tr>
<tr>
<td>Lutz et al.</td>
<td>Prospective</td>
<td>152 patients for primary and secondary prevention</td>
<td>Rifaximin versus systemic antibiotics versus no therapy</td>
</tr>
<tr>
<td>Mostafa et al.</td>
<td>Prospective randomized</td>
<td>70 patients for secondary prevention</td>
<td>Rifaximin versus norfloxacin</td>
</tr>
<tr>
<td>Shamseya et al.</td>
<td>Prospective cohort</td>
<td>86 patients with HCV-related liver cirrhosis for primary or secondary prevention</td>
<td>Rifaximin versus norfloxacin</td>
</tr>
<tr>
<td>Assem et al.</td>
<td>Prospective randomized</td>
<td>334 cirrhotic patients for primary prevention</td>
<td>Rifaximin versus norfloxacin versus alternating norfloxacin and rifaximin</td>
</tr>
<tr>
<td>Elfert et al.</td>
<td>Prospective randomized-controlled</td>
<td>262 cirrhotic patients for secondary prevention</td>
<td>Rifaximin versus norfloxacin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To detect the impact of rifaximin on the occurrence and characteristics of SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, single-center, cohort of patients admitted to an inpatient internal medicine service</td>
</tr>
</tbody>
</table>
| Population | Inclusion:  
- Older than 17 years of age  
- Undergoing diagnostic paracentesis  
- Diagnosis of ascites due to cirrhosis  

Exclusion:  
- Non-cirrhotic ascites  
- Combined rifaximin and systemic antibiotics  
- Presence of permanent peritoneal catheter |
| Intervention | Group 1: No prophylaxis  
Group 2: Rifaximin 400 mg PO TID  
Group 3: PO Systemic antibiotics |
| Endpoint | Compare the frequency of SBP amongst the different groups |
| Methods |  
- 152 patients underwent at least one diagnostic paracentesis during the study period  
- Concomitant medications and baseline characteristics were collected  
- Patients had follow up examinations at the time of discharge from the hospital and if patients represented to the department within 16 weeks  
- SBP was diagnosed based on PMN cell count |
| Statistical Analysis |  
- For quantitative data, the Wilcoxon-Mann-Whitney-U test and the Kruskal-Wallis-test  
- For qualitative data, the Fisher’s exact test  
- Kaplan-Meier plot was used along with the log-rank test for mortality |
| Results | Baseline Characteristics  
| Characteristic | No Prophylaxis (n=108) | Rifaximin (n=27) | Systemic Antibiotics (n=17) | P values |
| Age | 60 (28-86) | 61 (38-74) | 62 (51-77) | 0.75 |
| Male | 74 (69%) | 10 (60%) | 17 (100%) | 0.63 |
| Child-Pugh A/B/C | 1%/57%/43% | 0%/33%/67% | 12%/47%/41% | 0.02 |
| MELD Score | 17 (6-41) | 18 (8-41) | 15 (6-26) | 0.35 |
| Lactulose | 59 (55%) | 27 (100%) | 11 (65%) | 0.001 |
| Previous SBP | 8 (7%) | 4 (15%) | 15 (89%) | <0.001 |
| Previous HE | 9 (8%) | 27 (100%) | 2 (12%) | <0.001 |
| Acute gastrointestinal bleeding | 10 (9%) | 4 (15%) | 1 (6%) | 0.67 |

- SBP occurred in:  
  - 24 (22%) patients in group 1  
  - 8 (30%) patients in group 2  
  - 0 (0%) patients in group 3  

Absorbed systemic antibiotics significantly reduced SBP occurrence compared to no prophylaxis (p=0.04) and rifaximin (p=0.02)

Features of SBP Infections  
| Characteristic | No prophylaxis (n=24) | Rifaximin (n=8) | P value |
| Child Pugh C | 15 (63%) | 8 (100%) | 0.07 |
| Previous HE | 5 (21%) | 8 (100%) | <0.0001 |
| Previous SBP | 6 (25%) | 8 (100%) | 0.000 |
| Proton Pump Inhibitor Therapy | 20 (84%) | 8 (100%) | 0.55 |
| Positive Culture | 11 (46%) | 4 (50%) | 1.0 |
| Resistance to 3rd generation cephalosporins | 5 (46%) | 1 (25%) | 0.6 |
| Multi-drug resistance | 5 (46%) | 1 (25%) | 0.48 |
| Nosocomial Infection | 13 (54%) | 3 (38%) | 0.69 |
Culture positive SBP
- No prophylaxis group were significant for *E.coli* (45%), *Enterococcus* (27%), *Serratia* (9%), *Staphylococcus* (9%), and *Enterobacter* (9%)
- Rifaximin group were significant for *Klebsiella* (75%), and *Pasteurella* (25%)

Author’s Conclusion
Rifaximin pre-treatment did not lead to a reduction in SBP occurrence in hospitalized patients with advanced liver disease. Further controlled studies need to be conducted to determine what patient populations will benefit from rifaximin.

Critique
Strengths:
- Compared rifaximin use to systemic therapy and no preventive therapy
- Patients received HE dosing, 400 mg PO TID of rifaximin

Limitations:
- Small, single center study
- Short follow up time
- Statistically significant differences in baseline characteristics
- Compliance assessment
- Did not assess safety

Reviewer’s Assessment
- Rifaximin did not reduce SBP in this study, however, the rifaximin group patient’s cirrhosis were more severe according to Child-Pugh scoring
- With limited information on how long patients were on rifaximin prior to the study and compliance, efficacy of rifaximin and long term effectiveness is unknown


Purpose
Test the efficacy of rifaximin in comparison with norfloxacin for the prevention of SBP in HCV related cirrhosis

Design
Prospective longitudinal cohort study

Population
Inclusion:
- Admitted to Hepatology and Gastroenterology unit at Alexandria University
- Previous SBP episode
- High risk for SBP (see SBP prevention section for criteria)

Exclusion:
- Non-HCV cirrhosis etiologies
- Recent abdominal surgery
- Abdominal malignancy
- Portal vein thrombosis
- Splenectomy
- Hypersensitivity to study medications

Intervention
Group 1: Rifaximin 400 mg PO TID
Group 2: Norfloxacin 400 mg PO daily

Endpoints
- Primary: Occurrence of SBP
- Secondary: Hepatocellular carcinoma (HCC), compliance failure, death or liver transplantation and overall survival (1-year of treatment without facing study endpoints)

Methods
- 86 patients with HCV-related cirrhosis were enrolled in the study and matched by age, sex and Child-Pugh Score
- Patients were evaluated monthly to assess compliance failure and complications
  - Compliance failure was defined as patients who were lost to follow up or discontinuation of study medication for more than 7 days
- Patients who developed SBP or other complications were treated according to the AASLD guidelines
- SBP was diagnosed in accordance with AASLD guidelines
  - PMN > 250 cells/mL in ascitic fluid
- Patients were followed for up to 1 year

Statistical Analysis
- Statistical analysis of data performed deemed significant at an alpha of 0.05
- Categorical data was tested with Chi-square and Fisher’s Exact test
- Quantitative variables were evaluated with t-test and Mann Whitney test
- Kaplan-Meier analysis was used to examine survival and compliance
## Results

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Rifaximin (n=43)</th>
<th>Norfloxacin (n=43)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50.3 + 9.0</td>
<td>52.7 + 8.5</td>
<td>0.425</td>
</tr>
<tr>
<td>Male</td>
<td>34 (79.1%)</td>
<td>34 (74.4%)</td>
<td>1</td>
</tr>
<tr>
<td>Child-Pugh B/C</td>
<td>10(23.3%)/33(76.7%)</td>
<td>10(23.3%)/33(76.7%)</td>
<td>1</td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>31 (72.1%)</td>
<td>34 (79.1%)</td>
<td>0.808</td>
</tr>
</tbody>
</table>

### Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rifaximin (n=43)</th>
<th>Norfloxacin (n=43)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HE</td>
<td>2 (4.7%)</td>
<td>4 (9.3%)</td>
<td>0.676</td>
</tr>
<tr>
<td>SBP</td>
<td>2 (4.7%)</td>
<td>6 (14.0%)</td>
<td>0.265</td>
</tr>
<tr>
<td>Months to SBP development</td>
<td>9.5 (9.0-10.0)</td>
<td>5.0 (3.0-10.0)</td>
<td>0.129</td>
</tr>
<tr>
<td>Culture positive</td>
<td>0/2 (0%)</td>
<td>1/6 (16.7%)</td>
<td>1</td>
</tr>
<tr>
<td>HRS</td>
<td>1 (2.3%)</td>
<td>1 (2.3%)</td>
<td>1</td>
</tr>
<tr>
<td>HCC</td>
<td>5 (11.6%)</td>
<td>4 (9.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>3 (7.0%)</td>
<td>4 (9.3%)</td>
<td>1</td>
</tr>
</tbody>
</table>

- Rates of compliance were lower with rifaximin (81.4%) compared to norfloxacin (90.7%) 
  - Months to compliance failure was statistically lower with rifaximin (6.75 ± 1.28) compared to norfloxacin (9.0 ± 0.82); p=0.010 
  - Most common reasons for difficulty with adherence to rifaximin were dosing frequency and cost 
- Gastrointestinal ADE were reported in both the norfloxacin (27.9%) and rifaximin (25.6%) 
- Headaches, dizziness and asthenia were reported in 9.3% of the patients receiving norfloxacin and weakness and fatigue were reported in 4.7% of the patients receiving rifaximin 
- No statistically significant differences with regards to ADE

### Author’s Conclusion

Rifaximin is comparable to norfloxacin and an appropriate alternative for long term primary and secondary SBP prophylaxis. Financial burden and compliance with regimen pose an issue with rifaximin therapy. Larger randomized controlled trials are needed to confirm results evaluate dosing considerations and long term efficacy and safety.

### Critique

**Strengths:**
- Compared rifaximin use to standard therapy 
- Included a high risk patient population and patients with a history of SBP 
- Longer study duration

**Limitations:**
- Single center study 
- Study design and selection bias 
- Statistical evaluation 
- Did not explain means of assessing compliance 
- Study medications were purchased by patients 
- Did not collect concomitant medications for cirrhosis

### Reviewer’s Assessment

- Rifaximin is similar to norfloxacin in reducing incidences of SBP 
- Compliance, however, is a limitation to therapy and should be considered prior to initiation 
- Agree with author’s that results should be confirmed with larger trials and evaluation of dosing to improve compliance should be considered

| **Purpose** | Compare the safety and efficacy of rifaximin versus norfloxacin for the secondary prevention of SBP in patients with liver cirrhosis and ascites |
| **Design** | Randomized, controlled, 48-week, open-label, parallel-group trial conducted in Egypt |
| **Population** | Inclusion:  
  - Diagnosis ascites  
  - Previous episode of SBP  
  - Admitted to Tanta University Hospital  
Exclusion:  
  - Active gastrointestinal bleeding  
  - Hepatocarcinoma or other malignancies  
  - Bacterial infection at admission  
  - Recent quinolone use within 6 weeks  
  - HIV  
  - HE  
  - Pregnancy or lactation  
  - Allergy to study drugs |
| **Intervention** | Group 1: Rifaximin 400 mg PO TID  
Group 2: Norfloxacin 400 mg PO daily |
| **Endpoints** | Occurrence of SBP at 6 months, mortality and ADE |
| **Methods** |  
  - After discharge, eligible patients were randomized to study arms  
  - Patients were followed monthly for 6 months to rule out complications and adverse effects from medication use  
  - Ascitic fluid examination was performed at months 2 and 6  
  - If SBP infection occurred, study medications were discontinued and treatment initiated  
  - Compliance assessed through discussion with patients and medication envelopes  
  - Duration of study, including recruitment and follow up, was 18 months |
| **Statistical Analysis** |  
  - Sample size of 262 patients required to assess primary endpoint with a power of 80%  
  - Two sided significance level of 5% and a non-inferiority margin of 15%  
  - Student’s t-test was used to compare independent samples from two groups when the samples were not normally distributed  
  - Mann-Whitney U-test to compare independent samples when the samples were not normally distributed  
  - X²-test was performed to compare categorical data |
| **Results** | 290 cirrhotic patients with ascites and a previous episodes of SBP were evaluated inclusion  
  - 262 patients met inclusion and were randomized  
  - 28 patients did not complete follow up in the rifaximin group  
    - Lost to follow up (n=6)  
    - Consent withdrawn (n=4)  
    - Death (n=18)  
  - 39 patients did not complete follow up in the norfloxacin group  
    - Lost to follow up (n=4)  
    - Consent withdrawn (n=3)  
    - Death (n=32)  

<table>
<thead>
<tr>
<th><strong>Baseline Characteristics</strong></th>
<th>Rifaximin (n=131)</th>
<th>Norfloxacin (n=131)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.78 ± 7.52</td>
<td>54.12 ± 7.19</td>
<td>0.783</td>
</tr>
<tr>
<td>Male</td>
<td>74 (56.5%)</td>
<td>68 (51.9%)</td>
<td>0.535</td>
</tr>
<tr>
<td>Child-Pugh Score (B/C)</td>
<td>58(44.3%)/73(55.7%)</td>
<td>63(48.1%)/68(51.9%)</td>
<td>0.620</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (13.7%)</td>
<td>21 (16.03%)</td>
<td>0.728</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>27.4 g/L</td>
<td>28.1 g/L</td>
<td>0.104</td>
</tr>
<tr>
<td>Platelets</td>
<td>100.4</td>
<td>98.04</td>
<td>0.715</td>
</tr>
<tr>
<td>Total ascitic fluid protein</td>
<td>11 g/L</td>
<td>10 g/L</td>
<td>0.817</td>
</tr>
</tbody>
</table>
### Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rifaximin (n=103)</th>
<th>Norfloxacin (n=92)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>4 (3.88%)</td>
<td>13 (14.13%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Culture Positive</td>
<td>2 (50%)</td>
<td>8 (61.5%)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>18 (13.74%)</td>
<td>32 (24.43%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Tolerated medication</td>
<td>88 (85.4%)</td>
<td>59 (64.1%)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

- Both positive cultures in the rifaximin arm were significant for *E. coli*
- Cultures from the norfloxacin group were significant for *E. coli* (n=3), *pseudomonas* (n=1), and gram positive cocci (n=4)
- All positive culture SBP episodes were resistant to norfloxacin
- No serious adverse effects were reported; gastrointestinal adverse effects were most commonly reported for both rifaximin and norfloxacin

### Author’s Conclusion

Rifaximin was more effective than norfloxacin in treatment of secondary prevention; in addition, HE related mortality and adverse effects were fewer in the rifaximin group.

### Critique

**Strengths:**
- Randomized controlled trial
- Excluded patients with recent antibiotic use
- Larger group of patients

**Limitations:**
- Single center
- Did not report concomitant medications for disease state
- Assessed compliance, but did not report finding
- Excluded HE patients

### Reviewer’s Assessment

- Rifaximin is safe and effective for secondary SBP prevention
- Limitations to the study, however, include unknown compliance, which may be a limiting factor in rifaximin’s use

### Conclusion

#### I. Summary

a. SBP is the most common infection in cirrhosis patients and is associated with increased mortality
b. Available guidelines recommend patients with a history of SBP and those with risk factors for development receive long term antibiotics to prevent occurrence
c. Long term antibiotic use increases patients risk for the following:
   i. ADE specific to recommended agents
   ii. Increased risk for CDAD and supra-infections
   iii. Development of resistance and decreased response to first line treatment therapy

#### II. Recommendations

a. Based on current literature, rifaximin does prevent episodes of SBP and may offer an alternative to standard therapy
b. Would not recommend rifaximin as a first line agent at this time due to:
   i. Limited information regarding long term efficacy and resistance development
   ii. Patient cost and compliance

- Would consider rifaximin 400 mg TID as prophylaxis therapy in the following clinical situations:
  i. Patients being initiated on rifaximin for HE who also require SBP prevention
  ii. Patients who develop resistance to guideline recommended therapies
  iii. Patients who experience severe ADE or have a contraindication to first line therapies
d. Further studies investigating alternative dosing intervals for rifaximin may be beneficial in improving compliance and cost
References


22. Xifaxan (rifaximin) [prescribing information]. Raleigh, NC: Salix Pharmaceuticals Inc; November 2015.


Hepatic fibrosis is the wound healing response of the liver to many causes of chronic injury. Iterative injury causes inflammatory damage, matrix deposition, parenchymal cell death and angiogenesis leading to progressive fibrosis, which eventually leads to cirrhosis. Once cirrhosis is established, the potential for reversing this process is decreased and complications develop. If the cause of fibrosis is eliminated, resolution (that is, complete reversal to near-normal liver architecture) of early hepatic fibrosis can occur. In cirrhosis, although resolution is not possible, regression fibrosis improves clinical outcomes.

Appendix B:

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 Point</th>
<th>2 Point</th>
<th>3 Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>Less than 2</td>
<td>2-3</td>
<td>Greater than 3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Greater than 3.5</td>
<td>2.8-3.5</td>
<td>Less than 2.8</td>
</tr>
<tr>
<td>Prothrombin (seconds prolonged)/INR</td>
<td>1-3/ Less than 1.8</td>
<td>4-6/ 1.8-2.3</td>
<td>Greater than 6/ Greater than 2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>States 1-2</td>
<td>Stages 2-3</td>
</tr>
</tbody>
</table>

5 to 6 points = A  7 to 9 points = B  10-15 points = C
## Appendix C:

### Clinical trials for SBP prophylaxis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Incidence of SBP</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gines et al. 1990</td>
<td>Secondary prophylaxis</td>
<td>Norfloxacin 400mg daily versus placebo</td>
<td>12.5% versus 35% (p&lt;0.05)</td>
<td>17.5% versus 25% Non-significant (NS)</td>
</tr>
<tr>
<td>Soriano et al. 1991</td>
<td>Primary and secondary prophylaxis</td>
<td>Norfloxacin 400mg daily versus no treatment</td>
<td>0% versus 22.6% (p&lt;0.05)</td>
<td>7.5% versus 12.8% NS</td>
</tr>
<tr>
<td>Singh et al. 1995</td>
<td>Primary and secondary prophylaxis</td>
<td>Sulfamethoxazole(800mg)/trimethoprim(160mg) 5 days per week versus no treatment</td>
<td>3.3% versus 23.3% (p&lt;0.05)</td>
<td>6.6% versus 20% NS</td>
</tr>
<tr>
<td>Rolachon et. al. 1995</td>
<td>Primary and secondary prophylaxis</td>
<td>Ciprofloxacin 500mg weekly versus placebo</td>
<td>3.6% versus 21.8% (p&lt;0.05)</td>
<td>14.3% versus 18.8% NS</td>
</tr>
<tr>
<td>Novella et al. 1997</td>
<td>Primary prophylaxis</td>
<td>Norfloxacin 400mg daily versus norfloxacin 400mg daily ONLY during hospitalization</td>
<td>1.8% versus 17% (p&lt;0.05)</td>
<td>23.2% versus 30.2% NS</td>
</tr>
<tr>
<td>Grange et al. 1998</td>
<td>Primary prophylaxis</td>
<td>Norfloxacin 400mg daily versus placebo</td>
<td>0% versus 9.4% (p&lt;0.05)</td>
<td>15% versus 18.5% NS</td>
</tr>
<tr>
<td>Bauer et al. 2002</td>
<td>Secondary prophylaxis</td>
<td>Norfloxacin 400mg daily versus rufloxacin 400mg weekly</td>
<td>15% versus 30.7% NS</td>
<td>7.5% versus 12.8% NS</td>
</tr>
<tr>
<td>Alvarez et al. 2005</td>
<td>Primary and secondary prophylaxis</td>
<td>Norfloxacin 400mg daily versus sulfamethoxazole(800mg)/trimethoprim(160mg) 5 days per week</td>
<td>9.4% versus 16% NS</td>
<td>21.9% versus 20% NS</td>
</tr>
<tr>
<td>Fernandez et al. 2007</td>
<td>Primary prophylaxis</td>
<td>Norfloxacin 400mg daily versus placebo</td>
<td>5.7% versus 30.3% (p&lt;0.05)</td>
<td>28.6% versus 39.3% NS</td>
</tr>
<tr>
<td>Terg et al. 2008</td>
<td>Primary prophylaxis</td>
<td>Ciprofloxacin 500mg daily versus placebo</td>
<td>4% versus 14% NS</td>
<td>12% versus 28%</td>
</tr>
<tr>
<td>Lontos et al. 2014</td>
<td>Primary and secondary prophylaxis</td>
<td>Norfloxacin 400mg daily versus sulfamethoxazole(800mg)/trimethoprim(160mg) 5 days per week</td>
<td>5% versus 5% NS</td>
<td>27.5% versus 17.5% NS</td>
</tr>
</tbody>
</table>
Appendix D:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Number of Isolates</th>
<th>Rifaximin (mcg/mL)</th>
<th>Norfloxacin (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS- S. epidermidis</td>
<td>10</td>
<td>≤ 0.007</td>
<td>64</td>
</tr>
<tr>
<td>MR- S. epidermidis</td>
<td>20</td>
<td>≤ 0.007</td>
<td>32</td>
</tr>
<tr>
<td>MS-S. aureus</td>
<td>20</td>
<td>≤ 0.007</td>
<td>128</td>
</tr>
<tr>
<td>MR- S. aureus</td>
<td>20</td>
<td>0.06</td>
<td>&gt;128</td>
</tr>
<tr>
<td>PS-E. faecalis</td>
<td>20</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>PR- E. faecium</td>
<td>16</td>
<td>16</td>
<td>&gt;128</td>
</tr>
<tr>
<td>E. coli</td>
<td>20</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>MDR-E. coli</td>
<td>23</td>
<td>16</td>
<td>128</td>
</tr>
<tr>
<td>MDR-Klebsiella pneumoniae</td>
<td>27</td>
<td>64</td>
<td>128</td>
</tr>
<tr>
<td>MDR- Proteus mirabilis</td>
<td>5</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>MDR-Citrobacter, Morganella and Enterobacter</td>
<td>5</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>MDR-P. aeruginosa</td>
<td>13</td>
<td>16</td>
<td>128</td>
</tr>
<tr>
<td>MDR-A. baumannii</td>
<td>14</td>
<td>4</td>
<td>&gt;128</td>
</tr>
</tbody>
</table>

MDR, multidrug-resistant; MS, methicillin-susceptible; MR, methicillin-resistant; PS, penicillin-susceptible; PR, penicillin-resistant
### Appendix E:

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Patient population</th>
<th>Treatments</th>
<th>SBP Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanouneh et al. 30</td>
<td>Retrospective</td>
<td>404 patients for primary prevention</td>
<td>Rifaximin (n=49) 400 mg TID for HE or lactulose intolerance and non-rifaximin group (n=355)</td>
<td>11% with rifaximin versus 32% in control group (p=0.002) Transplant free survival benefit with rifaximin (72% versus 57%; p=0.045)</td>
</tr>
<tr>
<td>Lutz et al. 32</td>
<td>Prospective</td>
<td>152 patients for primary and secondary prevention</td>
<td>Rifaximin (n=27) 400 mg TID prescribed for HE, systemic antibiotics (n=17) and no prophylaxis (n=108)</td>
<td>SBP occurred in 30% with rifaximin versus 22% with no prophylaxis versus 0% with systemic antibiotics (p=0.04 for systemic antibiotics versus no prophylaxis and p=0.02 for systemic antibiotics versus rifaximin)</td>
</tr>
<tr>
<td>Mostafa et al. 36</td>
<td>Prospective randomized</td>
<td>70 patients for secondary prevention</td>
<td>Rifaximin (n=40) 800 mg daily versus norfloxacin (n=30) 400mg daily</td>
<td>0% with rifaximin versus 16.6% with norfloxacin; no p value reported</td>
</tr>
<tr>
<td>Shamseya et al. 35</td>
<td>Prospective cohort</td>
<td>86 patients with HCV-related liver cirrhosis for primary or secondary prevention</td>
<td>Rifaximin (n=43) 400 mg TID versus norfloxacin (n=43) 400mg daily</td>
<td>4.7% with rifaximin versus 14% with norfloxacin developed SBP (p=0.265) No significant difference in mortality</td>
</tr>
<tr>
<td>Assem et al. 33</td>
<td>Prospective randomized</td>
<td>334 cirrhotic patients for primary prevention</td>
<td>Rifaximin (n=82) 500 mg BID versus norfloxacin (n=78) 400mg daily versus alternating norfloxacin and rifaximin (n=79)</td>
<td>SBP free: 68.3% with rifaximin versus 56.4% with norfloxacin versus 74.7% with combined (statistically significant between norfloxacin and combined group) No significant differences in mortality</td>
</tr>
<tr>
<td>Elfert et al. 34</td>
<td>Prospective randomized-controlled</td>
<td>262 cirrhotic patients for secondary prevention</td>
<td>Rifaximin (n=131) 400 mg TID versus norfloxacin (n=131) 400 mg daily</td>
<td>SBP occurrence: 3.88% with rifaximin versus 14.33% with the norfloxacin (p=0.04) Mortality: 13.74% with rifaximin and 24.43% with norfloxacin (p=0.044)</td>
</tr>
</tbody>
</table>