Spontaneous Bacterial Peritonitis: antibiotic prophylaxis

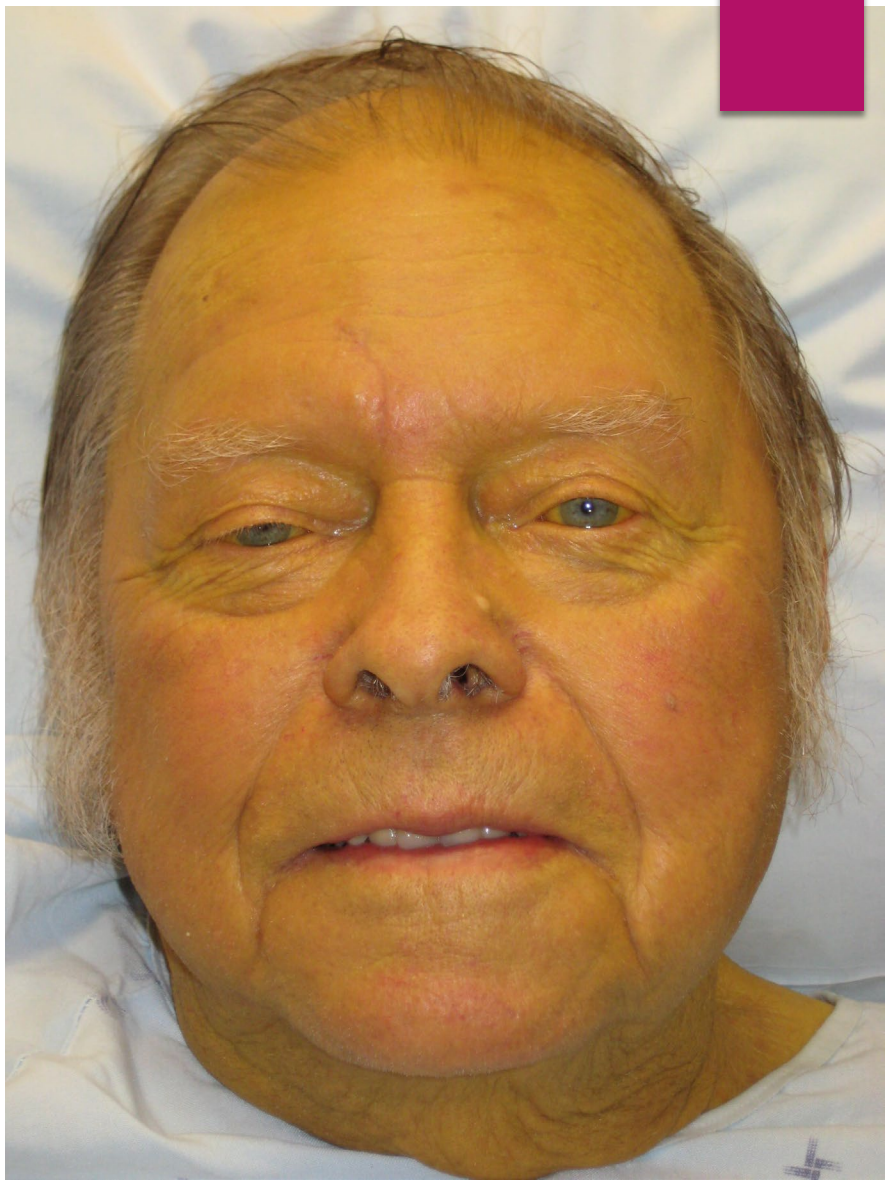
BEST PRACTICES…AT LEAST AS FAR AS WE CAN TELL

Outline

- Literature review of secondary prophylaxis and current guidelines
- Literature review of primary prophylaxis **without** GI hemorrhage and current guidelines
- Literature review of primary prophylaxis **with** GI hemorrhage and current guidelines
- What should we be doing in Montana?

Gene:

- 68 yo man with long standing alcohol use
- Established diagnosis of liver cirrhosis
- Presents with abdominal pain and fevers
- Exam showing distention and tenderness
- Peritoneal fluid analysis
  - 500 PMN's
  - Ascitic Fluid Protein 1.0g/dL
  - Stain with Gram negative rods



Gene:

- 68 yo man with long standing alcohol use
- Established diagnosis of liver cirrhosis
- Presenting with abdominal pain and fevers
- Exam showing distention and tenderness
- Paracentesis:
  - 500 PMN's
  - Ascitic Fluid Protein 1.0g/dL
  - Stain with Gram negative rods
- **Diagnosis of SBP established**
- **Started on ceftriaxone**

What is gene's estimated risk of mortality in the acute phase of SBP?

A. 1 – 5%
B. 5 – 25%
C. 10 – 50%
D. 25 – 75%

Gene:

- 68 yo man with long standing alcohol use
- Established diagnosis of liver cirrhosis
- Presenting with abdominal pain and fevers
- Exam showing distention and tenderness
- Paracentesis:
  - 500 PMN's
  - Ascitic Fluid Protein 1.0g/dL
  - Stain with Gram negative rods
- Diagnosis of SBP established
- Started on ceftriaxone
- **Luckily the antibiotics work**
- **Gene shows clinical improvement**

What are the most likely organisms to find on culture?

A. Gram negatives such as E. coli
B. Gram positives such as staph aureus
C. Gram positives such as enterococcus
D. Multi-drug resistant organisms (VRE, MRSA)

Gene:

- 68 yo man with long standing alcohol use
- Established diagnosis of liver cirrhosis
- Presenting with abdominal pain and fevers
- Exam showing distention and tenderness
- Paracentesis:
  - 500 PMN's
  - Ascitic Fluid Protein 1.0g/dL
  - Stain with Gram negative rods
- Started on ceftriaxone for SBP
- Clinically improves
- **Culture grows E. coli**
- **Completes 5 days of ceftriaxone and is ready for discharge**

What is Gene's risk of SBP recurrence within the next year?

A. 25%
B. 50%
C. 70%
D. 100%

Gene:

- 68 yo man with long standing alcohol use
- Established diagnosis of liver cirrhosis
- Presenting with abdominal pain and fevers
- Exam showing distention and tenderness
- Paracentesis:
  - 500 PMN's
  - Ascitic Fluid Protein 1.0g/dL
  - Stain with Gram negative rods
- Started on ceftriaxone for SBP
- Clinically improves
- **Culture grows E. coli**
- **Completes 5 days of ceftriaxone and is ready for discharge**

What is Gene's 1-year mortality risk after developing one episode of SBP?

A. 5 – 10%
B. 10 – 25%
C. 30 – 60%
D. 60 – 90%

Spontaneous Bacterial Peritonitis:
Quick STATS

- Incidence: 10-30% of those with cirrhosis
- Most cases caused by enteric gram negatives but growing presence of gram positives and MDROs
  1. E. coli
  2. Klebsiella pneumoniae
  3. Staph aureus
  4. Enterococcus Faecalis
  5. Enterococcus faecium
- MDRO's (VRE, MRSA, ESBL's, quinolone-resistant Gram Neg) are now at **35%** of overall infections in patients with cirrhosis (not just SBP)
- Short term mortality risk: ~30% (development of sepsis, HRS, liver failure)
- Recurrence within 1 year: ~70%
- 1 year mortality risk ranging from 30 to 90%

Norfloxacin Prevents Spontaneous Bacterial Peritonitis Recurrence in Cirrhosis: Results of a Double-blind, Placebo-controlled Trial

PERE GINÉS,[1] ANTONI RIMOLA,[1] RAMÓN PLANAS,[4] VICTOR VARGAS,[5] FRANCESC MARCO,[2] MANUEL ALMELA,[2] MONTSERRAT FORNÉ,[6] MARIA LUISA MIRANDA,[7] JOSEP LLACH,[1] JOAN MANUEL SALMERÓN,[1] MARIA ESTEVE,[4] JOSEP MARIA MARQUÉS,[3] MARIA TERESA JIMÉNEZ DE ANTA,[2] VICENTE ARROYO[1] AND JOAN RODÉS[1]

[1]Liver Unit and [2]Microbiological and [3]Toxicology Laboratories, Hospital Clínic i Provincial of Barcelona; [4]Gastroenterology Unit; Hospital Germans Trias i Pujol of Badalona; [5]Liver Unit, Hospital de la Vall d'Hebró of Barcelona. [6]Department of Internal Medicine; Hospital Mútua of Terrassa and [7]Department of Internal Medicine; Residencia Virgen del Rocío of Sevilla, Spain

Eighty cirrhotic patients who had recovered from an episode of spontaneous bacterial peritonitis were included in a multicenter, double-blind trial aimed at comparing long-term norfloxacin administration (400 mg/day; 40 patients) vs. placebo (40 patients) in the prevention of spontaneous bacterial peritonitis recurrence. At entry, both groups were similar with respect esophageal candidiasis). These results indicate that long-term selective intestinal decontamination with norfloxacin is an effective and safe measure to prevent spontaneous bacterial peritonitis recurrence caused by aerobic gram-negative bacilli in cirrhosis. (HEPATOLOGY 1990;12:716-724.)

Gines et. al. (1990)

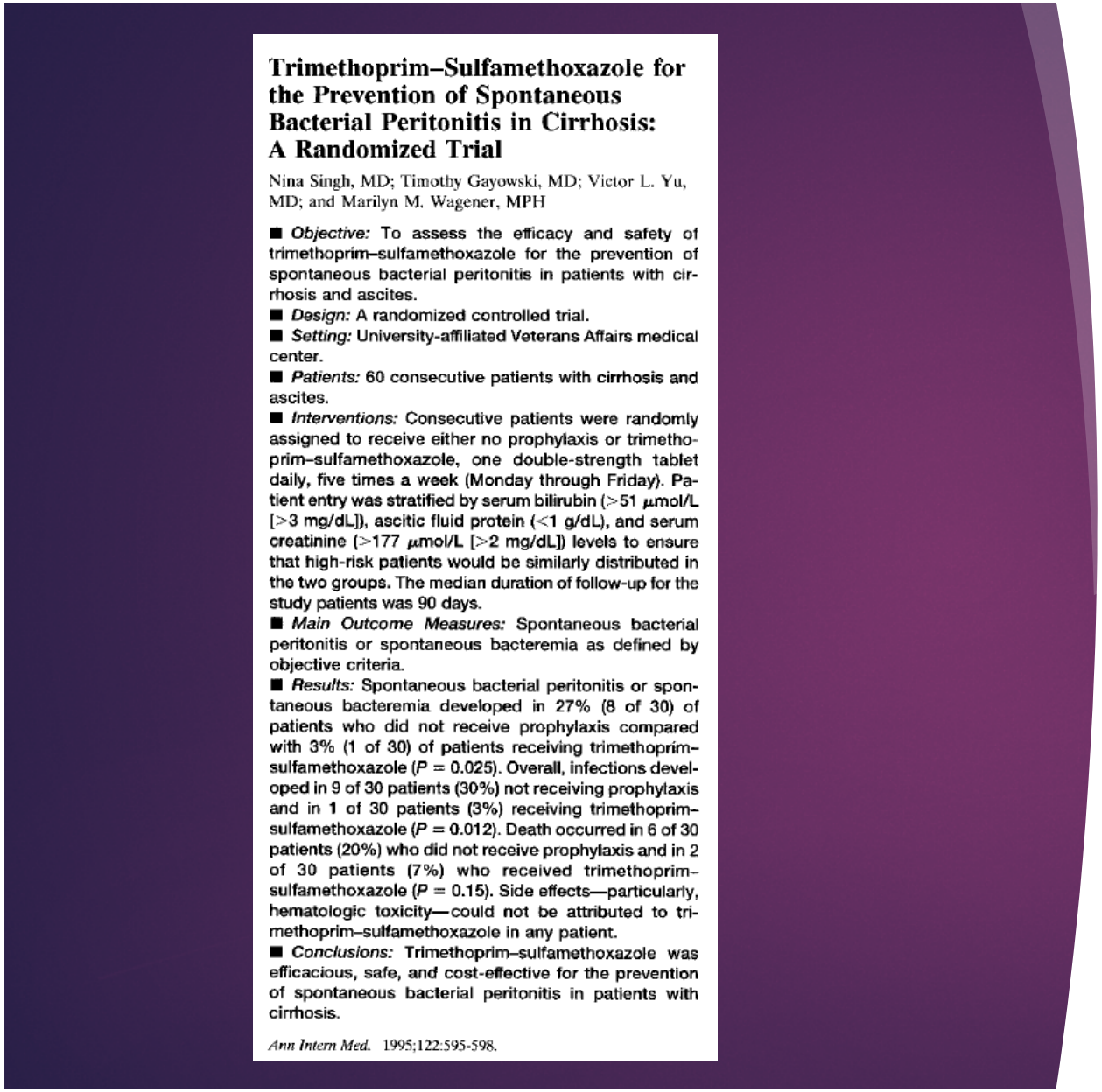
- Spanish Study conducted in the late 80's and published in 1990.
- First double blind, placebo-controlled trial for SBP prophylaxis
- Randomized 80 patients with recent diagnosis of SBP
- 400mg/d of norfloxacin or placebo
- Followed for average of 6 months
- **14 patients** from the placebo group developed SBP
- **5 patients** from the norfloxacin group developed SBP
- Estimated 1 yr probability of recurrence on norfloxacin was 20% versus 68% with placebo
- **Concluded that norfloxacin is effective in significantly reducing the risk of bacterial translocation and recurrent SBP**

NORFLOXACIN

- Fluoroquinolone
- incompletely absorbed in the gut
- highly active against aerobic gram-negative bacilli
- low activity against anaerobic bacteria
- rarely causes bacterial resistance
- Favorable side effect profile when administered chronically
- A particularly good agent for **selective intestinal decontamination**
- **adopted as the drug of choice for secondary SBP prophylaxis until it was withdrawn from the U.S. market in 2014**

Unanswered questions…?

- What do we use when the norfloxacin runs out?
- What about Bactrim?
- What about another fluoroquinolone like Cipro?



Trimethoprim–Sulfamethoxazole for the Prevention of Spontaneous Bacterial Peritonitis in Cirrhosis: A Randomized Trial

Nina Singh, MD; Timothy Gayowski, MD; Victor L. Yu, MD; and Marilyn M. Wagener, MPH

■ *Objective:* To assess the efficacy and safety of trimethoprim–sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in patients with cirrhosis and ascites.
■ *Design:* A randomized controlled trial.
■ *Setting:* University-affiliated Veterans Affairs medical center.
■ *Patients:* 60 consecutive patients with cirrhosis and ascites.
■ *Interventions:* Consecutive patients were randomly assigned to receive either no prophylaxis or trimethoprim–sulfamethoxazole, one double-strength tablet daily, five times a week (Monday through Friday). Patient entry was stratified by serum bilirubin (>51 μmol/L [>3 mg/dL]), ascitic fluid protein (<1 g/dL), and serum creatinine (>177 μmol/L [>2 mg/dL]) levels to ensure that high-risk patients would be similarly distributed in the two groups. The median duration of follow-up for the study patients was 90 days.
■ *Main Outcome Measures:* Spontaneous bacterial peritonitis or spontaneous bacteremia as defined by objective criteria.
■ *Results:* Spontaneous bacterial peritonitis or spontaneous bacteremia developed in 27% (8 of 30) of patients who did not receive prophylaxis compared with 3% (1 of 30) of patients receiving trimethoprim–sulfamethoxazole ($P = 0.025$). Overall, infections developed in 9 of 30 patients (30%) not receiving prophylaxis and in 1 of 30 patients (3%) receiving trimethoprim–sulfamethoxazole ($P = 0.012$). Death occurred in 6 of 30 patients (20%) who did not receive prophylaxis and in 2 of 30 patients (7%) who received trimethoprim–sulfamethoxazole ($P = 0.15$). Side effects—particularly, hematologic toxicity—could not be attributed to trimethoprim–sulfamethoxazole in any patient.
■ *Conclusions:* Trimethoprim–sulfamethoxazole was efficacious, safe, and cost-effective for the prevention of spontaneous bacterial peritonitis in patients with cirrhosis.

Ann Intern Med. 1995;122:595-598.

- U.S. Study 1995
- VA patients with cirrhosis and ascites
- Primary and secondary prophylaxis
- Compared Mon-Fri Bactrim to no prophylaxis
- 1 of 30 patients got SBP in Bactrim group
- 8 of 30 patients got SBP in no treatment group
- Concluded that **Bactrim is effective**
- But **low-quality study** without blinding and controlling for heterogenous patient population.
- Low enrollment & low event rate

ENSAIO CLÍNICO / CLINICAL TRIAL

TRIMETHOPRIM-SULFAMETHOXAZOLE VERSUS NORFLOXACIN IN THE PROPHYLAXIS OF SPONTANEOUS BACTERIAL PERITONITIS IN CIRRHOSIS

Roberto Fiolic **ALVAREZ**[1], Angelo Alves de **MATTOS**[1], Esther Buzaglo Dantas **CORRÊA**[2], Helma Pinchemel **COTRIM**[3] and Tereza Virginia S. B. **NASCIMENTO**[4]

ABSTRACT - ***Background*** – The prognosis of patients with chronic liver disease and spontaneous bacterial peritonitis is poor, being of great importance its prevention. ***Aim*** - To compare the effectiveness of trimethoprim-sulfamethoxazole versus norfloxacin for prevention of spontaneous bacterial peritonitis in patients with cirrhosis and ascites. ***Patients and Methods*** - Fifty seven patients with cirrhosis and ascites were evaluated between March 1999 and March 2001. All of them had a previous episode of spontaneous bacterial peritonitis or had ascitic fluid protein concentration ≤1 g/dL and/or serum bilirubin ≥ 2.5 mg/dL. The patients were randomly assigned to receive either 800/160 mg/day of trimethoprim-sulfamethoxazole 5 days a week or 400 mg of norfloxacin daily. The mean time of observation was 163 days for the norfloxacin group and 182 days for the trimethoprim-sulfamethoxazole group. In the statistical analysis, differences were considered significant at the level of 0.05. ***Results*** - According to the inclusion criteria, 32 patients (56%) were treated with norfloxacin and 25 (44%) with trimethoprim-sulfamethoxazole. Spontaneous bacterial peritonitis occurred in three patients receiving norfloxacin (9.4%) and in four patients receiving trimethoprim-sulfamethoxazole (16.0%). Extraperitoneal infections occurred in 10 patients receiving norfloxacin (31.3%) and in 6 patients receiving trimethoprim-sulfamethoxazole (24.0%). Death occurred in seven patients (21.9%) who received norfloxacin and in five (20.0%) who received trimethoprim-sulfamethoxazole. Side effects occurred only in the trimethoprim-sulfamethoxazole group. ***Conclusion*** - In spite of the reduced number of patients and time of observation, trimethoprim-sulfamethoxazole and norfloxacin were equally effective in spontaneous bacterial peritonitis prophylaxis, suggesting that trimethoprim-sulfamethoxazole is a valid alternative to norfloxacin.

HEADINGS – Peritonitis. Liver cirrhosis. Ascites. Trimethoprim-sulfamethoxazole combination. Norfloxacin.

Alvarez et. al. 2005

- Brazilian trial with mixed primary and secondary prophylaxis patients
- Randomly assigned daily **norfloxacin to 32 patients** and **Trimethoprim/sulfamethoxazole 5x/week to 25 patients**
- Spontaneous bacterial peritonitis occurred in:
  - 3 patients receiving **norfloxacin (9.4%)**
  - 4 patients receiving **trimethoprim-sulfamethoxazole (16.0%)**
- Concluded that **Bactrim was not inferior** to norfloxacin
- Low quality study:
  - not blinded
  - low numbers
  - significant differences between study groups

- 2014
- 80 patients with advanced liver disease
- Primary or secondary prophylaxis
- Norflox 400mg/d versus Bactrim 160/800 daily
- Followed for 1 year
- 2 patients out of 40 developed SBP in both groups
- Concluded that **Bactrim not inferior to norfloxacin** in preventing SBP
- Again, not a very high-quality study
  - Heterogenous study population
  - Small numbers

A randomized controlled study of trimethoprim-sulfamethoxazole versus norfloxacin for the prevention of infection in cirrhotic patients

Steve Lontos [1], Edward Shelton, Peter W Angus, Rhys Vaughan, Stuart K Roberts, Adam Gordon, Paul J Gow

Affiliations + expand

PMID: 24612987 DOI: 10.1111/1751-2980.12132

Abstract

Objective: To prospectively compare norfloxacin (N) with trimethoprim-sulfamethoxazole (T-S) in preventing infection in cirrhotic patients.

Methods: Cirrhotic patients at high risk of spontaneous bacterial peritonitis (SBP) were recruited and assigned N (400 mg daily) or T-S (160/800 mg daily). Patients were followed up for 12 months. The primary end-point was the incidence of infection. Secondary end-points included the incidence of SBP, bacteremia, extraperitoneal infection requiring antibiotic treatment, liver transplantation, death, side effects and rate of resistance to N or T-S.

Results: A total of 80 patients with a mean age of 53.0 ± 9.3 years were prescribed N (n = 40) or T-S (n = 40). Child-Pugh status, model for end-stage liver disease and risk factors for SBP were similar between the groups. There were 10 episodes of infections in the N group and 9 in the T-S group (P = 0.79). Two patients each in the N and T-S group developed SBP (P = 0.60). There was a difference in the rate of transplantation favoring N (P = 0.03) but not death. The number of adverse events for N (n = 7) and T-S (n = 10) were similar (P = 0.59), with T-S being associated with an increased risk of developing a definite or probable adverse event compared to N (22.5% vs 0%, P = 0.01).

Conclusions: This study failed to demonstrate a difference between N and T-S groups in their effects on preventing infection in patients with liver cirrhosis. T-S can be considered an alternative first-line therapy for infection prophylaxis.

Unanswered questions…?

- What do we use when the norfloxacin runs out?
- What about Bactrim? **Probably not inferior**
- What about another fluoroquinolone like Cipro?

Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: A randomized, placebo-controlled study ☆,☆☆

Rubén Terg[1,*], Eduardo Fassio[2], Mónica Guevara[3,†], Mariano Cartier[1], Cristina Longo[2], Romina Lucero[1], Cristina Landeira[2], Gustavo Romero[1], Nora Dominguez[2], Alberto Muñoz[1], Diana Levi[1], Carlos Miguez[1], Raquel Abecasis[1]

[1]*Unidad de Hígado, Hospital de Gastroenterología "Dr. Bonorino Udaondo", Sección Hepatología, Av. Caseros 2061, 1264 Buenos Aires, Argentina*
[2]*Hospital Prof. Alejandro Posadas, Buenos Aires, Argentina*
[3]*Hospital Clinic Barcelona, Ciberehd, Ciber de Enfermedades Hepaticas y Digestivas, España, Universidad del Salvador, Buenos Aires, Argentina*

Terg et al 2008

- Argentina
- **100 patients** with cirrhosis and ascitic protein of less than 1.5g/dL
- Randomized, double blinded
- **Ciprofloxacin 500mg/d versus placebo**
- Followed for **1 year**
- **7 of the 50 patients** in placebo group got SBP
- **2 of 50 patients** in the cipro group got SBP
- Unfortunately, low numbers and low event rates made for an **insignificant P value of 0.07**
- The difference in mortality was significant with 86% taking cipro versus 66% taking placebo surviving the 12 months (p 0.04)
- Concluded that **cipro can improve mortality** when taken for primary SBP prophylaxis

Unanswered questions…?

- What do we use when the norfloxacin runs out?
- What about Bactrim? Probably not inferior
- What about another fluoroquinolone like Cipro? **Not a bad choice.**
- What about other non-absorbable antibiotics like Rifaximin?

Randomized-controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis

Asem Elfert, Lobna Abo Ali, Samah Soliman, Shimaa Ibrahim and Sherief Abd-Elsalam

Background and aims Spontaneous bacterial peritonitis (SBP) is a serious complication of liver cirrhosis with a high recurrence rate and a marked increase in mortality. Norfloxacin is used widely for the secondary prophylaxis of SBP; however, its extensive long-term use has led to an increase in the incidence of quinolone-resistant and Gram-positive SBP. Rifaximin is a nonabsorbable broad-spectrum antibiotic and does not appear to promote emergence of resistance. The aim of this study was to compare the safety and efficacy of rifaximin versus norfloxacin for the secondary prevention of SBP in patients with liver cirrhosis and ascites.
Materials and methods Two hundred and sixty two cirrhotic patients with ascites and a previous episode of SBP were assigned randomly to receive either 1200 mg rifaximin or 400 mg of norfloxacin daily for 6 months. All patients were monitored clinically each month and with ascitic fluid examination at the end of 2 and 6 months if not clinically suspected of recurrence earlier.
Results Recurrence of SBP was significantly lower in the rifaximin group (3.88 vs. 14.13%) compared with the norfloxacin group ($P=0.04$). The mortality rate was significantly decreased in the rifaximin group (13.74 vs. 24.43%) compared with the norfloxacin group ($P=0.044$). The causes of death between the two groups did not show a significant difference ($P=0.377$), but encephalopathy-related deaths were three folds higher in the norfloxacin group. There was a significant decrease in the side effects in the rifaximin group versus the norfloxacin group ($P=0.033$).
Conclusion Rifaximin was more effective than norfloxacin in the secondary prevention of SBP. Encephalopathy-related mortality and side effects were fewer in the rifaximin group. Eur J Gastroenterol Hepatol 28:1450–1454

Elfert et al. 2016

- RTC done in Egypt
- **195 patients** with prior SBP randomized to rifaximin 400mg TID or Norfloxacin 400mg/d
- Followed for **6 months**
- Not blinded
- **4 out of 103 on rifaximin** developed SBP versus **13 out of 92 patients on norfloxacin** (3.8% vs 14.1%)
- Mortality was lower with rifaximin (13.7% versus 24.4%)
- Encephalopathy related deaths were three-fold higher in norfloxacin group
- Concluded that rifaximin was effective for secondary SBP prophylaxis and reduced rates of hepatic encephalopathy
- Rifaximin, similar to norfloxacin, has poor systemic absorption and covers gram negative and gram-positive pathogens
- Less risk of promoting resistance

Unanswered questions…?

- What do we use when the norfloxacin runs out?
- What about Bactrim? Probably not inferior
- What about another fluoroquinolone like Cipro? Not a bad choice.
- What about other non-absorbable antibiotics like Rifaximin? **Good choice, but pricey**
- **What's the latest?**

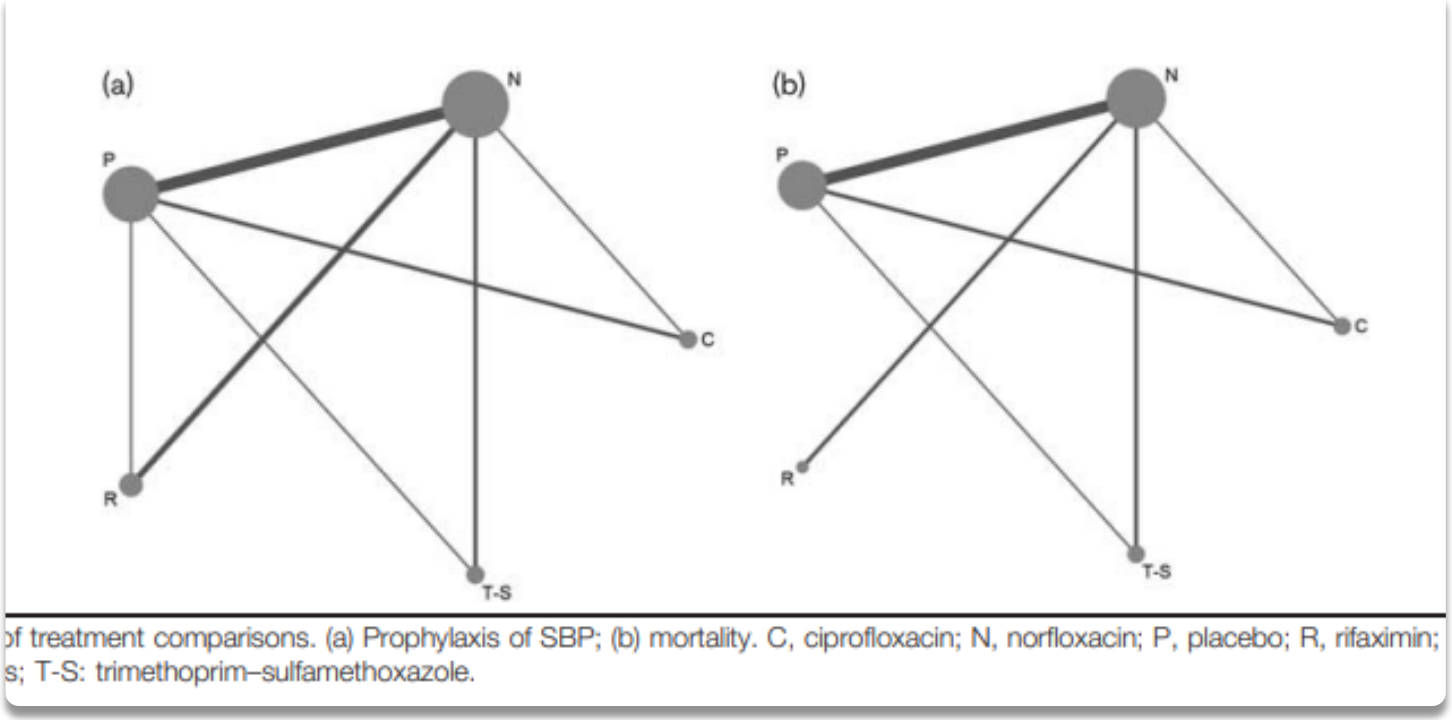
Norfloxacin, ciprofloxacin, trimethoprim–sulfamethoxazole, and rifaximin for the prevention of spontaneous bacterial peritonitis: a network meta-analysis

Wancong Wang[a,*], Jiahui Yang[c,*], Chuan Liu[a,*], Pan Song[b], Wenzhen Wang[a], Huimei Xu[d] and Xingzhou Xia[a]

For the prevention of spontaneous bacterial peritonitis (SBP) in cirrhotic patients with ascites, prophylactic antibiotics are recommended as a standard regimen. This study aimed to assess the efficacy of norfloxacin (N), ciprofloxacin (C), trimethoprim–sulfamethoxazole (T-S), and rifaximin (R) in the prevention of SBP. We searched the electronic databases including PubMed, Cochrane Library, Embase, and Web of Science from inception till 1 August 2018. The randomized-controlled trials that compared N, C, T-S, R, and placebo (P) were identified. A network meta-analysis (NMA) was carried out using the software STATA 14.0 and Revman 5.3. We included 16 studies involving 1984 participants in the NMA for SBP prevention. The NMA results showed that, compared with those treated with P (reference), patients treated with C, N, or R had a lower incidence of SBP and mortality. Similarly, the incidences of SBP and mortality for R were lower than those for N. The probabilities of ranking results showed that R ranked first with respect to the outcomes of the incidence of SBP and mortality. According to our results, R seemed to be the optimal regimen for protecting against SBP in patients with cirrhosis and ascites. However, considering the limitations of our study, additional high-quality studies are required in this respect. Eur J Gastroenterol Hepatol 31:905–910

Wang et al 2019

- Network meta-analysis
- 16 RCTs including 1,984 patients
- Looked at **primary and secondary prophylaxis** in a heterogenous group of patients.
- **Mortality**: Concluded that norfloxacin, rifaximin, and Bactrim had a survival benefit with **rifaximin having the best Odds Ratio.**
- **SBP recurrence**: Cipro, norfloxacin, and rifaximin were superior to placebo. Bactrim was not.



of treatment comparisons. (a) Prophylaxis of SBP; (b) mortality. C, ciprofloxacin; N, norfloxacin; P, placebo; R, rifaximin; s; T-S: trimethoprim–sulfamethoxazole.

Guidelines and Expert Consensus on Secondary SBP prophylaxis

American Assoc. for the Study of Liver Disease (AASLD) 2021:

- "Patients who have recovered from an episode of SBP should receive long-term prophylaxis with daily norfloxacin. In settings in which norfloxacin is unavailable, oral ciprofloxacin is acceptable."
- There is no high-quality direct evidence to support the use of cipro, Bactrim, or rifaximin.
- They recommend **ciprofloxacin**

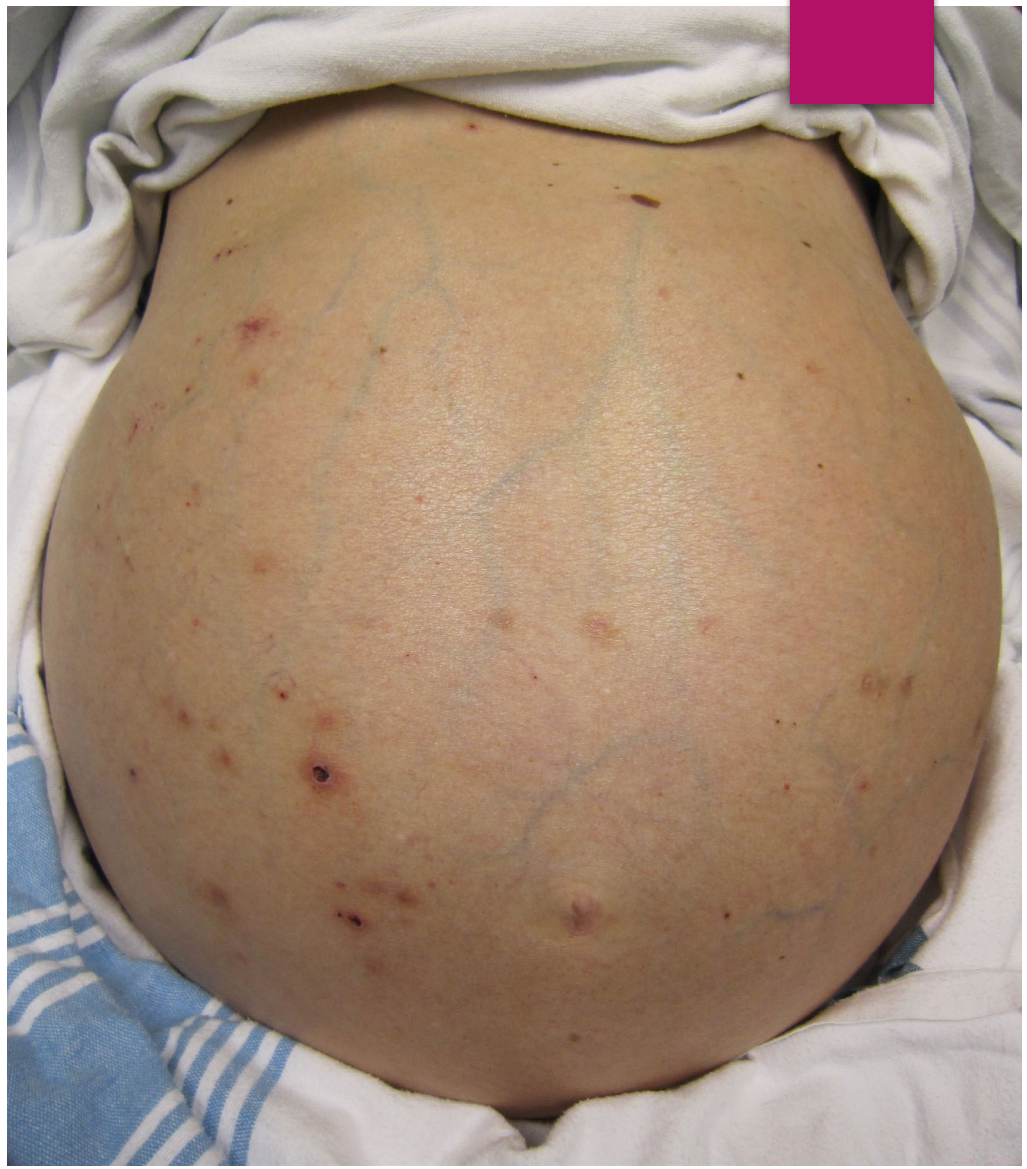
European Assoc for the Study of the Liver (EASL) 2018:

- Administer norfloxacin 400mg/d until death or liver transplant
- No strong evidence to support rifaximin
- No suggestion on SBP prophy for patients on rifaximin for hepatic encephalopathy
- Recommend liver transplant due to high risk of recurrence and mortality.

Primary Prophylaxis

Paula: 45 yo with liver cirrhosis

- Presents with 2 weeks of increasing abdominal distention
- No fevers, mild dyspnea
- Exam shows tense abd without tenderness
- Labs: Na 133, BUN 30, Cr 1.7, AST 45, ALT 22, T bili 4.0
- MELD 24. Child-Pugh 10 (class C).
- Diagnostic/Therapeutic Paracentesis: 3.5L
  - PMN 50/mm3
  - T protein 1.0g/dL
  - Gram stain negative, culture pending
- Feels much better after paracentesis



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  - Gram stain negative, culture pending
- Feels much better after paracentesis

Patient is requesting discharge from the ED.

Who would start this patient on antibiotic prophylaxis for SBP?

GASTROENTEROLOGY 2007;133:818–824

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis

JAVIER FERNÁNDEZ,[*] MIQUEL NAVASA,[*] RAMÓN PLANAS,[‡] SILVIA MONTOLIU,[‡] DAVID MONFORT,[§] GERMAN SORIANO,[§] CARMEN VILA,[‖] ALBERTO PARDO,[¶] ENRIQUE QUINTERO,[¶] VICTOR VARGAS,[#] JOSE SUCH,[**] PERE GINÈS,[*] and VICENTE ARROYO[*]

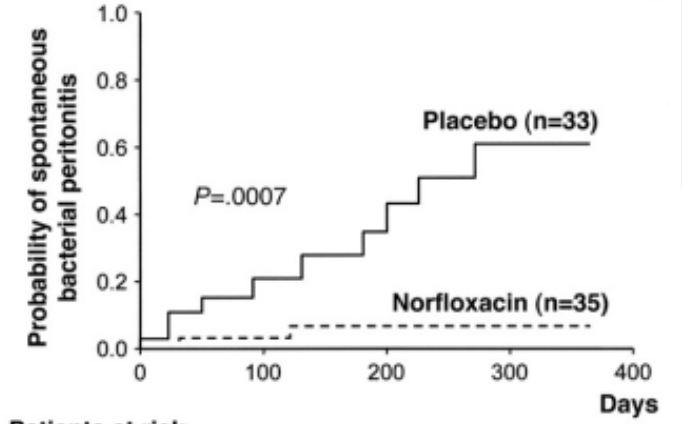
[*]Liver Unit, Hospital Clínic Barcelona, Barcelona, Spain; [‡]Gastroenterology Unit, Hospital Germans Trias i Pujol, Barcelona, Spain; [§]Gastroenterology Unit, Hospital Santa Creu i Sant Pau, Barcelona, Spain; [‖]Gastroenterology Unit, Hospital del Mar, Barcelona, Spain; [¶]Gastroenterology Unit, Hospital Universitario de Canarias, Tenerife, Spain; [#]Gastroenterology Unit, Hospital Vall d'Hebron, Barcelona, Spain; and [**]Gastroenterology Unit, Hospital Universitario, Alicante, Spain

Fernandez et al. 2007

- Study done in Spain with patients recruited from 2000-2004
- Double-blind, placebo-controlled trial
- Inclusion criteria: adults 18-80years, **ascitic protein less than 1.5g/dL**, and **renal dysfunction** or severe **liver failure**
  - Renal dysfunction defined as: Cr >1.2, BUN >25 or Na <130
  - Severe liver failure defined as: Child-Pugh >9 with total bilirubin >3.0
- **68 patients** randomized to **norfloxacin versus placebo**
- SBP RESULTS: 2/35 in norfloxacin group and 10/33 in placebo group (P = 0.02)
- 85% of Gram Neg Bacilli isolated in the norfloxacin group were quinolone resistant versus 1.6% in the placebo group

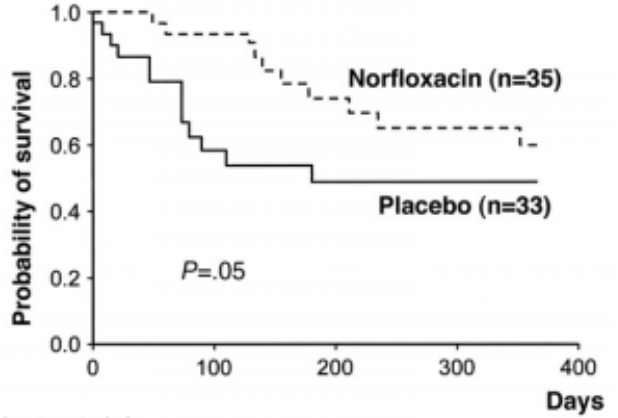
Fernandez et al 2007 Conclusions:

- Norfloxacin is effective in reducing risk of developing a first episode of SBP and improving survival in patients with advanced cirrhosis and low ascitic protein levels
- Norfloxacin improves 1 year survival in this population
- Effect on mortality appears to wane at the 1-year point and is most apparent at the 3-month point.



Patients at risk					
Norfloxacin	35	26 (1)	17 (2)	14 (2)	10 (2)
Placebo	33	13 (5)	7 (8)	2 (10)	1 (10)

Figure 1. Probability of developing SBP in patients receiving norfloxacin (*dotted line*) or placebo prophylaxis (*continuous line*). Figures in parentheses indicate the cumulative number of subjects who developed SBP.



Patients at risk					
Norfloxacin	35	26 (2)	17 (7)	14 (9)	10 (10)
Placebo	33	13 (11)	7 (13)	2 (13)	1 (13)

Figure 3. Probability of 1-year survival in patients receiving norfloxacin (*dotted line*) or placebo prophylaxis (*continuous line*). Figures in parentheses indicate the cumulative number of subjects who died.

Terg et al 2008

- Argentina
- 100 patients with cirrhosis and ascitic protein of less than 1.5g/dL
- Randomized, double blinded
- Ciprofloxacin 500mg/d versus placebo
- Followed for 1 year
- 7 of the 50 patients in placebo group got SBP
- 2 of 50 patients in the cipro group got SBP
- Unfortunately, low numbers and low SBP rates made for an insignificant P value of 0.07
- The difference in mortality was significant with 86% taking cipro versus 66% taking placebo surviving the 12 months (p 0.04)
- Concluded that cipro can improve mortality when taken for primary SBP prophylaxis

Summary of findings for the main comparison.

Antibiotic prophylaxis compared with placebo or no treatment for spontaneous bacterial peritonitis in cirrhotic patients with ascites, without gastro-intestinal bleeding

Patient or population: Cirrhotic patients with ascites, without gastro-intestinal bleeding and no current spontaneous bacterial peritonitis

Settings: Both outpatients and inpatients

Intervention: Antibiotic prophylaxis

Comparison: Placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of partici-pants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no treatment	Antibiotic prophylaxis				
Spontaneous bacterial peritonitis	**Medium risk population**		RR 0.20 (0.11 to 0.37)	538 (7)	+OOO very low[1,2,3,4,5]	
	226 per 1000	45 per 1000 (25 to 84)				
Mortality	**Medium risk population**		RR 0.61 (0.43 to 0.87)	538 (7)	+OOO very low[1,2,3,6]	
	200 per 1000	122 per 1000 (86 to 174)				

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; eg: 'exempli gratia' (Latin) - for example; RR: Relative risk; GRADE: GRADE Working Group grades of evidence (see footnotes)

GRADE Working Group grades of evidence
High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (+++O): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++OO): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality (+OOO): We are very uncertain about the estimate.

Guidelines and Expert Consensus on Primary SBP prophylaxis without GI hemorrhage

American Assoc. for the Study of Liver Disease (AASLD) 2021:

- Primary SBP prophylaxis can be considered in select patients with cirrhosis and low ascitic protein concentration (<1.5 g/dL) and renal dysfunction or liver failure
- Renal dysfunction defined as: Cr >1.2, BUN >25 or Na <130
- Liver Failure defined as Child-Pugh >9 with total bilirubin >3.0

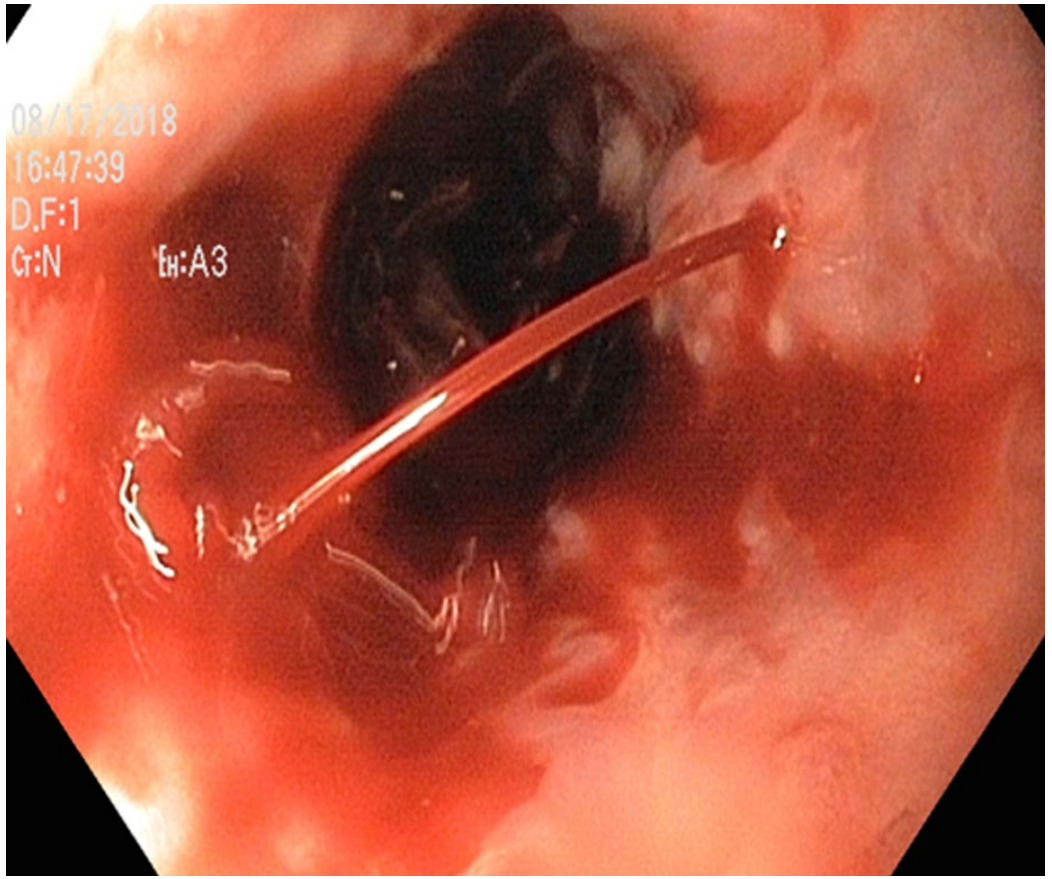
European Assoc for the Study of the Liver (EASL) 2018:

- Primary prophylaxis with norfloxacin (400 mg/day) in patients with Child-Pugh score ≥9 and serum bilirubin level ≥3 mg/dl, with either impaired renal function or hyponatremia, and ascitic fluid protein lower than 1.5 g/dL is recommended
- Norfloxacin prophylaxis should be stopped in patients with long-lasting improvement of their clinical condition and disappearance of ascites

Primary Prophylaxis in Hemorrhage

Harry: 55 yo with liver cirrhosis

- Presents with nausea and bloody emesis
- Known esophageal varices
- Exam shows pale man, distended abd without tenderness, blood in the corner of his mouth
- Started on octreotide, pantoprazole, and IV fluids
- Stabilized and taken for urgent endoscopy where acute variceal hemorrhage was found and ligated



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Estimated risk of spontaneous bacterial peritonitis in the setting of acute GI hemorrhage? 22%

What is the risk of mortality in this setting?

~30%

How does preventing infection in this patient change his chance of death?

9% increase in survival

Antibiotic Prophylaxis for the Prevention of Bacterial Infections in Cirrhotic Patients With Gastrointestinal Bleeding: A Meta-Analysis

Brigitte Bernard,[1] Jean-Didier Grangé,[2] Eric Nguyen Khac,[1] Xavier Amiot,[2] Pierre Opolon,[1] and Thierry Poynard[1]

- 1999
- Meta-analysis of 5 RTCs comparing antibiotic prophylaxis to no treatment to prevent bacterial infections in cirrhotic patients with GI bleeding
- 534 patients total. 264 treated with antibiotic prophylaxis and 270 were not.
- Antibiotic regimens were mostly fluoroquinolones (cipro commonly used)
- Followed for average of 20 days
- Average percentage of patients free from SBP was 95% in treatment group compared to 87% in control group. Odds Ratio 1.88 (95% CI: 1.22-2.89, P= 0.004)
- The mean survival rate was 85% in the group of treated patients and 76% in the control group. Odds ratio1.88 (95% CI: 1.22-2.89, P=0.004)

Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage

Javier Fernández [1], Luis Ruiz del Arbol, Cristina Gómez, Rosa Durandez, Regina Serradilla, Carlos Guarner, Ramón Planas, Vicente Arroyo, Miguel Navasa

- 2006
- RTC prompted by the higher incidence of infections caused by quinolone resistant bacteria
- 111 patients randomized to norfloxacin versus ceftriaxone
  - Advanced cirrhosis – ascites, malnutrition, bilirubin >3
- Treated for 7 days
- Infection (any source) found in 11% of ceftriaxone vs. 26% of norfloxacin
- SBP in 2% of ceftriaxone and 11% of norfloxacin (but not significant)
- 6 of 7 gram negative bacilli in the norfloxacin group were resistant to quinolones

Guidelines and Expert Consensus on Primary SBP prophylaxis in patients with cirrhosis and GI bleeding

American Assoc. for the Study of Liver Disease (AASLD) 2021:

- Antibiotic prophylaxis for SBP should be instituted in patients with cirrhosis and upper gastrointestinal hemorrhage. IV ceftriaxone 1 g/24 hours is the antibiotic of choice and should be used for a maximum of 7 days.
- Administered until hemorrhage has resolved and vasoactive drugs are stopped
- Can transition to PO cipro or Bactrim once patient is tolerating a diet.

European Assoc for the Study of the Liver (EASL) 2018:

- closely monitor patients with acute gastrointestinal bleeding
- initiate antibiotic prophylaxis at presentation of bleeding and continue for up to 7 days
- use ceftriaxone 1 g IV daily for 7 days if: decompensated cirrhosis, patients already on quinolone prophylaxis, hospital settings with high prevalence of quinolone-resistant infections
- use oral quinolones (such as norfloxacin 400 mg twice daily) in patients without above indications

What should we be doing??

- Ceftriaxone for cirrhosis and GI bleeding
  - Maximum of 7 days of therapy
  - can transition to PO abx once hemorrhage resolved and eating
- Antibiotics for secondary SBP prophylaxis
  - Most studied and recommended drug is norfloxacin
  - Cipro and Bactrim promoted as reasonable alternatives
  - Maybe emerging evidence supporting rifaximin
  - DO NOT do intermittent dosing of any antibiotic
- Antibiotics for primary SBP prophylaxis **without** GI bleeding
  - Only in high-risk patients
  - Order ascitic fluid protein to further risk stratify
  - I recommend Cipro or Bactrim until ascites is resolved or while waiting for liver transplant