Infectious Complications of Cirrhosis

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Dwain L. Thiele, M.D. has no financial interests or other relationships with commercial concerns related directly or indirectly with this program. Dr. Thiele will be discussing "off-label" uses in his presentation.

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Infectious illnesses are common in patients with cirrhosis. In part, this relates to the fact that cirrhosis itself is often a late complication of viral infection. In addition, in the U.S., adults with cirrhosis commonly have a history of alcoholism and / or injection drug use and thus have an increased risk for a variety of infectious illnesses epidemiologically associated with these practices. However, a unique set of infectious complications, distinct from the infectious complications of alcoholism and / or drug abuse, has been found to be common to all types of cirrhosis and to be a major source of morbidity and mortality in these patients.

In the 1950's and early 1960's a series of clinical reports noted the association between cirrhosis of the liver and bacteremias due to gram-negative bacilli that presented as "primary" blood borne infections without an obvious tissue source (1-3). In 1964, a seminal paper by Conn (4) described the syndrome of spontaneous bacterial peritonitis (SBP) and bacteremia in Laennec's cirrhosis. Over the ensuing two decades this syndrome of "SBP" came to be increasingly well characterized. Diagnosis and treatment of SBP soon became the focus of efforts to recognize and deal with the bacterial infectious complications of cirrhosis. In addition, infected ascites came to be viewed as the "tissue source" of the bacteremias first publicized by Whipple, Harris and Tisdale (1,2). Over the past two decades, progress has been made in both clarifying the pathogenesis of SBP and in dealing with this complication of cirrhosis in a prophylactic manner. This has led to a renewed appreciation for the increased incidence of bacteremias, either associated with or separate from episodes of SBP, in patients with cirrhosis and, in turn, to a better understanding of the important role that the liver plays in innate immunity to bacterial infection.

Bacteremia in Cirrhosis

Following early case reports identifying gram-negative bacteremia as a complication of advanced liver disease, a number of epidemiologic observations have confirmed that cirrhotics are at substantially higher risk for blood borne dissemination of a variety of bacterial pathogens. Among patients presenting to emergency care facilities (5) or admitted to general hospitals (6,7), cirrhosis has been identified as a major risk factor for development of bacteremia in patients without an apparent source as well as for bacteremia associated with respiratory, urinary tract and soft tissue infections. In a Danish study of patients hospitalized between January 1, 1975 and December 31, 1984, the yearly incidence of bacteremia among cirrhotic patients was 4.5% versus 0.99% among non-cirrhotic hospitalized patients (6). When adjusted for age, the relative risk of bacteremia among cirrhotics was found to be 7 fold higher than among other hospitalized patients. While *Escherichia coli* and other gram-negative colonic flora are among the most common causes of bacteremia in cirrhotics (6-8) staphylococcal, streptococcal and pneumococcal infections are also commonly noted (5-8) and a 5-10 fold increased risk for fatal bacteremic pneumococcal infections (9) and invasive Group B streptococcal disease (10) has been reported among patients with cirrhosis.

Patients with cirrhosis account for only 2-3% of most general hospital admissions (6,9,10). Thus, despite exhibiting a 5-7 fold higher risk for development of bacteremic, cirrhotics usually account for only 10-25% of cases of bacteremia among hospitalized patients. However, patients with cirrhosis account for 35-100% of cases of bacteremias secondary to a select group of organisms that typically produce minimal or only localized disease in healthy humans. In a review of published

cases of *Pasteurella multocida* bacteremia, 34% of cases reported worldwide and 77% of cases from a single hospital in France occurred in patients with cirrhosis (11). 40% of cases of *Pasteurella multocida* bacteremia in cirrhotics (11) are fatal. In contrast, a localized cellulitis is the most common outcome in normal humans infected by this gram-negative coccobacillus that is typically transmitted by animal bites. In two Spanish series of bacteremias due to *Campylobacter* species, 34-50% of patients had cirrhosis with mortality rates among cirrhotics being higher than in other bacteremic patients. Similarly, in a report from Taiwan (14), 36% of cases of *Aeromonas* bacteremias in a single hospital and 45% of *Aeromonas* bacteremias reported in a multi-hospital survey from Taiwan occurred in patients with cirrhosis. Even more impressive are reports of the prevalence of cirrhosis among individuals presenting with bacteremic illnesses caused by other *Vibrionaceae* family bacteria. Non-O1, non-O139 *Vibrio cholerae* bacteremia has been associated with underlying cirrhosis in 44% of Western cases and 75-100% of cases from Taiwan. Similarly, almost all cases of *Vibrio vulnificus* bacteremia appear to occur in cirrhotic patents (17-19).

In addition to exhibiting a higher rate of bacteremia following infection by a wide variety of bacterial pathogens, patients with cirrhosis exhibit an increased prevalence of localized infections by gram-negative enteric organisms. Gram-negative bacilli have been found to be involved in an appreciable fraction of cases of bacterial meningitis in cirrhotics with *Escherichia coli* being the most common causative agents (20). In addition to the rare cases of cellulitis or soft tissue infection by various *Vibrio* species in patients with cirrhosis, cases of *Escherichia coli, Klebsiella Pneumoniae* and *Pseudomonas aeruginosa* cellulitis have been reported in patients with advanced cirrhosis (21). Finally, as initially appreciated by Conn (4), spontaneous bacterial peritonitis caused by gram negative enteric organisms is common among adults with ascites secondary to cirrhosis but quite rare in ascites secondary to other etiologies (22). In children with nephrotic syndrome, a significant incidence of SBP is observed, but *S. pneumoniae* or other gram-positive organisms play a more prominent role (23).

Table 1

Risks of Bacterial Infectious Complications in Cirrhosis

5 - 10 fold ↑Risk	> 10 fold ↑Risk	> 90% of cases in cirrhotics
Bacteremia of inapparent cause	*Campylobacter* species bacteremia	*Vibrio vulnificus* bacteremia
Bacteremia in hospitalized patients	*Aeromonas* bacteremia	Spontaneous bacterial peritonitis in adults
Pneumococcal bacteremia	Non-O1 *Vibrio cholerae* bacteremia	
Invasive Group B streptococcal infection	*Pasteurella multocida* bacteremia	

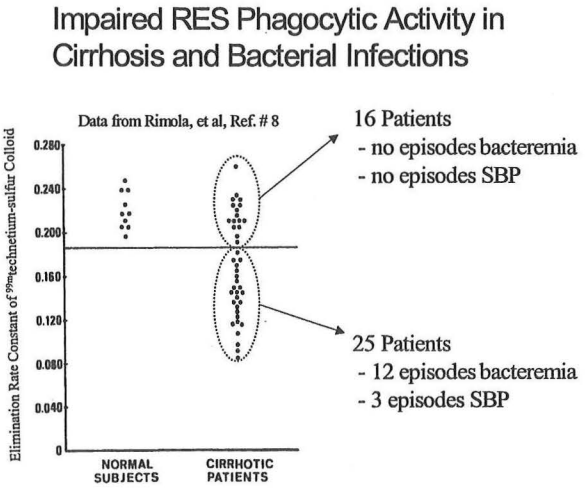
Effects of Cirrhosis on Host Immune Defenses

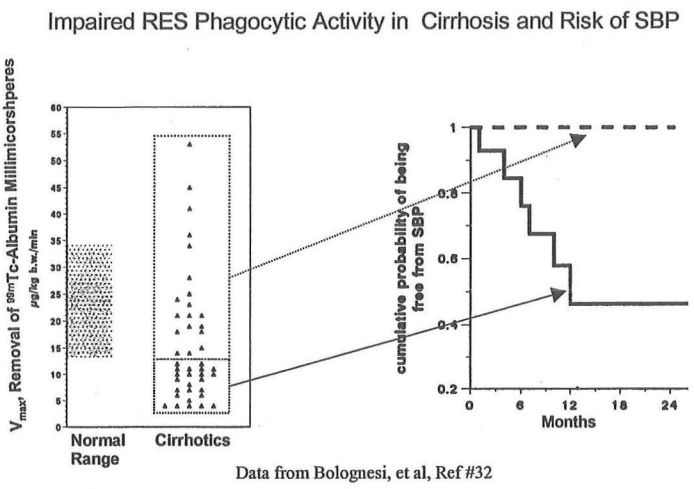
In fetal life, the liver is the major hematopoietic organ. However, in adult life, the liver is inhabited by only a small population of lymphocytes that predominately exhibit phenotypic and functional characteristics of NK cells, CD8+ T cells and non-conventional CD4-, CD8- or CD8 α/α

T cells (24). It is likely that these lymphocytes along with lymphocytes that migrate into the liver following infections play an important role in immune responses to hepatotropic viruses and other intracellular pathogens such as *Listeria monocytogenes*. However, with respect to antigen-specific immune responses, the liver appears to serve largely as a tolerogenic environment related to the paucity of Class II MHC expressing antigen presenting cells and the apparent evolution of mechanisms that permit the host to avoid overly exuberant immune responses to the plethora of environmental antigens and inflammatory stimuli delivered to the liver by the portal circulation (24).

In contrast to the apparently minor role that the liver plays in antigen-specific, adaptive immune responses, the liver is a principal site of innate immune responses. Not only is the liver the site of acute phase protein synthesis (25) but it also serves as the major reticuloendothelial organ responsible for phagocytic clearance of bacteria and other non-physiologic particles that enter the portal or systemic circulation (8, 26, 27). Synthesis of albumin and various clotting factors is diminished in patients with advanced cirrhosis and deficiencies in hepatic synthesis of these proteins is commonly used as a marker of liver disease severity. In contrast, levels of most hepatic phase proteins are elevated rather than depressed in patients with chronic liver disease (28). However, in humans with advanced cirrhosis as well as in animal models of cirrhosis (29,30), diminished levels of total hemolytic complement activity and of the complement proteins C3 and C4 are observed. Levels of opsonic C3b have been shown to be of critical importance in hepatic clearance of pneumococci and in a rat model of cirrhosis, reduced clearance of pneumococci has been associated with reduced complement levels (30,31). However, in this same model, animals with less advanced cirrhosis and normal serum complement levels nevertheless exhibited diminished clearance of pneumococci. Such findings as well as correlative studies performed in humans suggest that additional profound defects in hepatic reticuloendothelial function are present in cirrhosis and also play a critical role in susceptibility to bacterial infection.

Prior to the development of modern ultrasonographic, tomographic and magnetic imaging techniques, ^{99m}technetium-sulfur colloid was widely used in nuclear medicine scans of the liver performed for the purpose of assessing liver architecture and function. ^{99m}Technetium-sulfur colloid along with similar ^{99m}technetium- or ^{125}I-labeled macromolecules are removed from the circulation by the reticuloendothelial system (RES) with the majority of these radioactive markers cleared by the liver Kupffer (+/- endothelial) cells in normal humans (8, 27, 28). In



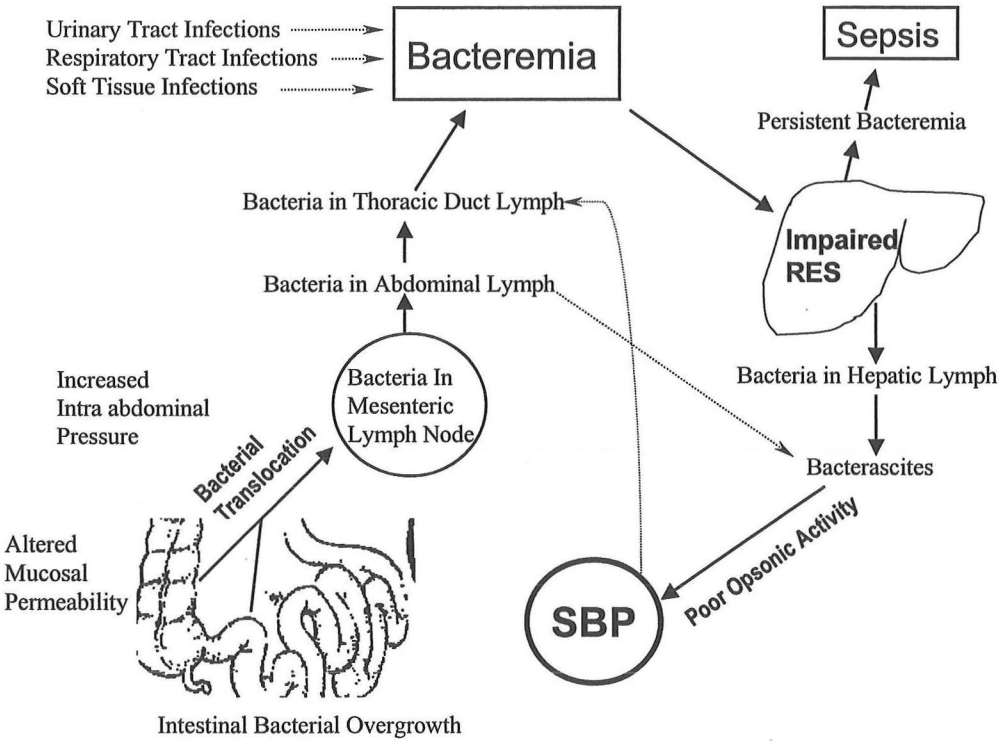


patients with various forms of liver disease, the degree of impairment in RES function varies widely and correlates imperfectly with degree of portal hypertension or with other markers of hepatic synthetic function such as serum bilirubin or albumin levels or degree of prothrombin time prolongation (8, 28), although closer correlation between degree of RES dysfunction and levels of hypergammaglobulinemia is noted (8,28). Of great interest, however, is the finding by Rimola, et al (8) that "spontaneous" bacteremias and peritonitis appear to occur exclusively in cirrhotic patients with depressed RES function. In more recent prospective studies by Bolognesi, et al (32), all patients who developed spontaneous bacterial periotonitis were found to have diminished rates of removal of ^{99m}technetium labeled millimicrospheres by the liver RES and when compared to other commonly measured clinical parameters, diminished RES function was found to be the best predictor of this infectious complication. These observations confirm the much earlier experimental findings and conclusions by Beeson, et al who reported that the liver is the most active site of clearance of bacteria from the blood of patients with bacterial endocarditis (26).

Role of Bacterial Translocation from the Gastrointestinal Tract in Infectious Complications of Cirrhosis

Studies designed to investigate mechanisms responsible for gram-negative bacteremias and /or the manifestations of multiple organ failure that develop in patients with trauma, burn injuries or severe respiratory infections have led to the concept of "bacterial translocation" from the gastrointestinal tract (33) as a mechanism whereby enteric bacteria enter the bloodstream and trigger the clinical syndrome of gram-negative sepsis and / or the systemic inflammatory response syndrome that leads to multiple organ failure. Bacterial translocation is defined as the passage of viable bacteria from the gastrointestinal tract to extraintestinal sites such as mesenteric lymph nodes, the liver or the bloodstream. In animal models, bacterial translocation is promoted by changes in gastrointestinal function that permit intestinal bacterial overgrowth, increased intestinal permeability or deficiencies in host phagocytic defenses (33-35). In animal models of shock and gut hypoperfusion in which mucosal epithelium is damaged, bacteria translocate between epithelial cells to directly enter the blood stream, whereas in models in which the intestinal barrier is not damaged, bacteria translocate by an intracellular route through either specialized M cells overlying Peyer's patches or through other intestinal epithelial cells to enter the lymphatics draining into mesenteric lymph nodes (33-35).

In a rat model of carbon tetrachloride induced cirrhosis and ascites, Runyon, et al (36) as well



as other groups of investigators (37) have found evidence for translocation of gram-negative enteric flora to mesenteric lymph nodes. Moreover, in this animal model of cirrhosis and ascites, spontaneous bacterial peritonitis is observed only in animals with bacterial translocation. In addition, organisms cultured from ascitic fluid are invariably also present in mesenteric node cultures. Colony counts of these organisms were found to be higher in mesenteric lymph nodes than ascitic fluid (36). Finally, while 47% of mesenteric node cultures were polymicrobial only 7% of ascitic fluid cultures were positive for more than one organism. These observations argue that bacteria that translocate to mesenteric lymph nodes are the likely source of ascitic fluid colonization and the development of "spontaneous" bacterial peritonitis in cirrhotics. Differential propensity for translocation and/or the "filtering" effect of mesenteric nodes also appears to be a plausible explanation for the observation that bacteremias and / or episodes of SBP in cirrhotics are usually caused by enteric flora such as *Escherichia coli* or *Klebsiella Pneumoniae*, whereas the most abundant colonic flora, anaerobes and enterococci, are rarely identified as causative agents. These features of SBP are in striking contrast to peritonitis secondary to bowel perforation where polymicrobial infections representative of overall intestinal flora are more typical.

A number of mechanisms have been proposed as explanations for bacterial translocation in cirrhosis. Edema of the small intestine and colonic mucosa due to portal hypertension and secondarily altered mucosal permeability have been proposed as one potential cause for bacterial translocation (36,37). However, efforts to induce bacterial translocation in animal models by creation

of portal hypertension alone have met with mixed results with one group of investigators finding that acute portal hypertension is associated transiently with translocation of bacteria to mesenteric lymph nodes, while chronic portal hypertension is not (38). Others have found a detectable incidence of bacterial translocation in portal hypertensive rats, but noted a much more striking increase in bacterial translocation among portal hypertensive rats following hemorrhagic shock (39).

Such observations have led to the suggestion that factors other than portal hypertension such as diminished intestinal macgrophage function and / or opsonic activity must also play a role in the observed prevalence of bacterial translocation in cirrhosis. In addition, in the rat model of carbon tetrachloride induced cirrhosis and ascites, diminished intestinal transit times, bacterial overgrowth in the small intestine and increased bowel permeability have been observed with frequency of bacterial translocation found to be highest in animals manifesting both intestinal bacterial overgrowth and increased bowel permeability (37). Humans with cirrhosis and bacteremia have also been found to have increased intestinal permeability (40) as well as evidence of small intestinal bacterial overgrowth (41). Finally, increased intra abdominal pressure produced by intraperitoneal infusion of balanced salt solutions in animal models has been associated with an increased incidence of bacterial translocation (42) suggesting that the increased intra abdominal pressure associated with ascites may also play a role in bacterial translocation in cirrhosis.

Clinical Predictors of Bacterial Infectious Complications of Cirrhosis

The spectrum of bacteria isolated from patients with cirrhosis as well the nature of immune defects observed in humans and animals with cirrhosis argue that bacterial translocation from the gastrointestinal tract in combination with diminished opsonic activity and greatly impaired RES function in cirrhosis most likely accounts for much of the increased prevalence of bacteremia and other serious bacterial infectious complications of cirrhosis. However, mesenteric lymph node cultures cannot be easily obtained or followed sequentially in clinical settings and assessment of RES function with radioisotope techniques appears to be a dying clinical practice.

With recognition that SBP is both a common infectious complication of cirrhosis and is frequently, though not invariably, an associated finding in cirrhotic patients with gram-negative bacteremia, identification and management of SBP has become a major focus of clinical efforts to deal with the bacterial infectious complications of cirrhosis. In multiple clinical studies (43-48), the best single, commonly available laboratory parameter found to predict risk for development of SBP has been the presence of very low total protein concentrations (< 1.0 g/dl). It has been postulated that the predictive value of low total protein concentrations relates to the correlation between total protein levels and levels of individual proteins such as fibronectin, C3, and immunoglobulin molecules that contribute to opsonic activity in ascitic fluid (43-48). This hypothesis has been substantiated in a study where levels of individual complement and immunoglobulin proteins as well as total protein and overall functional opsonic activity were assessed. In step-wise Cox regression analysis, ascitic fluid opsonic activity rather than total protein level was found to independently correlate with risk of development of SBP (46). However, again, when only common clinical data were included in statistical analyses, ascitic fluid total protein levels were found to be the best predictor of SBP risk (46). While ascitic fluid total protein levels of < 1 g/dl clearly separates patients at high risk from

those with low risk of SBP, only 20-30% of such high risk patients with cirrhosis and ascites have been found to develop SBP after 1-3 years of follow-up (43, 45-47). In contrast, in patients with any prior episode of SBP, the risk of future SBP episodes rises dramatically with approximately 70% of survivors of a first SBP episode having a recurrent episode within 1 year of follow-up (44). Aside from low protein / low opsonic activity in ascitic fluid, the only other parameters found to further stratify low protein ascites patients have been markers of severe liver disease and / or portal hypertension such as prolonged prothrombin times (44), elevated serum bilirubin levels (46, 47) and thrombocytopenia (47).

When risk for any type of bacterial infection is assessed among hospitalized patients with cirrhosis, the most commonly identified risk factor for serious bacterial infection has been the presence of gastrointestinal hemorrhage (49,50).The association between gastrointestinal hemorrhage and bacterial infections in cirrhotics initially focused attention on the possible role of disruption of the GI mucosa by peptic disease or by endoscopic therapies directed at management of GI bleeding. However, the risk of infection appears to be independent of cause of bleeding (51) and the organisms identified in blood, ascitic, urine or other body fluid cultures are distinct from those identified in transient bacteremic episodes following esophageal variceal ligation or sclerosis (52). Rather, data from the human trauma literature (33-35) as well as from experimental animal models indicates that hemorrhage has direct adverse effects on RES function (53) as well as being one of the stresses capable of enhancing bacterial translocation across the gastrointestinal epithelium (39,42). In addition to being a common complication in patients with GI bleeding, the development of bacterial infections in such patients has also been found to be associated with a higher rate of rebleeding (51,52) which has been attributed to the adverse effects of bacterial infection on hemostasis in patients with decompensated cirrhosis (55).

Management of Infectious Complications of Cirrhosis

With increased awareness of the bacterial infectious complications in cirrhosis, a number of changes in clinical practice have improved clinical outcomes. These changes include an appreciation of the often subtle clinical manifestations of infection in patients with cirrhosis, adoption of guidelines for collection of appropriate cultures and ascitic fluid analyses and the use of broad spectrum, non-nephrotoxic antibiotics that provide adequate coverage of gram-negative enteric organisms. Since SBP, unlike peritonitis associated with a perforated viscus, may or may not be associated with severe abdominal pain or physical exam findings suggestive of peritoneal irritation (4,7, 56), ascitic fluid analysis are recommended not only in patients presenting with abdominal pain and frank peritonitis but also in any cirrhotic with new onset ascites or with established ascites complicated by fever, encephalopathy or unexplained renal failure. Similarly, since 20% of cirrhotics hospitalized for gastrointestinal bleeding have major bacterial infections at time of admission, GI bleeding in a patient with cirrhosis is sufficient grounds for obtaining both blood cultures and analysis and culture of urine and ascites (57). In cirrhotics presenting with readily apparent foci of infections in the urinary tract, lung, soft tissues or meninges, the greater propensity for dissemination in the bloodstream and the higher frequency of gram negative bacterial etiologies must be taken into consideration in planning therapy.

Standard guidelines for presumptive diagnosis of SBP (ascitic fluid PMN count ≥ 250/mm^3 in patients with cirrhosis) and antibiotic therapy of SBP (cefotaxime, 2g iv q 8 hours) have been established (58) and widely adopted. Adherence to these guidelines appears to have decreased both mortality rates and incidence of nephrotoxicity previously associated with aminoglycoside use (58). Recently, oral ofloxacin has been shown to be of comparable efficacy (59) in a subset of patients with uncomplicated SBP (no shock, ileus, GI bleeding, encephalopathy or renal insufficiency) while in more seriously ill patients, addition of intravenous albumin preserves renal function and improves mortality (60)

However, despite improved recognition of risk for bacteremia and SBP in cirrhotics and development of safe and highly effective antibiotic regimens for treatment of these complications, mortality rates have remained high even when appropriate therapy is initiated in a timely fashion. This has led to assessment of the benefit of prophylactic antibiotics in patients with cirrhosis and established risk factors for life threatening infections. Thus far, 5 randomized prospective trials of prophylactic antibiotic therapy in patients with cirrhosis and acute gastrointestinal hemorrhage (61-65) and another 5 randomized prospective trials of prophylactic antibiotic therapy in patients with cirrhosis and ascites (66-70) have been performed to assess effect on incidence of serious infections and mortality. In addition, meta-analyses of these trials have been published (71,72).

As detailed in tables 2 and 3,the results of these trials have been remarkably uniform despite differences in antibiotic regimens and etiology of cirrhosis. In studies assessing efficacy of antibiotic

Table 2

Results of Randomized Clinical Trials of Antibiotic Prophylaxis for the Prevention of Bacterial Infections in Cirrhotic Patients with Upper Gastrointestinal Bleeding

1st Author	Patients with:			Significant Reduction in:				
(# patients)	Ascites	Child C	Antibiotic Regimen	All Infection	Bacteremia	SBP	UTI	Mortality
Rimola[61] (N=140)	31%	unclear	Gent/Vanc/Nyst or Neo/Col/Nyst*	Yes (35%→16%)	Yes** (21%→9%)	Yes**	No (13%→4%)	Yes (24%→10%)
Soriano[62] (N = 119)	24%	20%	Oral Norfloxacin 400 mg BID x 7d	Yes (37% →10%)	Yes (10%→0%)	No (4%→2%)	Yes (19%→0%)	No (12%→7%)
Blaise[63] (N=91)	43%	78%	Ofloxacin,400mg q d x 7d, + Amox/Clav †	Yes (67%→20%)	Yes (38%→13%)	No (16%→7%)	Yes (22%→2%)	No (36%→24%)
Pauwels[64] (N=64)	45%	77%	Amox(1g)/Clav. TID, Cipro. 200 mg BID‡	Yes (53%→13%)	Yes (38%→7%)	Yes (21%→3%)	No (6% →0%)	No (24%→13%)
Hsieh[65] (N=120)	48%	38%	Oral Cipro, 500mg, BID x 7 d	Yes (45%→10%)	Yes (23%→0%)	Yes (13%→3%)	Yes (18%→5%)	No (30%→22%)
			Meta-analysis, Bernard, et al,[72]	**Yes (45%→14%)**	**Yes (27%→8%)**	**Yes (13→5%)**	Not Analyzed	**Yes (24%→15%)**

* Oral gentamicin, 200 mg; vancomycin, 500 mg; and nystatin, 10^6 units q 6h to first 40 patients then oral neomycin, 1 gm; colistin, 1.5 x 10^6 units and nystatin, 10^6 units q 6 h to next 38 treated patients.

** Bacteremias and /or spontaneous bacterial peritonitis analyzed together.

† Ofloxacin given intravenously until patient could take oral medication. Amoxicillin, 1 g, and clavulanic acid, 200 mg given intravenously prior to each endoscopy.

‡Antibiotics given intravenously until patient taking oral medications until 3 days after cessation of bleeding.

prophylaxis in cirrhotic patients with upper gastrointestinal bleeding (UGIB), 4 of 5 studies enrolled all cirrhotics with UGIB who were not already overtly infected or on antibiotics. One study (64) enrolled all Child-Pugh C patients meeting these criteria, but only Child-Pugh A/B patients with rebleeding. Some studies enrolled nearly equal numbers of patients with cirrhosis due to alcoholic liver disease versus other causes (61,62) while others enrolled patients with predominately alcoholic liver disease (63, 64) or viral liver disease (65). As detailed in Table 2, the percentage of patients with advanced Child-Pugh C cirrhosis enrolled in these trials ranged from 20-78%. In all studies, the majority of cases of gastrointestinal hemorrhage were attributed to esophageal and/or gastric varices (66-100%).

Despite differences in etiology and severity of cirrhosis, all studies found that prophylactic antibiotics significantly reduced overall incidence of infections as well as incidence of bacteremia and/or frank sepsis (Table 2). In all studies, the incidence of SBP and urinary tract infections was reduced in patients on therapy but this reduction did not achieve statistical significance in every trial. In 3 of 5 studies, significant reduction in bacterial infections seemed entirely related to reduced incidence of gram-negative enteric bacterial infections in blood, urine and ascites (61,62,65), while in 2 studies (63,64) similar reductions in gram-negative and gram positive infections were seen. Likely this difference related to the use of amoxicillin / clavulanic acid as part of the therapeutic regimen in these latter studies. While the most serious blood borne infections in cirrhotics with GI bleeding are usually gram-negative enteric organisms (predominately *Escherichia coli*), in the study by Blaise, et al which contained the highest percentage of Child's-Pugh C patients and where amoxicillin / clavulanic acid was infused prior to each endoscopy in the treatment group, a significant reduction in pneumonias due to both gram-positive cocci and to *H. Influenzae* was observed. When analyzed separately (65), infection rates and degree of reduction in these rates among recipients of antibiotic prophylaxis was not different among patients with UGIB secondary to varices or to other sources. In another study, where cost analysis was performed, total antibiotic costs were found to be reduced by use of antibiotic prophylaxis (64).

In only the largest study (61) was overall mortality reduced significantly in antibiotic prophylaxis recipients, but in all studies there was a trend towards decreased mortality in the recipients of prophylactic antibiotics. Furthermore, in a meta-analysis of these 5 trials, a significant reduction in mortality rate from a mean of 24% in controls to a mean of 15% in antibiotic prophylaxis recipients was noted. Results of meta-analysis as well as perusal of results of individual trials indicates that rates of serious infections are reduced by 2/3 in recipients of antibiotic prophylaxis while a 1/3 reduction in mortality rates is observed. This reduction in mortality rate is remarkable in this group of patients with predominately variceal sources of bleeding since severity of liver disease and rebleeding are the major factors predicting survival in this patient cohort (51,55, 62-64).

As detailed in table 3, trials assessing benefit of antibiotic prophylaxis in cirrhotics with ascites and risk factors for SBP have revealed similar levels of benefit with respect to reducing SBP rates. In each individual trial as well as when 4 of the trials were analyzed by meta-analysis, antibiotic prophylaxis significantly reduced risk of SBP and/or overall risk of infection by gram-negative enteric bacteria at a benefit rate (2/3 reduction in incidence) similar to that seen when

Table 3

Results of Randomized Clinical Trials of Antibiotic Prophylaxis for the Prevention of Spontaneous Bacterial Peritonitis in Cirrhotic Patients with Ascites

1st Author (# patients)	Entry Criteria	Incidence Prior SBP	Therapy	Significant Reduction In: All infection	Bacteremia	SBP	Mortality
Gines[66] (N=80)	Episode of SBP	100 %	Norfloxacin, 400 mg po q d	Not analyzed	Not analyzed	Yes (35%→12%)	No (25%→18%)
Soriano[67] (N=63)	Ascites, AF T. Prot.<1.5 g/dl	6 %	Norfloxacin, 400 mg po q d*	Yes (42%→3%)	No (3%→3%)	Yes (23%→0%)	No (16%→6%)
Rolachon[68] (N=60)	Ascites AF T. Prot.<1.5 g/dl	12 %	Ciprofloxacin, 750 mg po q wk	No (34%→14%)	No (9%→7%)	Yes (22%→4%)	No (19%→14%)
Singh[69] (N=60)	Ascites	22 %	Trimeth/Sulfameth 1 DS tab po M-F	Yes (30%→3%)	No (10%→0%)	Yes (27%→3%)	No (20%→7%)
Grange[70] (N=107)	Ascites AF T. Prot.<1.5 g/dl	0 %	Norfloxacin, 400 mg po q d	Yes (17%→2%)	No (7%→2%)	No (9%→0%)	No (19%→15%)
		Meta-analysis**, Bernard, et al[71]		**Yes (39%→17%)**	**Not analyzed**	**Yes (28%→9%)**	**Yes (27%→18%)**

AF = ascitic fluid
*Therapy continued only during hospitalization.
**Trial by Soriano, et al not included in meta-analysis.

antibiotic prophylaxis is given to patients with UGIB. Survival benefit was not demonstrated in any individual trial and was noted by only 1 of 2 statistical methods employed in meta-analysis with benefit most apparent in patients with the most severe liver disease (71). Economic analysis of use of antibiotic prophylaxis in patients at high risk for SBP (73) has indicated greatest benefit in those patients with prior episodes of SBP (cost savings of $8545-9251/yr) and those with ascitic fluid total protein levels of < 1 g/dl ($3980-4692/yr). In contrast to the results in trials in which antibiotic prophylaxis is limited to brief intervals while hospitalized for GIB (61-65) or ascites (67), longer term use of daily quinolone antibiotic regimens has been associated with rapid emergence of (74-77) of quinolone resistant enteric flora and is associated with a higher incidence of severe hospital acquired staphylococcal infections. These findings have led previously enthusiastic advocates of continuous daily norfloxacin prophylaxis in patients with ascites, to stop routine use of such regimens and adopt more selective approaches (76,77). Of note, in the study by Rolachon, et al using once weekly ciprofloxacin, emergence of quinolone resistant organisms was not noted even after 6 months of therapy (68).

Summary

The patient with cirrhosis should be viewed as "immunocompromised". Unlike other immunocompromised patient populations with defects in T cell or granulocyte function, defects in mononuclear phagocyte function predominate in patients with cirrhosis. This defect in phagocyte function along with factors that increase rates of bacterial translocation from the intestines leaves these patients especially vulnerable to bacteremias and infections of ascites and other body fluids by gram negative enteric organisms. A number of strategies are available to reduce the morbidity, cost and mortality from these complications. These include: (1) routine use of pneumococcal and

influenza vaccination, (2) avoidance of high risk situations such as ingestion of uncooked shellfish or other seafood or excess use of indwelling catheters in hospitalized patients, (3) anticipation of the increased propensity for bacteremia and for infection by gram-negative enteric organisms when designing therapeutic regimens for patients with cirrhosis and evidence of active bacterial infection and finally, (4) use of antibiotic prophylaxis in high risk patients. Specifically, all cirrhotic patients presenting with upper gastrointestinal bleeding should receive brief courses of antibiotic prophylaxis (such as ciprofloxacin 1 g/d IV or PO for 7 d) initiated immediately after collection of baseline blood +/- body fluid cultures (57,58,78). In patients with low protein ascites (<1g/dl), antibiotic prophylaxis is recommended in short term courses during all hospitalizations and as continuous outpatient therapy in those patients with prior episodes of SBP (58,78). Routine use of continuous quinolone antibiotic therapy as primary prophylaxis for SBP in outpatients is not recommended because of increased appearance of antibiotic resistant flora in such patients (58,78). Selective use of intermittent antibiotic regimens (such as ciprofloxacin, 750 mg q wk or trimethoprim-sulfamethoxazole, 1 DS tab M-F) can be considered for primary prophylaxis in cirrhotic patients with low protein (< 1 g/dl) ascites and other characteristics increasing risks for SBP and / or bacteremia.

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