

**Spontaneous Bacterial Peritonitis in
Cirrhotic Ascites:
Basic Medicine in the Molecular Age**

Robert K. Ockner, M.D.

Professor of Medicine Emeritus

Liver Center and Division of Gastroenterology

University of California, San Francisco

May 7, 2009

Robert K. Ockner, M.D.

Robert K. Ockner, M.D. is Professor of Medicine Emeritus of the University of California, San Francisco (UCSF). He graduated from Pomona College (1957) and Harvard Medical School (1961), completed residency training in internal medicine on the Harvard Medical Service of the Boston City Hospital (1966), clinical and research fellowship training in gastroenterology at the Massachusetts General Hospital (1968), and served for 2 years as Clinical Associate in Medicine in the Digestive Diseases Unit at the National Institutes of Health (1963-65). He joined the faculty of the Department of Medicine at UCSF (1968-2004), advancing to Professor of Medicine, and serving as Chief of Clinical Gastroenterology at Moffitt-Long Hospital (1971-82), Director of the Division of Gastroenterology (1983-90), and Director of the UCSF Liver Center (1983-98). He has been a member of the American Association for the Study of Liver Disease, the International Association for Study of the Liver, the American Gastroenterological Association, the Association of American Physicians, the American Society for Clinical Investigation, and the American College of Physicians.



Robert K. Ockner, M.D.

He served as President of the American Association for the Study of Liver Diseases (1983-84), Editor-in-Chief of Gastroenterology (1981-86), Co-Editor of Progress in Liver Diseases (1992-97), and Consulting Editor for Digestive Diseases for the 19th and 20th editions of the Cecil Textbook of Medicine. He was a member of the National Digestive Diseases Advisory Board (1987-91; chairman, 1988-89). His NIH-funded research (1969-96) focused primarily on fatty acid metabolism and the fatty acid binding proteins, which he first described in 1972. His interest in the broader importance of fatty acids in health and disease led to new concepts and hypotheses, developed and presented in a single-author book before his October, 2004 retirement (Integration of Metabolism, Energetics, and Signal Transduction: Unifying Foundations in Cell Growth and Death, Cancer, Atherosclerosis, and Alzheimer Disease; Springer, New York; 2004). Since retirement, he and his wife Elaine have lived in Southern California, where he continues to survey advances in medical sciences that are related to the hypotheses advanced in his book.



Spontaneous Bacterial Peritonitis (SBP)

- Acute bacterial peritonitis without primary infection, perforation, or ischemia of abdominal organ
- Advanced liver disease (most are CTP-C) with ascites; HRS may develop in 1/3; age/MELD score independent prognostic factors (Nobre, EJGH 2008)
- Bacterial infection in cirrhosis:
 - 30-50% of hospitalized cirrhotic patients (SBP in 25-30%)
 - 45% in cirrhotics with g.i. bleed (28% mortality)
 - schistosomal liver disease in absence of chronic hepatitis?

Spontaneous Bacterial Peritonitis: Topics for Discussion

- General description of the syndrome
- Pathogenesis
- Clinical presentation
- Differential diagnosis
- Clinical diagnosis
- Newer tests
- Treatment and prevention
- Summary

Pathogenesis of SBP: Current Concepts

- Impaired immunity in advanced chronic liver disease
 - ↓ complement, RES function, phagocytosis
 - ? ↑ gut permeability
 - bacterial overgrowth: PPI may predispose (69% of SBP used, 31% of controls - retrospect.) (Bajaj Am J Gast 2009); SID in schistosomiasis → ↑ ascites C3, opsonic and bactericidal activity (ElAggan J Egypt Soc Parasit 1993)
- Bacterial translocation, lumen to mesenteric nodes
 - invasion of peritoneal surfaces and ascites fluid
- Systemic inflammatory response, +/- sepsis
- ↑ proinflammatory cytokines (TNF α , IL-6, etc.)

QuickTime™ and a
decompressor
are needed to see this picture.

Clinical Presentation of the SBP Patient

- “Typical” picture: fever, abdominal pain, peritoneal signs in the setting of cirrhosis and ascites
- BUT, symptoms and signs may be quite variable:
 - afebrile without symptoms or peritoneal signs
 - mental change or portalsystemic encephalopathy
 - progressive increase in serum creatinine
 - progressive deterioration in liver function
- Thus, all hospitalized patients with cirrhosis and ascites should be evaluated for SBP

SBP: Differential Diagnosis

- Secondary peritonitis (perforated, ischemic, or inflamed abdominal organ, pelvic inflammation)
- Peritoneal carcinomatosis
- Tuberculous peritonitis
- Causes of ascites not usually associated with SBP suggest key role of abnormal portal/hepatic structure and function: nephrotic syndrome, constrictive pericarditis, protein-losing enteropathy

SBP Diagnosis: Essential Studies

- Diagnostic paracentesis: all hospitalized cirrhosis and ascites patients (large volume only as indicated)
- Tests to be performed: ascites fluid and imaging
 - WBC and neutrophil (PMN) counts; RBC if fluid bloody
 - bedside aerobe/anaerobe cult. (10ml → blood cult. bottles)
 - protein (usually < 1.0 g/dL), amylase, glucose, LDH
 - gram stain; cytology; Tbc stain/PCR/culture
 - Imaging: flat/upright; soluble contrast, CT/MRI (prn)

SBP: Ascites Fluid Cell Count

- Initially, cell counts may be only basis for making diagnostic and therapeutic decisions
- Polymorphonuclear neutrophils (PMN)
 - “normal”: $< 250/\text{mm}^3$
 - suggestive of SBP: $> 250/\text{mm}^3$
 - strongly suggestive of SBP: $> 500/\text{mm}^3$
- If fluid bloody, allow one PMN for each 250 RBC
- If cell count high, but most are not PMNs, consider peritoneal tuberculosis or carcinomatosis

Bacterial Culture of Ascites in SBP

- Use of blood culture bottles (10ml ascites) ↓s false negatives (may be 30-50%); bacteremia in 50%
- Culture results may not be available before 36-48 hr
- “Always” a single organism, esp. coliforms, Klebsiella, Strep pneumoniae, enterococci
- Anaerobes unusual (approx. 2% of cases)
- Findings suggestive of secondary peritonitis:
 - >1 organism; gas/bowel contents; ascites
 - LDH > serum; protein >1.0g/dL; glucose <50mg/dl

SBP Cell Count & Culture Variants

- “Classical” SBP: >250 PMN/mm³; 48hr culture +
- Culture Negative Neutrocytic Ascites (CNNA)
 - PMN >250 /mm³
 - culture negative at 48 hr.
- Monomicrobial non-Neutrocytic Bacterascites (MNB)
 - PMN <250 /mm³
 - culture positive at 48 hr; antibiotic Rx usually indicated
- For all variants except MNB, early decision to start antibiotics based on initial PMN count

SBP Diagnosis: Newer Tests

- Bacterial DNA
 - specific: organism identified 4X faster (Sugihara, Intern. Med. 2009)
 - non-specific (culture negative fluid):
 - activates macro Φ / TNF α , \uparrow HRS/SBP/death (ElNaggar, J Med Micro '08)
+ in 1/3 cirrhotic/ascities; poor prognosis (Zapater, Hepatology. '08)
- Procalcitonin, C-reactive protein (ElDahab, AALJ 2007)
 - acute phase reactant proteins produced in liver
 - serum procalcitonin predictive of SBP diagnosis and severity
- Lactoferrin: may dx SBP vs. non-SBP (Parsi, Gastro 2009)
- Leukocyte esterase reagent strips to estimate PMN count: faster than manual, but studies conflicting
- Automated cell counter: faster than manual, same results

SBP: Initial Challenges in Diagnosis and Treatment

- Symptoms/signs often absent or non-specific
- Laboratory test results incomplete:
 - ascites fluid culture not usually available until 48 hr.
 - presumptive diagnosis depends on ascites PMN count
 - secondary peritonitis not ruled out; inform surgeons
- Actions to be initiated as soon as possible:
 - antibiotic Rx early if PMN $>250/\text{mm}^3$
 - evaluation of ? secondary peritonitis as indicated
 - albumin i.v. (e.g. 50ml, 20% qdx3) if bili >4 , creat. > 1 mg/dl; may \downarrow endotoxin, TNF α , IL-6 (Chen, Scand J Gast 2009)

Treatment of SBP: Initial Antibiotic Choice

- Pending culture, Rx with 3rd gen. cephalosporins, 5-8 d; Ceftriaxone, Cefotaxime; or, amoxicillin/clavulanate
- Preferred vs. aminoglycosides (nephrotoxicity) and fluoroquinolones (increasing bacterial resistance)
- Cover anaerobes if secondary peritonitis suspected
- Choice of agent depends on antibiotic sensitivities and local experience; community acquired vs. nosocomial
- Current antibiotic Rx of SBP: “impression, not evidence” (Chavez-Tapia, Cochrane Database Syst. Rev. 2009)
- Continuing close clinical follow-up essential

Treatment of SBP:

Follow-up Decisions at 48 Hours

- Repeat PMN count
 - if PMN ↓ is $\geq 50\%$, finish 5-day antibiotic course
 - if PMN ↓ is $<50\%$ or ↑, adjust antibiotics to sensitivities
- Results of culture
 - adjust antibiotics as indicated by response and sensitivities
 - if culture negative (CNNA), finish 5-day antibiotic course
 - pos. culture but initial PMN $<250/\text{mm}^3$ (MNB): Rx most, or obtain repeated PMN counts (newer tests helpful?)
 - anticipate 15-20% mortality in spite of antibiotic Rx

Treatment of SBP:

Long-Term Follow-Up and Prophylaxis

- Antibiotic treatment of patients with SBP risk factors
 - After successful treatment of acute SBP: norfloxacin 400mg/d, 1 yr.: → ↓ recurrence rate (40-70→20%)
 - Gastrointestinal bleeding (not necessarily variceal) in cirrhotic patient with ascites
 - 44% develop infections, with 28% mortality
 - short-term prophylaxis (norfloxacin or ceftriaxone, 7 days, →↓ infection (45 → 14%) and death (24 → 15%))
- HCV Rx →↑ SBP on OLT list (Carrion, J Hepatology, 2009)
- Continue management of ongoing liver disease
- Consider evaluation for liver transplantation

Spontaneous Bacterial Peritonitis: Summary

- Common complication of cirrhotic ascites
- Presenting features often non-specific; surgical consult prn
- Dx/Rx require continuing bedside evaluation, fluid analysis:
 - ascites PMN count, culture fluid with blood culture bottles
 - start antibiotics if PMN count $>250/\text{mm}^3$
 - repeat paracentesis with PMN count and culture at 48 hr., with adjustment of Rx as indicated
- Prophylaxis indicated for patients at risk (e.g., after Rx of SBP or g.i. bleed); bacterial resistance a common issue
- Treat chronic liver disease as indicated; newer tests may help