INSELGRUPPE

Spontaneous bacterial peritonitis

Portal Hypertension Session 10-29-2020

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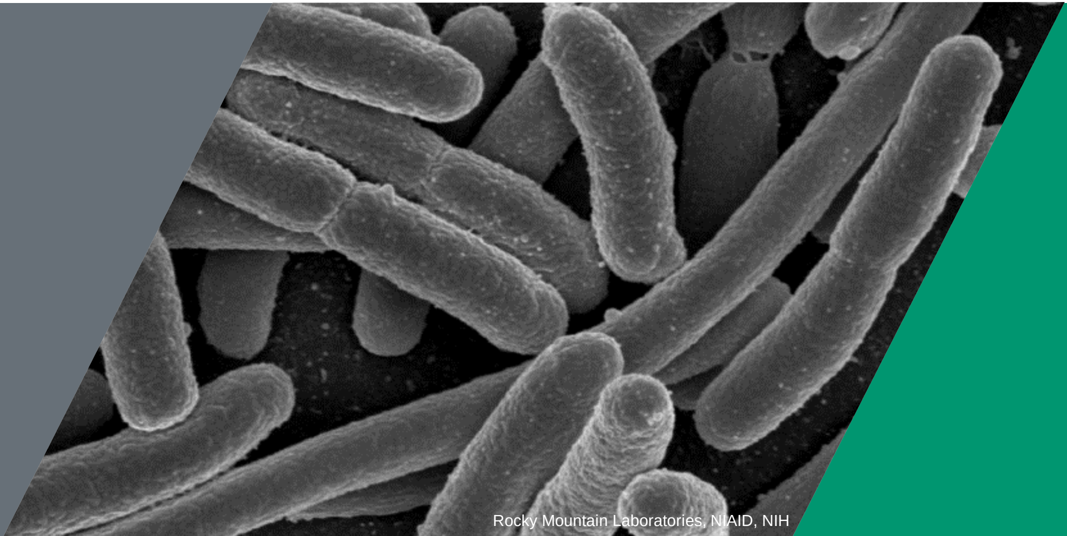


Rocky Mountain Laboratories, NIAID, NIH

Outline

- Definition of SBP and SBP variants
- Pathogenesis
- Clinical risk factors
- Diagnosis
- Treatment and prophylaxis

Definition of SBP and SBP variants

Definition of SBP

Spontaneous Peritonitis and Bacteremia in Laennec's Cirrhosis Caused by Enteric Organisms

A Relatively Common but Rarely Recognized Syndrome

HAROLD O. CONN, M.D., *New Haven, Connecticut*

TABLE 1. Clinical Manifestations

Patient	Initial Fever	Chills	Abdominal Pain	Rebound Tenderness	Hypoactive Bowel Sounds	Hypotension	Impending Hepatic Coma	No Free Air by X ray
	F							
1A	104	+	+	+	+	+	+	—
1B	104	+	+	+	+	+	+	+
2	102	+	+	+	+	+	+	+
3	101	+	+	+	0	+	+	+
4	101	+	+	+	+	+	+	+
5	101	+	+	+	+	+	+	+

TABLE 2. Laboratory Data

Patient	WBC	Serum Amylase	Ascitic Fluid					Blood Culture
			Turbidity	Specific Gravity	Leukocytes	Smear of Sediment	Culture	
	/mm³				*/mm³*			
1A	15,000	<200	+	1.013	—	Many polymorphonuclear leukocytes; gram-negative bacteria	*E. coli*	*E. coli*
1B	13,000	—	+	1.014	—	Many polymorphonuclear leukocytes; gram-negative bacteria	*E. coli*	*E. coli*
2	13,000	<200	+	1.015	13,000	Many polymorphonuclear leukocytes	*Aeromonas liquefaciens*	*Aeromonas liquefaciens*
3	11,000	<200	+	—	1,000	Many polymorphonuclear leukocytes; gram-negative bacteria	*E. coli*	*E. coli*
4	42,000	<200	+	1.018	1,400	Many polymorphonuclear leukocytes	Enterococcus	Enterococcus
5	6,000	<200	+	1.019	2,700	Many polymorphonuclear leukocytes	*E. coli*	*Aeromonas liquefaciens*

Ascitic fluid infection without an evident intra-abdominal surgically treatable source

Conn, H. O. *Ann. Intern. Med.* **60**, 568 (1964).

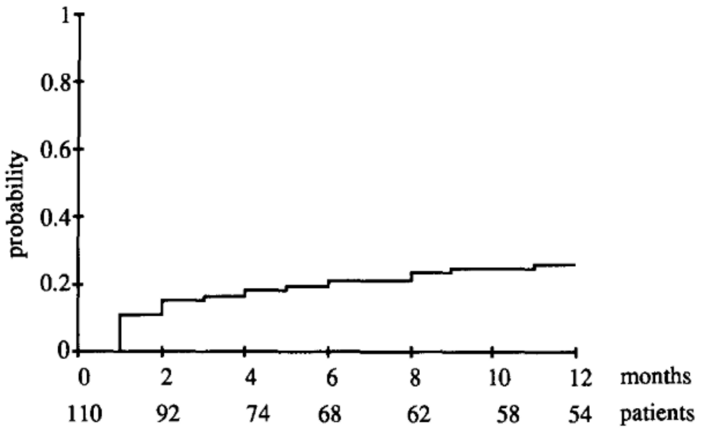
Variants of ascitic fluid infection

	PMN count cells/mm^3	Culture
Spontaneous bacterial peritonitis	≥ 250	single organism
Culture-negative neutrocytic ascites	≥ 250	negative
Monomicrobial nonneutrocytic bacterascites	<250	single organism
Secondary bacterial peritonitis	≥ 250	polymicrobial
Polymicrobial bacterascites	<250	polymicrobial

Infection = Positive culture **OR** elevated PMN count

Sheer, T. A. & Runyon, B. A. *Dig. Dis.* **23**, 39–46 (2005).

How frequent is SBP?



Distribution of infectious episodes according to the type of infection

Type of infection	Isolated episodes	Associated episodes	Repeated episodes	Total
SBP	14	14	4	32 (31.07%)
UTI	11	7	8	26 (25.24%)
Pneumonia	18	4	0	22 (21.37%)
Dermatolog. infections	10	2	0	12 (11.65%)
Septicaemia	3	1	0	4 (3.88%)
Bacterial endocarditis	2	1	0	3 (2.91%)
Others[a]	3	1	0	4 (3.88%)
Total	61 (59.22%)	30 (29.13%)	12 (11.65%)	103 (100%)

SBP, spontaneous bacterial peritonitis; UTI, urinary tract infections; Dermatolog., dermatological.
[a]Others (1 case of pulmonary tuberculosis; 1 case of bacterial colitis; 1 case of hepatic abscess; 1 case of bacterial colangitis).

~20% of cirrhotic patients with ascites in 1 y

One of the most common infections in cirrhotic patients

Andreu, M. *et al. Gastroenterology* **104**, 1133–1138 (1993).
Caly, W. R. & Strauss, E. *J. Hepatol.* **18**, 353–358 (1993).

Pathogenesis

Pathogenesis – Early hypotheses

Discussion

What is the pathogenesis of this syndrome? Is it primarily a bacteremia with secondary seeding of the ascitic fluid, or does it represent a peritonitis with secondary bacteremia? The most satisfying hypothesis suggests that both occur sequentially. It assumes that the initial event is the escape of bacteria from the intestinal tract into the blood, causing transient bacteremia. In the cirrhotic patient, in whom the bacterial filtering mechanism of the liver is impaired, the duration of such bacteremia is prolonged. This offers the organisms greater opportunity to invade the ascitic fluid and to cause bacterial peritonitis, which in turn causes a secondary bacteremia.

Conn, H. O. *Ann. Intern. Med.* **60**, 568 (1964).

Pathogenesis – Small-intestinal bacterial overgrowth (SIBO)

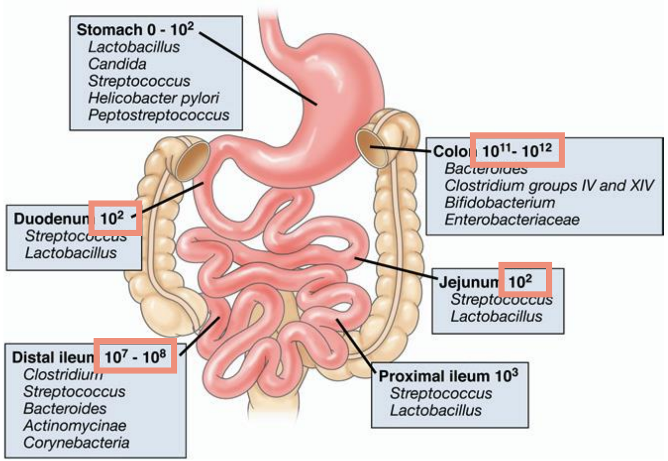


Table 3. Results of Quantitative Jejunal Cultures in 70 Patients With Cirrhosis

Patients (n)	$SIBO_{D1}$
All (70)	61
Not on acid-suppressive therapy*	
Child Pugh Class	
A (17)	41
B (15)	33
C (8)	63
Total (40)	43
On acid-suppressive therapy*	
Child Pugh Class	
A (12)	92
B (9)	67
C (9)	100
Total (30)	87†

~60% of cirrhotic patients have SIBO (>10^5 jejunal CFU)

Reasons:

- Disturbed motility
- Paneth cell disorders
- Portal-hypertensive enteropathy

Sartor, R. B. *Gastroenterology* **134**, 577–594 (2008).
Bauer, T. M. *et al. Am. J. Gastroenterol.* **96**, 2962–7 (2001).

Pathogenesis – Translocation (I)

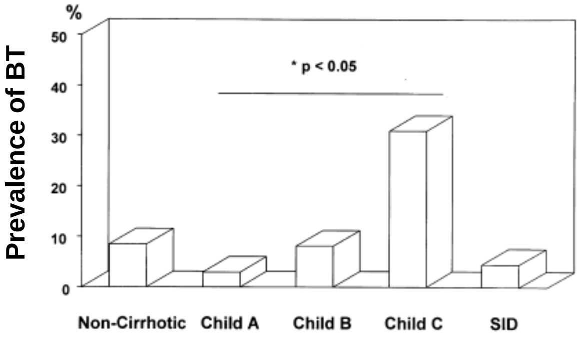
Flora of the 16 rats with cirrhosis that translocated and had culture-positive ascitic fluid

Ascitic fluid culture	Mesenteric lymph node culture	Colonies per mg of ascitic fluid / Colonies per mg of lymph node
E. coli	*E. coli*	0.34
E. coli	*E. coli*	0.125
E. coli	*E. coli*	0.5
E. coli	*E. coli*	0.93
E. coli	*E. coli* & *Morganella morganii*	0.016
E. coli & Shigella	*E. coli* & Shigella	0.62
E. coli	*E. coli* & Micrococcus	0.024
Klebsiella oxytoca	*E. coli* & *Klebsiella oxytoca*	0.22
E. coli	Enterobacter	0.175
Pseudomonas aeruginosa	Shigella	0.21
Proteus mirabilis	*Proteus mirabilis*	0.015
Klebsiella pneumoniae	*Klebsiella pneumoniae*	0.25
Klebsiella oxytoca	*Klebsiella oxytoca*	0.034
Citrobacter freundii	*Citrobacter freundii*	0.32
Gram-negative rod	Gram-negative rod	0.2
Nonenterococcal Group D Strep	Nonenterococcal Group D Strep	0.33

- Frequent translocation of enteric bacteria into MLN in a rat cirrhosis model
- Same organisms in MLN and ascitic fluid

Runyon, B. A., Squier, S. & Borzio, M. *J. Hepatol.* **21**, 792–796 (1994).

Pathogenesis – Translocation (II)



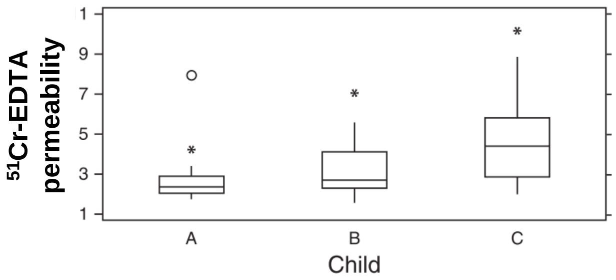
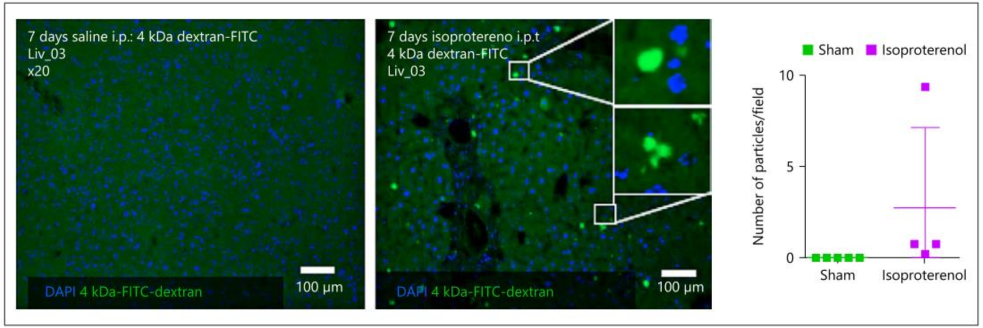


TABLE 3. Effect of Propranolol on Bacterial Translocation, Intestinal Bacterial Overgrowth, Intestinal Transit, and Intestinal Permeability of Cirrhotic Rats With Ascites

	Placebo	Propranolol
Number of animals	12	13
Portal pressure (mm Hg)	20.9 ± 4	17.2 ± 4*
Bacterial translocation (%)	58	15*
Spontaneous bacterial peritonitis (%)	33	8
Intestinal bacterial overgrowth (%)	67	15*
Aerobic bacterial stool count (logCFU/g)	7.7 ± 0.3	7.1 ± 0.3†
Intestinal transit (geometric center ratio)	0.23 ± 0.1	0.44 ± 0.1†
Intestinal permeability (% urinary excretion of ^{99m}Tc-DTPA)	16.4 ± 7	19.5 ± 8

*$P < .05$ vs. placebo.
†$P < .01$ vs. placebo.

- The gut of cirrhotic patients is "leaky" (and immunodeficient)
- Barrier defect is aggravated by beta-adrenergic signals

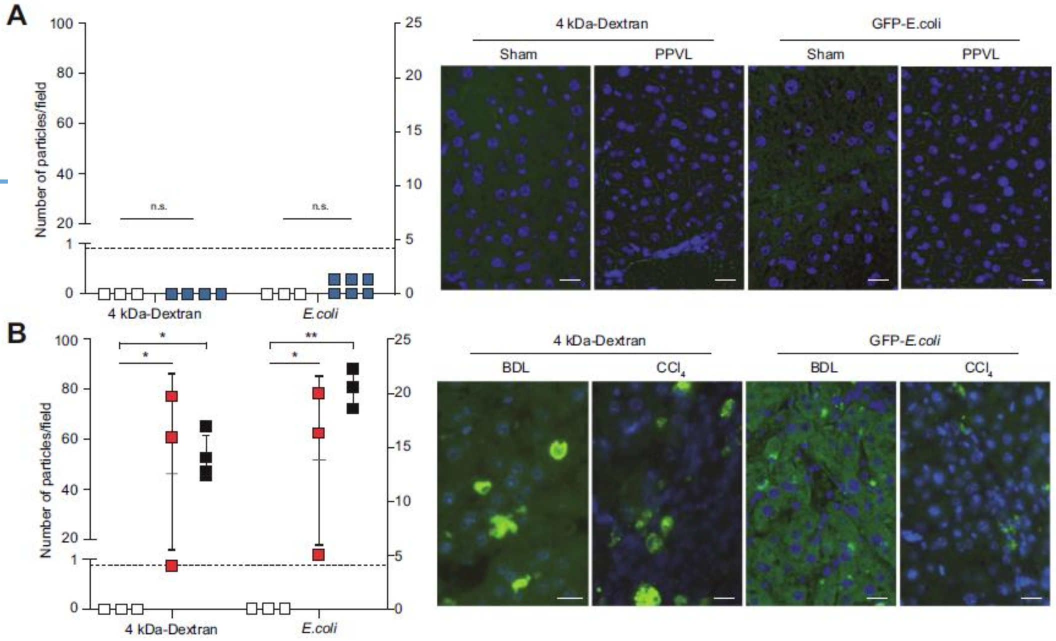


Cirera, I. *et al. J. Hepatol.* **34**, 32–37 (2001).
Scarpellini, E. *et al. Am. J. Gastroenterol.* **105**, 323–327 (2010).
Pérez-Paramo, M. *et al. Hepatology.* **31**, 43–48 (2000).
Sorribas, M. *et al. Digestion* (2019). doi:10.1159/000502112

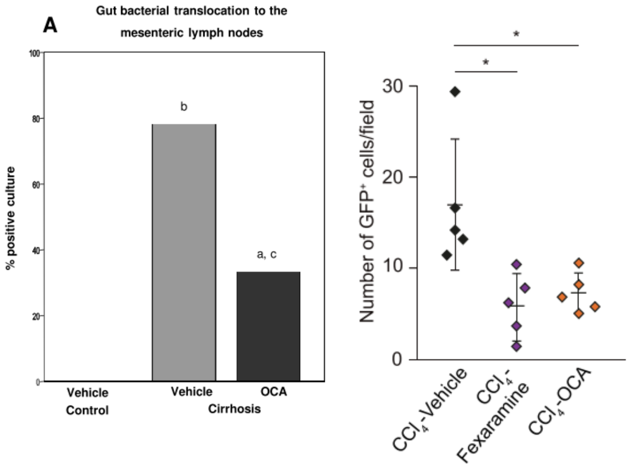
Pathogenesis – Translocation (III)

PPVL

CCl_4



Role of FXR



- PH alone does not increase BT
- FXR agonists can restore barrier

Sorribas, M. *et al. J. Hepatol.* **71**, 1126–1140 (2019).
Úbeda, M. *et al. J. Hepatol.* **64**, 1049–1057 (2016).

Pathogenesis – Reduced opsonic activity

TABLE 1. ASCITIC FLUID AND SERUM ANALYSIS

Fluid	Parenchymal liver disease	Peritoneal carcinomatosis	Massive liver metastases	Cardiac	Miscellaneous
Ascitic fluid					
Total protein (gm/dl)	1.1 ± 0.7	3.80 ± 0.73	1.6 ± 0.6	2.4 ± 2.1	3.3 ± 0.9
CH_{100} (units/ml)	12.3 ± 10.7	62.1 ± 7.8	34.7 ± 16.7	33.8 ± 23.2	22.5 ± 9.5
C_3 (mg/dl)	16.8 ± 15.6	59.2 ± 10.6	43.5 ± 16.0	42.5 ± 37.5	44.0 ± 13.2
C_4 (mg/dl)	2.7 ± 3.5	17.5 ± 2.4	12.0 ± 2.2	9.3 ± 7.8	8.8 ± 7.1
Opsonic activity (log-kill)	0.69 ± 0.98	2.53 ± 0.22	2.60 ± 0.44	1.39 ± 1.46	2.50 ± 0.33

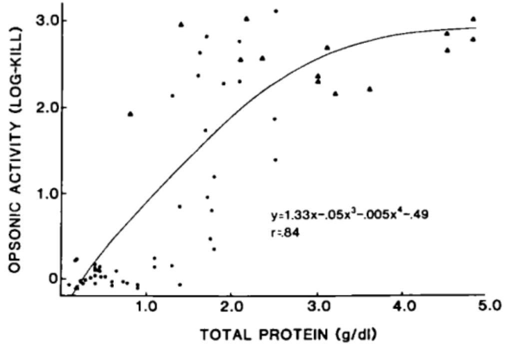
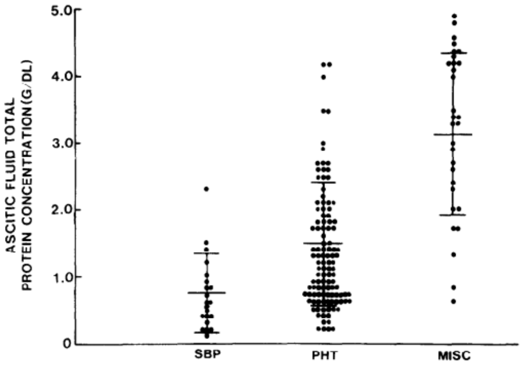


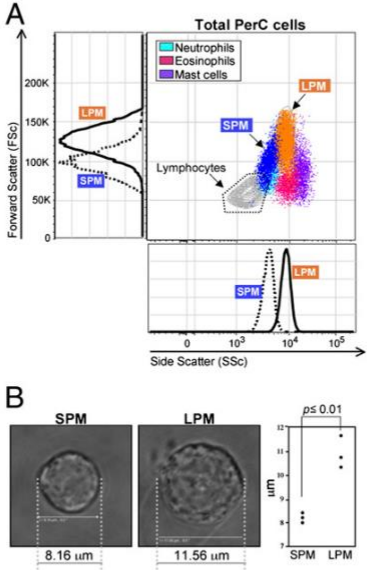
FIG. 1. Correlation of ascitic fluid opsonic activity and ascitic fluid total protein concentration; ●, cirrhotics; ▲, noncirrhotics.

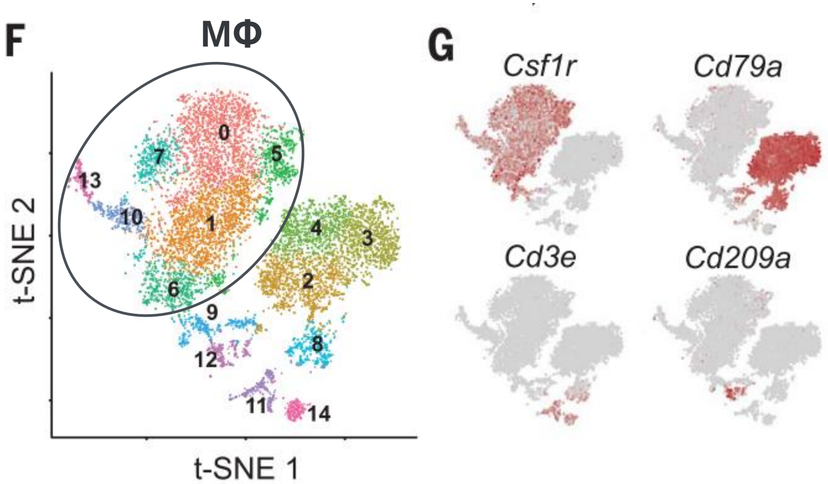


- Cirrhotic AF has reduced opsonic activity
- Low ascitic protein is associated with SBP

Runyon, B. A., Morrissey, R. L., Hoefs, J. C. & Wyle, F. A. *Hepatology* **5**, 634–7 (1985).
Runyon, B. A. *Gastroenterology* **91**, 1343–1346 (1986).

Pathogenesis – Peritoneal immune system (I)

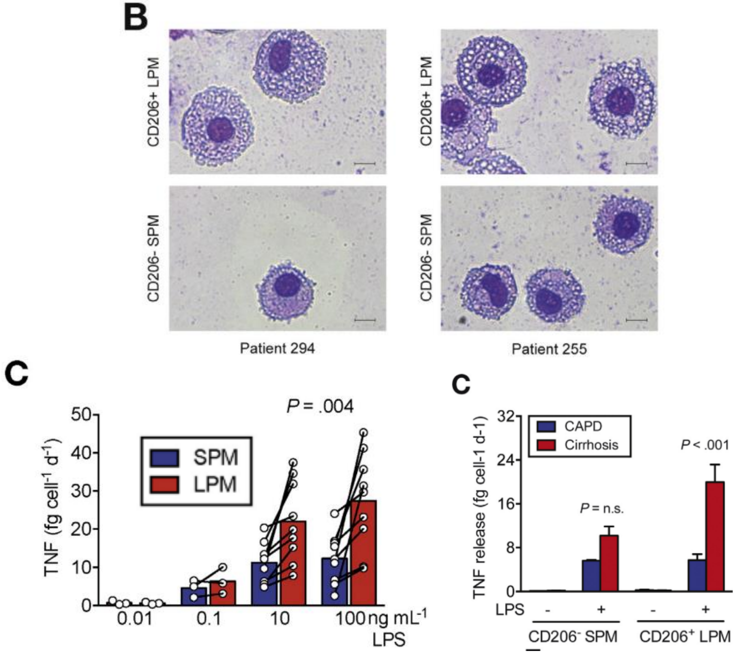


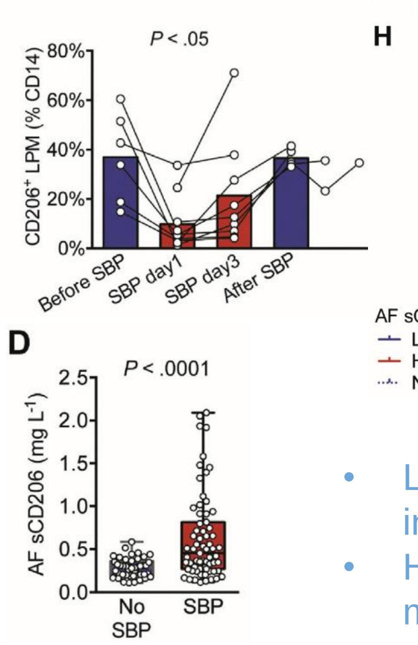


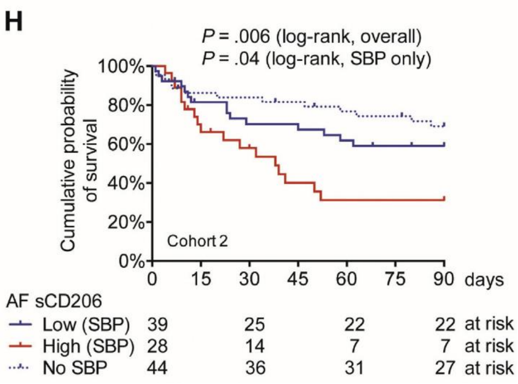
The peritoneal cavity of mice contains distinct subsets of resident and non-resident macrophages

Ghosn, E. E. B. *et al. Proc. Natl. Acad. Sci. U. S. A.* **107**, 2568–73 (2010).
Grootjans, J., Krupka N. *et al. Science* **363**, 993–998 (2019).

Pathogenesis – Peritoneal immune system (II)





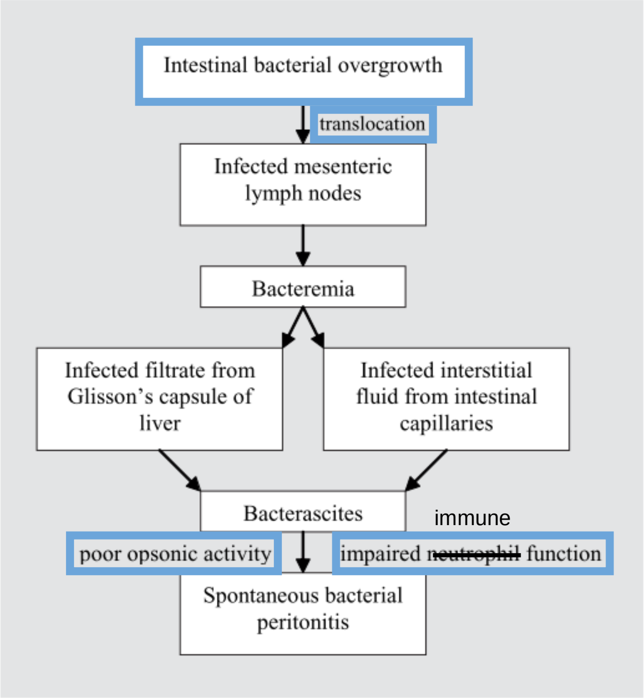


- Loss of LPM and increase in sCD206 in SBP
- High sCD206 predicts mortality

- Human peritoneal LPM are inflammatory
- LPM from cirrhotic patients: inflammatory↑↑

Stengel, S. *et al. Gastroenterology* **158**, 1745–1761 (2020).

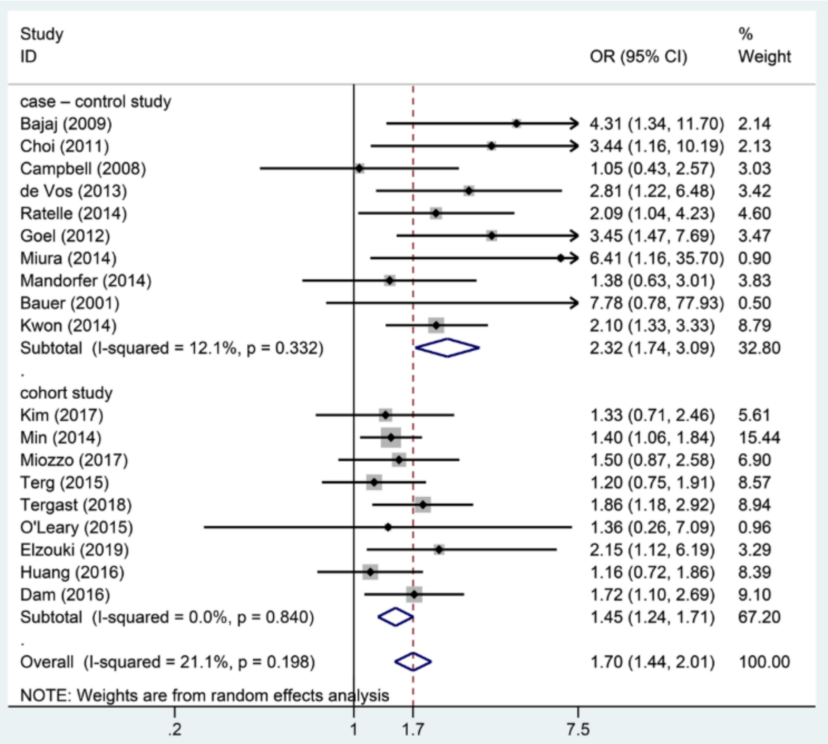
Pathogenesis of SBP – Summary



Sheer, T. A. & Runyon, B. A. *Dig. Dis.* **23**, 39–46 (2005).

Risk factors

Risk factors – PPI



- PPI use is associated with SBP
- Potential mechanism: SIBO

Lin, L. *et al*. *Hepatol. Res.* **50**, 233–245 (2020).

Risk factors – Ascitic protein

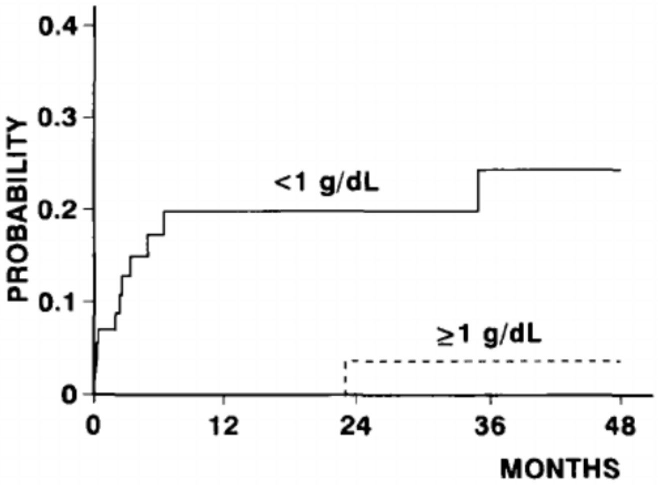


Table 4. Prognostic Variables in Cox's Regression Model

Variable	Regression coefficient	P
AF opsonic activity	−1.40511	0.0001
Serum albumin	0.10299	0.033
Prothrombin activity	−1.21597	0.038
Serum bilirubin	0.13869	0.046

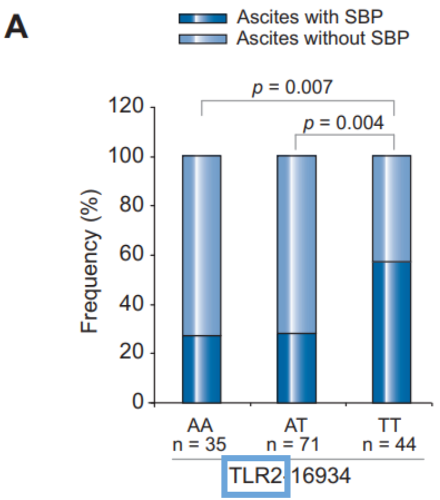
- Low AF protein is associated with SBP
- Mechanism: Low opsonic activity

Llach, J. *et al. Hepatology* **16**, 724–727 (1992).
Andreu, M. *et al. Gastroenterology* **104**, 1133–1138 (1993).

Risk factors – Genetic polymorphisms

Table 5. Numbers of Carriers of Any *NOD2* Risk Allele in Patients With Cirrhosis With and Without SBP (PMN Cell Count >250/μL)

(A) Prospective Analysis			
	SBP (PMN >250/μL)	No SBP (PMN <250/μL)	P (χ^2 test)
NOD2 risk allele	13	24	0.008
No *NOD2* risk allele	17	96	OR = 3.06 (95% CI 1.31–7.15)

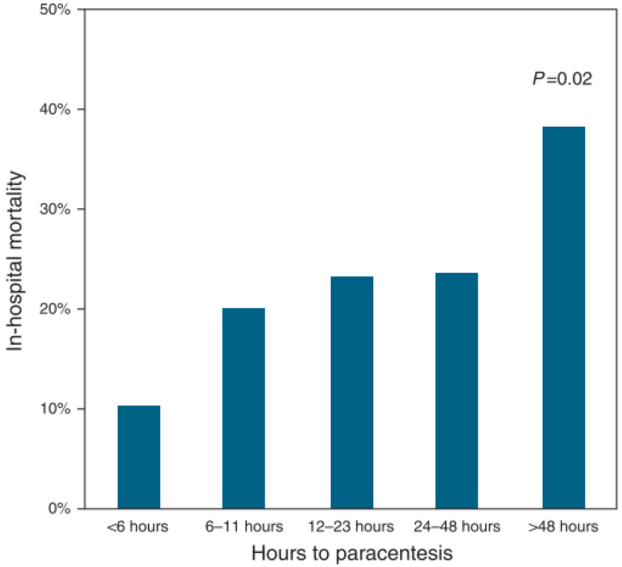


NOD2/TLR2 polymorphisms are associated with SBP

Appenrodt, B. *et al. Hepatology* **51**, 1327–1333 (2010).
Nischalke, H. D. *et al. J. Hepatol.* **55**, 1010–1016 (2011).

Diagnosis

Diagnosis



In cirrhotic patients with

- Fever
- Abdominal pain/tenderness
- Altered mental status
- Hypotension

Ascitic tap as early as possible

+3%/h in-hospital mortality

Kim, J. J. *et al. Am. J. Gastroenterol.* **109**, 1436–1442 (2014).

Diagnosis

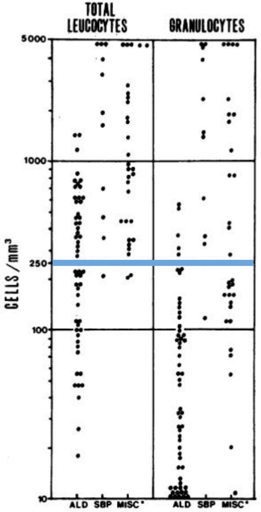


Figure 1.—Ascites fluid cell counts in 98 patients with uncomplicated alcoholic liver disease (ALD), spontaneous bacterial peritonitis (SBP) or miscellaneous conditions.

*See text

Table 1. Comparison of the Conventional Method of Ascitic Fluid Culture (and Its Modifications) to the Blood Culture Bottle Method (Using 10 ml of Inoculum)

Culture method	Episodes of bacterial growth: Positive	Episodes of bacterial growth: Negative	Total episodes	Positive (%)	Difference (%)
Conventional[a]	13	17	30	43	50
Blood culture bottle[a]	28	2	30	93	
Conventional[b] (plus two modifications)	17	13	30	57	36
Blood culture bottle[b]	28	2	30	93	

(optimistic)

- PMN are better than Leukocytes to discriminate between uncomplicated ascites and SBP
- **Bedside** inoculation of blood culture bottles with ≥10ml

Jones, S. R. *West. J. Med.* **126**, 344–346 (1977).
Runyon, B. A., Canawati, H. N. & Akriviadis, E. A. *Gastroenterology* **95**, 1351–1355 (1988).

Treatment and prophylaxis

Treatment – Choice of antibiotics (I)

Table 2 Causative microorganisms of spontaneous bacterial peritonitis, bacterascites and secondary peritonitis

Microorganisms	SBP (%)	Bacterascites (%)	Secondary peritonitis (%)
Monomicrobial			
Escherichia coli	37	27	20
Klebsiella pneumoniae	17	11	7
Pneumococcus	12	9	0
Streptococcus viridans	9	2	0
Staphylococcus aureus	0	7	11
Miscellaneous Gram-negative	10	14	7
Miscellaneous Gram-positive	14	10	0
Polymicrobial	1	0	53

SBP, spontaneous bacterial peritonitis.
Reproduced from *Sleisenger's & Fordtran's gastrointestinal and liver disease*, 7th ed, with permission from Elsevier.

- **3rd generation cephalosporin as early as possible**
- **Lack of high-quality RCTs**

"Practice [...] based on impression, not evidence"

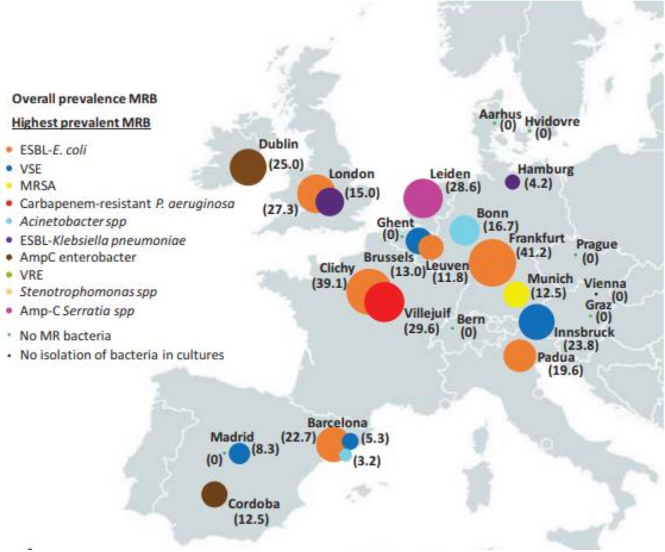
(Chavez-Tapia, N. C., Cochrane Database Syst. Rev. 2009)

Koulaouzidis, A. *et al. Postgrad. Med. J.* **83**, 379–383 (2007).

Treatment – Recent developments

Table 2. Microorganisms and 3rd-generation cephalosporins-resistant strains in SBP episodes.

		CA		HCR		NA		Total	
		N (%)	Resistant (%)*	N (%)	Resistant (%)*	N (%)	Resistant (%)*	N (%)	Resistant (%)*
Gram-negative bacteria	*E. coli*	39 (45.9)	1 (16.7)	36 (37.9)	5 (25.0)	25 (37.9)	4 (14.8)	100 (40.7)	10 (18.9)
	Klebsiella spp.	6 (7.1)	-	10 (10.5)	1 (5.0)	4 (6.1)	2 (7.4)	20 (8.1)	3 (5.7)
	Other *Enterobacteriaceae*	3 (3.5)	1 (16.7)	-	-	6 (9.1)	4 (14.8)	9 (3.7)	5 (9.4)
	P. aeruginosa	-	-	3 (3.2)	3 (15.0)	3 (4.5)	3 (11.1)	6 (2.4)	6 (11.3)
	A. baumannii	-	-	1 (1.1)	1 (5.0)	4 (6.1)	4 (14.8)	5 (2.0)	5 (9.4)
	A. hydrophyla	4 (4.7)	-	2 (2.1)	-	-	-	6 (2.4)	-
	C. jejuni	1 (1.2)	1 (16.7)	-	-	2 (3.0)	2 (7.4)	3 (1.2)	3 (5.7)
	Other Gram-negatives	1 (1.2)	-	3 (3.2)	-	2 (3.0)	1 (3.7)	6 (2.4)	1 (1.9)
	Anaerobes	-	-	-	-	2 (3.0)	2 (7.4)	2 (0.8)	2 (3.8)
	All Gram-negatives	54 (63.5)	3 (50.0)	55 (57.9)	10 (50.0)	48 (72.7)	22 (81.5)	157 (63.8)	35 (66.0)
Gram-positive bacteria	*S. pneumoniae*	13 (15.3)	-	8 (8.4)	-	3 (4.5)	-	24 (9.8)	-
	S. bovis	5 (5.9)	-	7 (7.4)	-	1 (1.5)	-	13 (5.3)	-
	S. agalactiae	3 (3.5)	-	1 (1.1)	-	1 (1.5)	-	5 (2.0)	-
	S. mitis	3 (3.5)	-	5 (5.3)	-	5 (7.6)	1 (3.7)	13 (5.3)	1 (1.9)
	S. sanguis	2 (2.4)	-	2 (2.1)	-	1 (1.5)	-	5 (2.0)	-
	S. salivarius	-	-	4 (4.2)	-	-	-	4 (1.6)	-
	Other *S. viridans*	2 (2.4)	-	3 (3.2)	-	2 (3.0)	-	7 (2.8)	-
	E. faecalis	-	-	4 (4.2)	4 (20.0)	1 (1.5)	1 (3.7)	5 (2.0)	5 (9.4)
	E. faecium	-	-	1 (1.1)	1 (5.0)	1 (1.5)	1 (3.7)	2 (0.8)	2 (3.8)
	Other *Enterococci*	1 (1.2)	1 (16.7)	2 (2.1)	2 (10.0)	-	-	3 (1.2)	3 (5.7)
	S. aureus	1 (1.2)	1 (16.7)	1 (1.1)	1 (5.0)	2 (3.0)	2 (7.4)	4 (1.6)	4 (7.5)
	Other Gram-positives	1 (1.2)	1 (16.7)	1 (1.1)	1 (5.0)	1 (1.5)	-	3 (1.2)	2 (3.8)
	All Gram-positives	31 (36.5)	3 (50.0)	39 (41.1)	9 (45.0)	18 (27.3)	5 (18.5)	88 (35.8)	17 (32.1)
Other	*Candida albicans*	-	-	1 (1.1)	1 (5.0)	-	-	1 (0.4)	1 (1.9)
TOTAL		85 (34.6)	6 (7.1)	95 (38.6)	20 (21.1)	66 (26.8)	27 (40.9)	246 (100)	53 (21.5)



- **Gram+ infections↑**
- **Resistance to 3rd-gen cephalosporins↑**

Ariza, X. *et al. J. Hepatol.* **56**, 825–832 (2012).
Fernández, J. *et al. J. Hepatol.* **70**, 398–411 (2019).

Treatment – Duration of antibiotics

Table 4. Results of the Trial

	Short course	P (95% CI)	Long course
No. of patients	43		47
Susceptible flora	27 (93.1)	NS	32 (94.1)
Infection-related mortality	0 (0)	NS (−12.3, 37)	2 (4.3)
Hospitalization mortality	14 (32.6)	NS (−32.1, 12.1)	20 (42.5)
Bacteriologic cure	27 (93.1)	NS (−14.5, 18.4)	31 (91.2)
Additional antibiotic needed because of resistance	2 (4.7)	NS	2 (4.3)
Normalized neutrophil count	38 (88.4)	NS	43 (91.5)
Afebrile in 72 h	23 (79.3)	NS	24 (75)
Pain-free in 72 h	20 (76.9)	NS	17 (68)
Side effect	2 (4.7)	NS	1 (2.1)
Relapse	1 (2.3)	NS	2 (4.3)
Reinfection	4 (9.3)	NS	4 (8.5)
Overall recurrence of infection	5 (11.6)	NS (−16.9, 14.6)	6 (12.8)
Superinfection	0 (0)	NS	0 (0)
Days of hospitalization	37 ± 38	NS	50 ± 68
Drug and administration costs/patient ($)	259 ± 34	<0.0001	486 ± 117

Short-course treatment (5d) is as efficacious as long-course therapy and significantly less expensive

Runyon, B. A., et al. *Gastroenterology* **100**, 1737–1742 (1991).

Treatment – Role of Albumin (I)

TABLE 2. CLINICAL OUTCOME ACCORDING TO THE ASSIGNED TREATMENT.*

OUTCOME VARIABLE	CEFOTAXIME (N=63)	CEFOTAXIME PLUS ALBUMIN (N=63)	P VALUE
Resolution of infection — no. (%)†	59 (94)	62 (98)	0.36
Duration of antibiotic therapy — days	6±1	5±1	0.48
Paracentesis for ascites after resolution of infection — no. (%)‡	16 (25)	14 (22)	0.83
Hospital stay — days	13±1	14±1	0.48
Renal impairment — no. (%)	21 (33)	6 (10)	0.002
Death — no. (%)			
In hospital§	18 (29)	6 (10)	0.01
At three months¶	26 (41)	14 (22)	0.03

TABLE 4. IN-HOSPITAL MORTALITY ACCORDING TO VARIABLES WITH INDEPENDENT PREDICTIVE VALUE.*

VARIABLE	CEFOTAXIME (N=63)		CEFOTAXIME PLUS ALBUMIN (N=63)	
	BUN <30 mg/dl	BUN ≥30 mg/dl	BUN <30 mg/dl	BUN ≥30 mg/dl
	no. of patients who died/total no. (%)			
Bilirubin <4 mg/dl				
Prothrombin time ≥60% of control	0/13	3/6 (50)	0/10	1/10 (10)
Prothrombin time <60% of control	0/7	2/8 (25)	0/14	2/5 (40)
Bilirubin ≥4 mg/dl				
Prothrombin time ≥60% of control	1/3 (33)	1/5 (20)	0/0	0/1
Prothrombin time <60% of control	4/12 (33)	7/9 (78)	0/16	3/7 (43)
Total	5/35 (14)	13/28 (46)	0/40	6/23 (26)

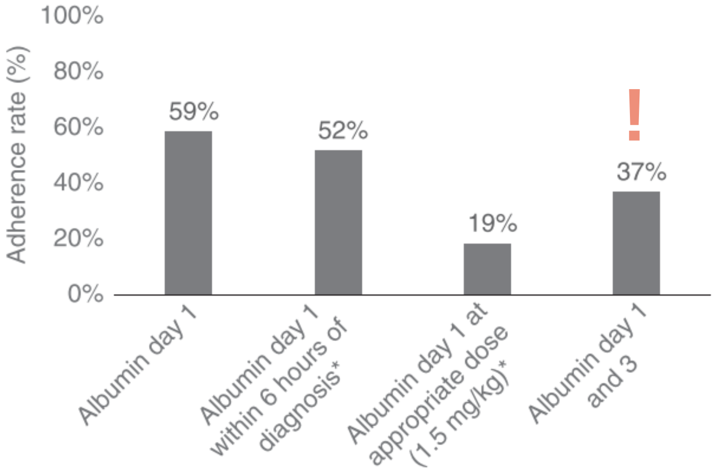
I.v. albumin → Renal impairment ↓ → Mortality ↓

Sort, P. *et al. N. Engl. J. Med.* **341**, 403–9 (1999).

Treatment – Role of Albumin (II)

Recommendation

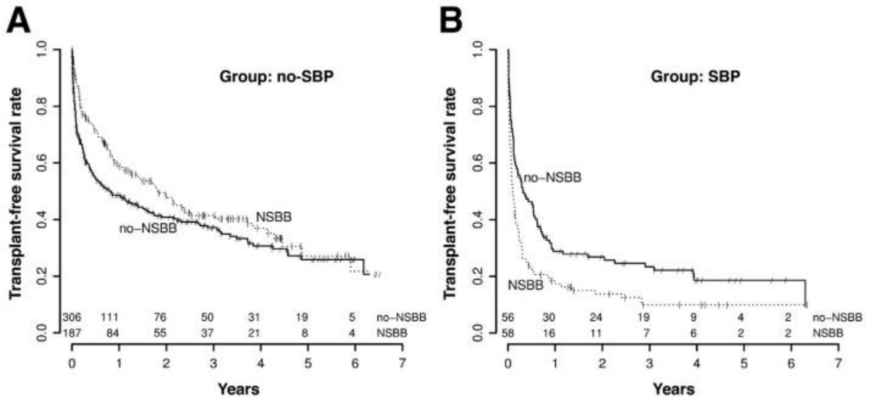
- The administration of albumin (1.5 g/kg at diagnosis and 1 g/kg on day 3) is recommended in patients with SBP **(I;1)**.



Don't forget the d3 albumin!

Angeli, P. *et al. J. Hepatol.* **69**, 406–460 (2018).
Peeraphatdit, T., et al. *Aliment. Pharmacol. Ther.* **42**, 241–2 (2015).

Treatment – What to do with NSBB?



- NSBBs in SBP were associated with hemodynamic instability, HRS and death in a retrospective analysis
- **But:**
  - Results not confirmed in other studies
  - NSBB prevent decompensation and death (PREDESCI)

→ Consider temporary NSBB stop and/or dose adjustment.

→ SBP is NO contraindication for NSBB

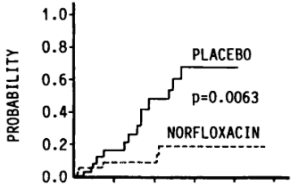
Mandorfer, M. *et al. Gastroenterology* **146**, 1680–1690 (2014).
Villanueva, C. *et al. Lancet* **393**, 1597–1608 (2019).

Prophylaxis

- 70% risk of SBP recurrence within 1 year

  Tító L. *et al. Hepatology* 1988

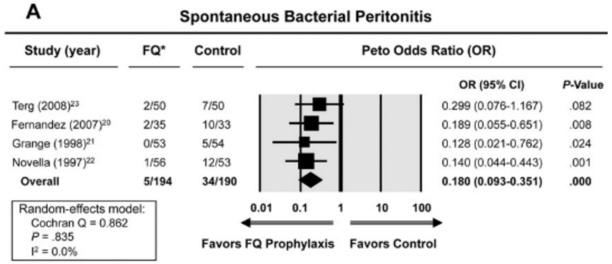
→ **Secondary prophylaxis is effective**



- Cirrhotic patients with AF protein <10 g/L and/or high serum bilirubin at high risk of developing SBP

  Llach, J. *et al. Hepatology* 1992

→ **Primary prophylaxis is effective in high-risk patients**



Agent of choice: Norfloxacin 400 mg/d

Ginés, P. *et al. Hepatology* **12**, 716–724 (1990).
Loomba, R. *et al. Clin. Gastroenterol. Hepatol.* **7**, 487–493 (2009).

Concluding remarks

- SBP is frequent and easy to miss
  → Diagnose and treat early, don't forget albumin

- Bacterial overgrowth/translocation and peritoneal immune status are critical
  → Critically assess PPI therapy
  → More studies needed to define roles of FXR agonists and peritoneal immunity

- Emergence of drug resistance is concerning
  → Consider broad-spectrum therapy in critically-ill patients and/or nosocomial infections
  → Observe local resistance patterns

- Role of NSBB is controversial
  → Do not routinely stop NSBB, consider dose adjustment

- Prophylaxis is important, but long-term survival poor after first episode of SBP
  → Consider transplant