PREVALENCE AND RISK FACTORS FOR SPONTANEOUS ASCITIC FLUID INFECTION IN OUTPATIENT CIRRHOTICS UNDERGOING THERAPEUTIC PARACENTESIS

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CERTIFICATE

This is to certify that the dissertation entitled **"PREVALENCE AND RISK FACTORS FOR SPONTANEOUS ASCITIC FLUID INFECTION IN OUTPATIENT CIRRHOTICS UNDERGOING THERAPEUTIC PARACENTESIS"** is the bonafide original work of **Dr. M. PAZHANIVEL** in partial fulfillment of the requirements for **D.M (GASTROENTEROLOGY) BRANCH – IV** Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in August 2010. The period of study was from January 2008 to December 2009.

Dr. C. VAMSADHARA., M.D.,PhD
DEAN
Govt. Stanley Medical College & Hospital,
Chennai-600 001.

Prof. V. JAYANTHI , M.D.,D.M,
Professor & Head
Department of Medical Gastroenterology
Govt. Stanley Medical College
Chennai-600 001.

DECLARATION

I, **Dr. M. PAZHANIVEL,** solemnly declare that the dissertation titled, "PREVALENCE AND RISK FACTORS FOR SPONTANEOUS ASCITIC FLUID INFECTION IN OUTPATIENT CIRRHOTICS UNDERGOING THERAPEUTIC PARACENTESIS**"** is a bonafide work done by me at Govt. Stanley Medical College & Hospital during 2007-2010 under the guidance and supervision of **Dr. V. JAYANTHI, M.D., D.M,** Professor and Head, Department of Medical Gastroenterology, Stanley Medical College, Chennai-600 001.

The dissertation is submitted to Tamilnadu, Dr. M.G.R. Medical University, towards partial fulfillment of requirement for the award of **D.M Degree (BRANCH – IV) in Gastroenterology.**

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Date:

(Dr. M. PAZHANIVEL)

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CONTENTS

INTRODUCTION

Ascites is the most common complication of cirrhosis followed by hepatic encephalopathy and variceal hemorrhage.[1] In the natural history of compensated cirrhosis, 50% of patients develop ascites during 10 years of follow up.1 It is the most common complication that leads to hospital admission. [2] 15% of patients with ascites succumb in 1 year and 44% in 5 years.[3] The major complications of ascites are refractory ascites, hepatorenal syndrome and spontaneous bacterial peritonitis.

Patients with cirrhosis and ascites show a higher susceptibility to bacterial infections mainly because of the inadequate defense mechanisms. The most frequent infectious and severe complication that occurs is spontaneous bacterial peritonitis (25%), followed by urinary infections (20%), pneumonia (15%) and bacteremia (12%) [4]

Spontaneous bacterial peritonitis (SBP) is a potentially life-threatening complication in cirrhosis and has typically been described in hospitalized patients. The prevalence of SBP in hospitalized patients with decompensated cirrhosis is 10% - 30%.[5-7] and 18% in those with hepatic encephalopathy. [8-9] One-third of patients with infected peritoneal fluid do not manifest overt signs or symptoms such as fever or abdominal pain at

initial presentation.[7] Also 7–27% of patients with cirrhotic ascites harbor occult peritoneal fluid infection at the time of hospital admission [6,7,10]

The incidence of spontaneous bacterial peritonitis in the outpatient setting is very low. Therapeutic paracentesis is the recommended treatment for patients with ascites that are resistant or refractory to other medical treatment. It also reduces the discomfort associated with tense ascites. It is usually done on an outpatient basis. The need for ascitic fluid cell count and cultures in asymptomatic cirrhotic patients following large-volume paracentesis (LVP) remains unclear. Although many of these patients are at increased risk for SBP due to their advanced liver disease, low protein ascites, and prior episodes of SBP, the need for routine ascitic fluid analysis in the outpatient setting remains unclear. [5]

American association for study of Liver disease practice guidelines recommend testing of ascitic fluid only for cell count and differential count for patients undergoing serial outpatient therapeutic paracenteses. [11-12] Bacterial culture is not necessary in asymptomatic patients undergoing serial large volume paracenteses.

Although the outcome with spontaneous bacterial peritonitis (SBP) and its variants has improved over the last decade, the in-hospital and 1-yr

mortality of patients with SBP remain approximately 30% and 50%, respectively.[7, 13-14] Because mortality is 20% even in treated spontaneous bacterial peritonitis patients, it is important not to miss the diagnosis. [15] Therefore, a high index of suspicion with a low threshold to perform a diagnostic paracentesis is required to make a rapid diagnosis of this potentially life-threatening infection in various clinical settings.

AIM

The aim of this study was to determine the prevalence and risk factors for

1) Spontaneous bacterial peritonitis (SBP)
2) Monomicrobial non-neutrocytic bacterascites (MNB) and
3) Culture-negative neutrocytic ascites (CNNA)

in asymptomatic cirrhotic outpatients undergoing therapeutic paracentesis.

REVIEW OF LITERATURE

Ascitic fluid infection can be classified into five categories based on ascitic culture results, polymorphonuclear (PMN) count, and presence or absence of a surgical source of infection. An abdominal paracentesis must be performed and ascitic fluid must be analyzed before a confident diagnosis of ascitic fluid infection can be made. A "clinical diagnosis" of infected ascitic fluid without a paracentesis is not adequate.

Table 1: Classification of Ascitic Fluid Infection

Spontaneous bacterial peritonitis
Monomicrobial non-neutrocytic bacterascites
Culture-negative neutrocytic ascites
Secondary bacterial peritonitis
Polymicrobial bacterascites (needle perforation of the bowel)

Spontaneous bacterial peritonitis:

Correia and Conn coined the term "spontaneous bacterial peritonitis" in 1975. Of the three subtypes of spontaneous ascitic fluid infection, the prototype is spontaneous bacterial peritonitis. The diagnosis of

spontaneous bacterial peritonitis is made when there is a positive ascitic fluid culture and an elevated ascitic fluid absolute PMN count (i.e., at least 250 cells/mm^3 [0.25×10^9/L]) without evidence of an intra-abdominal surgically treatable source of infection. [16] Therefore, although many patients with spontaneous bacterial peritonitis have a focus of infection (e.g., urinary tract infection or pneumonia), the diagnosis of spontaneous bacterial peritonitis is still appropriate unless the focus requires surgical intervention (e.g., a ruptured viscus). SBP is monomicrobial.

Monomicrobial non-neutrocytic bacterascites:

The criteria for diagnosis of *monomicrobial nonneutrocytic bacterascites* (MNB) include (1) a positive ascitic fluid culture for a single organism, (2) an ascitic fluid PMN count lower than 250 cells/mm^3 (0.25×10^9/L), and (3) no evidence of an intra-abdominal surgically treatable source of infection. [17] In the older literature, MNB was either grouped with spontaneous bacterial peritonitis or labeled "asymptomatic bacterascites." Because many patients with bacterascites have symptoms, the modifier "asymptomatic" seems inappropriate.

Culture-negative neutrocytic ascites:

Culture-negative neutrocytic ascites (CNNA) is diagnosed when (1) the ascitic fluid culture grows no bacteria, (2) the ascitic fluid PMN count is 250 cells/mm^3 (0.25×10^9/L) or greater, (3) no antibiotics have been given (not even a single dose), and (4) no other explanation for an elevated ascitic PMN count (e.g., hemorrhage into ascites, peritoneal carcinomatosis, tuberculosis, or pancreatitis) can be identified. [18] This variant of ascitic fluid infection seldom is diagnosed when sensitive culture methods are used.[19]

PATHOGENESIS

The pathogenesis of SBP in cirrhosis is mainly the consequence of bacterial translocation (BT). It is a process through which viable or non-viable bacteria and bacterial products (bacterial DNA or endotoxins) cross the intestinal lumen and come into the mesenteric lymph nodes or extraintestinal tissues. The BT is a perturbation of the equilibrium between the normal intestinal flora and the organism, leading to an inflammatory reaction that perpetuates, finally producing infection.

There are some mechanisms that are being proposed to explain BT in cirrhosis: the intestinal bacterial overgrowth, the structural and functional

alterations of the intestinal mucosal barrier and the deficiencies of the local immune response.[20-21]

Intestinal bacterial overgrowth:

The intestinal bacterial overgrowth plays a key role in BT in cirrhosis and is the result of the delayed intestinal transit existing in these patients. It seems that the sympathoadrenal stimulation, increased NO synthesis and the oxidative stress of the mucosa are the main causes for decreased intestinal motility. [22-23] Besides, although normally in the small intestine there is a more reduced microbial density compared to that of the colon, in cirrhotic patients an increase of the colonization process of the small intestine with bacteria from the colon (approx. 30- 50%) is recorded. [23]

Intestinal mucosal barrier:

The barrier of the intestinal mucosa includes defence mechanisms of secretory or physical type, against the microbial penetration. The secretory (first defence) mechanism is realized through the mucus secretion, the local immunoglobulins and the bile salts. The mucins are glycoproteins secreted by the epithelial cells that form an electro-negative

charged layer, and are attached to it, preventing the direct contact between the bacteria and the intestinal membrane. [24]

Immunoglobulins - particularly IgA - are secreted by plasma cells from the lamina propria and have three major roles:

- Binding to bacteria (that prevents their adhesion to the mucosa and the bacterial

  colonisation);

- Toxin and microorganism neutralization;

- Active transport role as IgA-antigen complex from the lamina propria back to the intestinal lumen.

The bile contributes to the local defence of the intestinal mucosa against bacterial aggression by decreasing internalisation of enteric bacteria, endotoxin neutralisation and inhibition of excess intestinal flora proliferation. The bile has a trophic role for the intestinal mucosa and an antiadherence effect for bacteria as well. [24] The concentration of bile acids in cirrhosis decreases in the intestinal lumen due to the reduced secretion, as well as to the increased deconjugation under the influence of the intestinal flora. The consequences of bile acid decrease are the facilitation of BT and the increasing process of translocation induced by endotoxins.

The physical (second defence) mechanism is represented by the intestinal epithelium - by its lack of permeability and its antimicrobial peptide active production. The structure of the intestinal epithelium with its cell junction disposal allows only the passage of very tiny molecules; preventing the bacterial or the macromolecular (lipopolysaccharides) transport. [24]

In hepatic cirrhosis two processes that alter the intestinal mucosa barrier occur: increased mucosal permeability (especially in patients with sepsis) because of the mucosa oxidative stress, enterocyte mitochondria malfunctioning, endotoxaemia, increased NO and proinflammatory cytokine level and the mucosal structural changes. The latter include the intercellular spaces enlargement, vasodilatation, edema, fibromuscular proliferation, decreased villi/crypts ratio, thickened muscularis mucosae and inflammation.[22, 24]

Another intestinal epithelium defence mechanism is the secretion of molecules with antimicrobial role (natural antibiotics), which have the capacity of destroying the microorganisms. Among these molecules a major role is by α-defensins, synthesized as a reaction to the presence of bacteria or lipopolysaccharides, and also the lysozyme and secretory phospholipase A2. These antimicrobial peptides are synthesized in the

Paneth cells localized at the bottom of each intestinal crypt, mostly in the jejunal and ileal region. Besides, most epithelial cells from the small intestine and the colon can secrete β-defensin - a peptide involved in the defence against commensal bacteria. [20, 24]

In addition to the mucosal local defence mechanisms (secretory and mechanical), there is at the intestine level the gut-associated lymphoid tissue (GALT) – considered the best immunologically represented "organ" which includes four compartments:

1- Peyer's patches;

2- Lymphocytes from the lamina propria (including the dendritic cells)

3- Intraepithelial lymphocytes

4- Mesenteric lymph nodes (MLN)

The structures that form GALT react to the presence of germs from the intestinal lumen by intraepithelial lymphocyte proliferation, germinative centre appearance in the lymphoid follicles and in the lamina propria and an increase of the secreted Ig level. In return, bacteria that form the commensal intestinal flora interact with the intestinal epithelium and can start up the primary immune response as well as the adaptative one.[24, 25]

The primary immune response is realized through the monocytes and dendritic cells from the intestinal mucosa and request some specific bacterial ligands recognition (PAMP = pathogen-associated molecular pattern) from corresponding receptors existing in most mononuclear cells (PRR = pattern recognition receptor). These receptors belong to a group named TLR (toll like receptor), the most important being TLR 2, 4 and 9. The stimulation of these receptors by bacterial ligands (lipopolysaccharides, lipoteichoic acid, peptidoglycans) activates the cytokine and chemokine synthesis and the antimicrobial gene transcription. The chemokines synthesized by the epithelial cell recruit dendritic cells in the mucosa.[24]

Luminal bacterial antigens are presented to dendritic cells by two mechanisms: indirect, using M cells or direct, using local antigen presenting cells (APC). M cells are specific cells from the epithelial layer, which overtake the antigen by endocytosis and transport it to the dendritic cells and local macrophages.[24] The direct mechanism consists of the takeover of antigens from local APC by emission of pseudopods among the epithelial cells.

Then, APC presents the microbial peptides to B and T lymphocytes from the intestinal mucosa or from the MLN, by using lymphatic afferent

vessels. APC will determine the type of the immune response stimulating Th "naïve" lymphocytes followed by their transformation in effector Th1, Th2 or mixed phenotype lymphocytes. The bacterial antigen presentation to the B lymphocytes determines secretion of IgA (or IgG) with a protective role for the intestinal mucosa.[24]

Another defence mechanism against bacterial aggression is represented by the lymphocyte T migration from the Peyer's patches after their exposure to antigen, to the lamina propria and the epithelium, where they mature and convert to T cytotoxic lymphocytes. The link between the primary immune response and the adaptative one is made by dendritic cells, which present bacterial antigens to B and T lymphocytes from the submucosa, but can transport them also to the MLN, where they determine a local immune response.[24] Bacterial destruction from the MLN (by mononuclear cells) is not followed by systemic immunity or intestinal inflammation. In cirrhosis, because of the local and systemic immune deficiencies, the BT process is followed by bacteremia and ascitic fluid inoculation. If the ascitic fluid complement level is low, this will determine a low bactericidal activity and thus a higher risk of SBP. [24, 26] The Kupffer cells have a special role in preventing infections in these patients. In healthy people, these local macrophages collaborate with neutrophils in the process of bacterial extraction from the circulation,

followed by their destruction. In patients with hepatic cirrhosis, because of intra- and extrahepatic shunts (due to portal hypertension), circulant bacteria do not come in contact with Kupffer cells, the result being bacteremia with ascitic fluid inoculation.[24] Qualitative neutrophil abnormalities (decreased phagocytosis capacity), low complement serum levels and the decreased function of macrophages' Fcy receptors can favour SBP.[24]

BACTERIOLOGY

Escherichia coli, streptococci (mostly pneumococci), and *Klebsiella* cause most episodes of spontaneous bacterial peritonitis and MNB in patients who are not receiving selective intestinal decontamination. The most apparent difference between the spontaneous forms of ascitic fluid infection and the secondary forms (secondary peritonitis and polymicrobial bacterascites) is that the former always are monomicrobial and the latter usually are polymicrobial.

Anaerobes have been found in approximately 1% of cases of spontaneous bacterial peritonitis and MNB.[17, 19] Selective intestinal decontamination causes a change in the bacteria isolated from patients in whom an ascitic infection develops. Gram-positive organisms usually are cultured from the ascitic fluid of these patients.[27]

Pathogens in Ascitic Fluid Infection[17,19]

	Frequency (%)	
Organism	**SBP**	**Monomicrobial Non-Neutrocytic Bacterascites**
Monomicrobial		
Escherichia coli	37	27
Klebsiella pneumoniae	17	11
Pneumococci	12	9
Streptococcus viridans	9	2
Staphylococcus aureus	0	7
Miscellaneous gram-negative	10	14
Miscellaneous gram-positive	14	30
Polymicrobial	1	0

CLINICAL SETTING

The spontaneous variants of ascitic fluid infection occur only in the setting of severe liver disease. The liver disease usually is chronic

(cirrhosis), but may be acute (fulminant hepatic failure) or subacute (alcoholic hepatitis). Cirrhosis of all causes can be complicated by spontaneous ascitic fluid infection. Spontaneous infection of noncirrhotic ascites is rare.

SBP usually occurs at the time of greatest ascites volume, but can be present in settings where the fluid is clinically undetectable. Ascites appears to be a prerequisite for the development of spontaneous bacterial peritonitis.

SBP in the absence of ascites is extremely unlikely. [28] The majority of patients with SBP have severe liver dysfunction. Toledo et al. demonstrated that 96% of patients with SBP had either Child-Pugh grade B or C.[29]

SYMPTOMS AND SIGNS

Although 87% of patients with spontaneous bacterial peritonitis are symptomatic at the time the infection is diagnosed, the symptoms and signs of infection are often subtle, such as a slight change in mental status and require a high index of suspicion.[18] Previously, there was often delay in diagnosis, which led to considerable mortality and morbidity.[30] The symptoms and signs manifested in all 3 variants of ascitic fluid infection are listed in the table below.

Patients with cirrhosis usually have hypothermia; therefore, any temperature > 37.8^0 C should be investigated, unless it is clearly caused by flu-like symptoms. Fever caused by SBP is differentiated from that of alcoholic hepatitis, in which the ascitic fluid neutrophil count is normal.[30]

Alterations in mental status may be subtle occurring in 50% [17, 33] and only apparent to someone close to the patient. Abdominal pain can be continuous and is different from tense ascites. Tenderness is a common feature.

Symptoms and Signs of Ascitic Fluid Infection[17,18, 31, 32]

	Frequency (%)		
Symptom or Sign	**SBP**	**Bacterascites**	**CNNA**
Fever	68	57	50
Abdominal pain	49	32	72
Abdominal tenderness	39	32	44
Rebound tenderness	10	5	0
Altered mental status	54	50	61

Paralytic ileus, hypotension and hypothermia are seen in advanced illness, where prognosis may be dire. Shock at the time of presentation is

a rare event [29], probably as a result of the current lower threshold to perform diagnostic paracentesis and earlier diagnosis. Decrements in renal function are seen in one-third of cases.[34] Thirteen percent of patients have no signs or symptoms.[30]

Without prompt paracentesis, the diagnosis and treatment of infected ascites may be delayed, often resulting in the death of the patient. A 'diagnostic tap' should be performed in all patients with ascites admitted to hospital. SBP in outpatients with cirrhotic ascites is less frequent, occurs in patients with less advanced liver disease, and may have a better outcome than its counterpart in hospitalized patients.[12]

PREVALENCE

Since the 1980s, routine paracenteses on hospitalization in patients with ascites have provided data regarding the prevalence of ascitic fluid infection. In the 1980s, approximately 10% of patients with ascites were infected at the time of hospital admission; of the subgroup of patients with cirrhosis, about 27% were infected.[35] At present, because of measures to prevent spontaneous bacterial peritonitis, the prevalence has dropped significantly.

Of patients with culture-positive ascitic fluid, about two thirds have neutrocytic ascitic fluid (spontaneous bacterial peritonitis), and one third have MNB.[17] The frequency of CNNA depends largely on the culture technique.

RISK FACTORS

The predisposing factors for SBP are severity of the liver disease, decreased protein and C3 level in the ascitic fluid, acute gastrointestinal bleeding, urinary tract infection, iatrogenic factors and previous SBP episodes. From these factors, the most important one is the severity of liver disease: about 70% of the patients which develop SBP are in Child C class. Besides, serum bilirubin level >2.5 mg/dl is an independent predictive factor of SBP.[25]

The low bactericidal activity of the ascitic fluid, demonstrated by a protein concentration <1g/dl, can favour SBP. Bacteriuria, frequent mostly in female cirrhotic patients, can be another factor that favours SBP; this is why screening and treatment of urinary infections have to be performed even in asymptomatic patients, and urinary catheterization must be avoided.

Regarding acute gastrointestinal bleeding, it has been ascertained that approx. 20% of the patients have SBP at the time of admission to the hospital and 30-40% develop bacterial infections during hospitalization for digestive hemorrhage – a possible explanation being that the hemorrhagic shock increases BT and intestinal permeability. Also for preventing bacteremia, vascular catheterization has to be reduced to a minimum. It has been documented that SBP surviving patients have an increased risk to recurrence.[4, 21]

DIAGNOSIS

Timely diagnosis of ascitic fluid infection requires a high index of suspicion and a low threshold for performing a paracentesis. The main indications for paracentesis in a patient with hepatic cirrhosis include: unexplained clinical deterioration, the onset of complications (hepatic encephalopathy and gastrointestinal bleeding), new onset ascites and at every hospitalization. Paracentesis should be avoided only in case of a suspicion of fibrinolysis or DIC.[4] Although patients with cirrhosis have coagulation disturbances, the paracentesis is associated with a very low risk of complications: abdominal wall hematoma (1%), hemoperitoneum (0,1%) and iatrogenic infections (0,1%).

If the ascitic fluid PMN count is elevated, the working diagnosis is ascitic fluid infection until proved otherwise. Although peritoneal carcinomatosis, pancreatitis, hemorrhage into ascites, and tuberculosis can lead to an elevated ascitic fluid PMN count, most cases of neutrocytic ascites are caused by bacterial infection. A predominance of PMNs in the WBC differential count lends further credence to the diagnosis of infection.

Although spontaneous bacterial peritonitis is approximately six times as common as surgical peritonitis in a patient with ascites, secondary peritonitis should be considered in any patient with neutrocytic ascites. Clinical symptoms and signs do not distinguish patients with secondary peritonitis from those with spontaneous bacterial peritonitis.[31] Even with free perforation of the colon into ascitic fluid, a classic surgical abdomen does not develop. Peritoneal signs require contact of inflamed visceral and parietal peritoneal surfaces, and such contact does not occur when there is a large volume of fluid separating these surfaces.

After paracentesis, the ascitic fluid should be inoculated immediately (at the patient‘s bedside) into blood-culture bottles (10ml in each bottle) that increases the diagnosis rate from 50 to 80%. Because almost half the SBP cases are associated with bacteremia and any bacterial infection in cirrhotic patients can lead to manifestations similar to SBP, blood and

urine cultures from these patients are useful.[4] The chest x-ray can show a right hydrothorax. If infection is suspected (and SBP diagnosis has been ruled out), thoracentesis is necessary in order to establish diagnosis because the spontaneous bacterial empyema can occur even without ascites or SBP.

The best time to repeat the paracentesis to assess the response to treatment is after 48 hours of therapy; by 48 hours, the ascitic PMN count will be lower than the pretreatment value and the ascitic culture will be negative in essentially every patient with spontaneous bacterial peritonitis who has received treatment with an appropriate antibiotic.[31] Whereas antibiotics alone cannot control secondary peritonitis, medical therapy rapidly cures spontaneous bacterial peritonitis. [31]

TREATMENT

Many years ago, the usual treatment for cirrhotic patients with ascites and SBP was the combination of a β-lactam plus an aminoglycoside. Because patients with SBP are very sensitive to the nephrotoxicity associated with use of aminoglycosides, this initial treatment scheme has been replaced with a third generation cephalosporin -Cefotaxim. It has been shown in a controlled trial to be superior to ampicillin plus tobramycin for the treatment of spontaneous bacterial peritonitis.[36] Fully 98% of causative

organisms were susceptible to cefotaxime, which did not result in superinfection or nephrotoxicity.[36]

Cefotaxime or a similar third-generation cephalosporin appears to be the treatment of choice for suspected spontaneous bacterial peritonitis.[35] Cefotaxime, 2 g intravenously every 8 hours, has been shown to result in excellent ascitic fluid levels (20-fold killing power after one dose).[37] In patients with a serum creatinine level greater than 3 mg/dL, the dosing interval may be extended to 12 hours. Neither a loading dose nor an intraperitoneal dose appears to be necessary or appropriate. The clinician should, however, write "first dose STAT" when ordering treatment, to avoid a delay in administration of the life-saving agent.

In patients with uncomplicated SBP (no gastrointestinal bleeding, hepatic encephalopathy, ileus, shock or renal failure), treatment with Ofloxacin or other oral quinolones for 8 days can be administrated. [38-41] A good response to therapy can be evaluated by clinical criteria (disappearance of signs and symptoms of infection), but the most important parameter remains the decrease to a half (from the pre-treatment value) of the PMN number in the ascitic fluid obtained by paracentesis after two days of treatment.[42] Studies that require further confirmation propose the addition of albumin (1.5 g/kg body weight the first day, then 1g/kg three more

days) to the Cefotaxime treatment for patients with renal failure and SBP. Albumin in these patients may improve the renal function by increasing the intravascular volume, because vasodilatation induced by cytokines released in excess reduces the effective arterial volume.[40, 43]

Patients with cirrhotic ascites who have convincing symptoms or signs of infection should receive treatment regardless of the ascitic fluid PMN count. Empirical treatment can be discontinued after only 2 to 3 days if the culture demonstrates no growth. Asymptomatic patients may not need treatment.[35, 42] The paracentesis should be repeated for cell count and culture in patients without clinical evidence of infection, once it is known that the initial culture result is positive. If the PMN count has risen to at least 250/mm^3 (0.25×10^9/L) or if symptoms or signs of infection have developed, treatment should be started. Culture results usually are negative in patients without a rise in the ascitic fluid PMN count on repeat paracentesis and without clinical evidence of infection, and these persons do not require treatment, because colonization has been eradicated by host immune defenses. If the clinical picture initially is unclear, the physician should err on the side of antibiotic treatment (with a non-nephrotoxic antibiotic).

Other adjuvant therapies in patients with SBP include prokinetics and probiotics. Prokinetics are used to shorten the intestinal transit time,

reducing thus the intestinal bacterial overgrowth and the risk of bacterial translocation. Encouraging results have been obtained by using Cisapride and Propranolol, the latter's β blocking effect antagonises the increased adrenergic tone existent in patients with cirrhosis and responsible for the decreased intestinal motility.

Probiotics are used for intestinal flora reequilibration, in favour to anaerobic protective bacteria. Bacteriotherapy with Lactobacillus seems to correct intestinal bacterial overgrowth, to stabilize mucosal barrier function and to stimulate the local defence mechanisms. [4, 24] Oral treatment with conjugated bile acids (cholylglycine and cholylsarcosine) for preventing BT is under evaluation. [24]

The decision to begin empirical antibiotic treatment in patients with bacterascites must be individualized. Many episodes resolve without treatment. The hospital mortality rate of 32% in patients with MNB is attributable at least in part to infection, however.[17] Therefore, treatment appears to be warranted in many patients. By definition, the ascitic PMN count is lower than 250 cells/mm^3 in this variant of ascitic fluid infection and the PMN count cannot be the only parameter on which to base the

Table 4: Treatment of Subtypes of Ascitic Fluid Infection

Diagnosis	Treatment
Spontaneous bacterial peritonitis	Five days of intravenous antibiotic to which the organism is highly susceptible (e.g., cefotaxime 2 g q8h empirically followed by more specific therapy after susceptibility results are available)
Monomicrobial non-neutrocytic bacterascites	Five days of intravenous antibiotic to which the organism is highly susceptible, if the patient is symptomatic or persistently culture-positive; not all patients with bacterascites require treatment
Culture-negative neutrocytic ascites	Five days of intravenous third-generation cephalosporin (e.g., cefotaxime 2 g q8h)

decision about empirical therapy. Most patients with MNB in whom the colonization does not resolve progress to spontaneous bacterial peritonitis and have symptoms or signs of infection at the time of the paracentesis that documents bacterascites.[17]

The physician will not know initially that the ascitic fluid culture is destined to be negative in a patient with CNNA; therefore, empirical

antibiotic treatment should be started. When the preliminary culture demonstrates no growth, it is helpful to repeat the paracentesis after 48 hours of therapy to assess the response of the PMN count to antibiotics. A dramatic decline in PMN count (always below the baseline pretreatment value and frequently a greater than 80% reduction) confirms a response to treatment. In such cases, a few more days of therapy probably is warranted. A stable ascitic fluid PMN count, especially with a predominance of lymphocytes and monocytes, suggests a nonbacterial (or mycobacterial) cause of ascitic fluid neutrocytosis, and the fluid should be sent for cytologic examination and mycobacterial culture. Because a negative culture result may be due to insensitive culture techniques, the prevalence of CNNA in a hospital that still uses conventional methods of culture can be reduced by convincing the microbiology laboratory to accept and process ascitic fluid submitted in blood culture bottles.[44]

Until the results of susceptibility testing are available, relatively broad-spectrum antibiotic therapy is warranted in patients with suspected ascitic fluid infection. After sensitivities are known, the spectrum of coverage usually can be narrowed.

Other Intravenous Antibiotics

Amoxicillin–clavulanic acid has been shown to be as effective as cefotaxime in a randomized trial.[45] Other antibiotics have been recommended as well but have been less well studied than has cefotaxime. Some newer drugs have been used to treat spontaneous bacterial peritonitis (without any data on antibiotic penetration into the ascitic fluid) on the basis of their spectrum of coverage and formulary constraints. Infection with organisms that are resistant to the empirical anti-biotic or use of drugs that do not enter the ascitic fluid in high enough concentrations to kill the bacteria may lead to death.

Oral Antibiotic Treatment

Oral ofloxacin has been reported in a controlled trial to be as effective as parenteral cefotaxime in the treatment of spontaneous bacterial peritonitis in patients who are not vomiting, in shock, bleeding, or in renal failure.[46] The dose studied was 400 mg twice daily. [46] Another study has demonstrated the efficacy of intravenous ciprofloxacin, 200 mg every 12 hours for 2 days, followed by oral ciprofloxacin, 500 mg every 12 hours for 5 days. [47]

Because of the possibility of fluoroquinolone resistance in patients receiving fluoroquinolones to prevent spontaneous bacterial peritonitis,

however, the empirical use of a fluoroquinolone to treat suspected spontaneous bacterial peritonitis should be avoided. Fortunately, bacterial isolates from patients with spontaneous bacterial peritonitis who were receiving fluoroquinolones for prophylaxis of this disorder remain susceptible to cefotaxime.[42]

DURATION OF TREATMENT

Infectious disease subspecialists generally recommend 10 to 14 days of antibiotic therapy for life-threatening infections. No data are available to support this duration of treatment in spontaneous ascitic fluid infections, however. The ascitic fluid culture becomes sterile after one dose of cefotaxime in 86% of patients.[31] After 48 hours of therapy, the ascitic fluid PMN count is always less than the pretreatment value in patients with a spontaneous ascitic fluid infection treated with appropriate antibiotics; frequently, an 80% reduction is observed at 48 hours. [31]

A randomized, controlled trial involving 100 patients has demonstrated that 5 days of treatment is as efficacious as 10 days in the treatment of spontaneous bacterial peritonitis and CNNA.[48] The average duration of oral ofloxacin treatment was 8 days in the only published trial.[46]

Narrowing the Spectrum of Coverage

After the results of susceptibility testing are available, an antibiotic with a narrower spectrum of activity usually can be substituted for the broad-spectrum drug (e.g., pneumococci usually will be sensitive to penicillin, and most *E. coli* species usually will be sensitive to ampicillin).

Intravenous Albumin

Renal impairment occurs in 33% of episodes of spontaneous bacterial peritonitis.[34] Spontaneous bacterial peritonitis leads to increased intraperitoneal nitric oxide production, which in turn further increases systemic vasodilatation and promotes renal failure.[49] Intravenous albumin (1.5 g/kg of body weight at the time the infection is detected and 1.0 g/kg on day 3) can increase intravascular volume and, in combination with cefotaxime, has been shown in a large randomized trial to reduce the risk of renal failure and improve survival compared with cefotaxime without albumin.[50] Because of the survival advantage, however, the use of intravenous albumin as an adjunct to antibiotic treatment has been recommended.[51]

EMPIRIC TREATMENT

Patients with ascitic fluid PMN counts of 250 cells/mm3 in a clinical setting compatible with ascitic fluid infection should receive empiric

antibiotic therapy.[16, 30] The ascitic fluid PMN count is more rapidly available than the culture and appears to be accurate in determining who really needs empiric antibiotic treatment. [16, 30] Delaying treatments until the ascitic fluid culture grows bacteria may result in the death of the patient from overwhelming infection.

In some patients, infection is detected at the bacterascites stage before there is a neutrophil response. Most patients resolve the colonization without antibiotics and without a neutrophil response.[17] An elevated ascitic fluid PMN count probably represents evidence of failure of the first line of defense, the peritoneal macrophages, to kill invading bacteria. Patients with bacterascites who do not resolve the colonization and who progress to SBP have signs or symptoms of infection at the time of the paracentesis that documents bacterascites.[17, 27]

The majority of patients with culture-positive neutrocytic ascites demonstrate rising bacterial counts and rising PMN counts when serial samples are obtained in rapid sequence before initiation of antibiotic therapy.[27]Patients with culture-negative neutrocytic ascites have similar signs, symptoms, and mortality as patients with SBP and warrant empiric antibiotic treatment.[18] The majority of patients with culture-negative neutrocytic ascites continue with this pattern of ascitic fluid analysis

when serial samples are obtained in rapid sequence before initiation of antibiotic therapy; 34.5% become culture-positive.[17]

The patient with alcoholic hepatitis may have fever, leukocytosis, and abdominal pain that can masquerade as SBP. In addition, they can develop SBP. These patients do not develop false-positive elevated ascitic fluid PMN counts because of peripheral leukocytosis[52]; an elevated PMN count must be presumed to represent SBP. Empiric antibiotic treatment (for presumed ascitic fluid infection) of patients with alcoholic hepatitis who have fever and/or peripheral leukocytosis can be discontinued after 48 hours if ascitic fluid, blood, and urine cultures demonstrate no bacterial growth.

Relatively broad-spectrum therapy is warranted in patients with suspected ascitic fluid infection until the results of susceptibility testing are available. Cefotaxime, a third-generation cephalosporin, has been shown to be superior to ampicillin plus tobramycin in a controlled trial.[36] Cefotaxime or a similar third-generation cephalosporin appears to be the treatment of choice for suspected SBP; it covers 95% of the flora including the three most common isolates: *Escherichia coli*, *Klebsiella pneumoniae*, and pneumococci. [36] Widespread use of quinolones to prevent SBP in high-risk subgroups of patients has led to a change in

flora with more gram-positives and quinolone-resistant bacteria in recent years.[53]

PREVENTION OF SBP

Certain subgroups of patients with cirrhosis and ascites are at increased risk for the development of SBP, including those with: (1) upper gastrointestinal bleeding, (2) prior episodes of SBP, and (3) low protein (<1 g/dl) ascites. The identification of risk factors for development of SBP has led to randomized controlled trials of prophylactic antibiotics.[5, 54-59]

Norfloxacin 400 mg/day orally has been reported to successfully prevent SBP.[54-55] Patients with digestive tract hemorrhage are more at risk in developing SBP; it is considered that 20% of them have SBP at admission and 30-40% will develop an infection during hospitalization. Norfloxacin 400 mg orally twice per day for 7 days helps prevents infection in patients with variceal hemorrhage.[56]A group in France reported a reduction in hospitalization mortality for patients with variceal hemorrhage from 43% 20 years ago to 15% recently; much of the reduced mortality was attributed to use of antibiotics to prevent infections.[60] An antibiotic can be given intravenously while the patient is actively bleeding; ofloxacin (400 mg/day) has been validated for this purpose.[57] A

meta-analysis of five trials in patients with cirrhosis and gastrointestinal bleeding has shown a survival advantage of 9.1% in the treated group.[61]

Parenteral antibiotics to prevent sclerotherapy-related infections do not appear to be warranted, based on a controlled trial.[62] It is the active bleeding that appears to be the risk factor for infection, not sclerotherapy.[63] Variceal banding has largely replaced sclerotherapy; antibiotics would be even less likely to be of benefit in the setting of banding.

The use of selective intestinal decontamination (SID) with norfloxacin in patients admitted to the hospital with low-protein ascites has also shown a reduction in the incidence of SBP from 22.5 to 0%.[56] Selective intestinal decontamination with norfloxacin or trimethoprim/ sulfamethoxazole in patients with prior SBP or low protein ascitic fluid does appear to be cost-effective.[64-65] Also selective intestinal decontamination does select resistant gut flora, which can subsequently cause spontaneous infection; fortunately, infection-causing bacteria that are resistant to quinolones are usually sensitive to cefotaxime.[66] Patients who develop SBP on quinolone prophylaxis should not receive these drugs for treatment but instead undergo treatment with a third-generation cephalosporin (i.e. cefotaxime).[46-47, 67]

Other prophylactic measures include:

1) Diuretics, which reduce the ascites volume and increase the ascitic fluid opsonic activity [5,68, 69]
2) Local infections treatment and eradication, before their dissemination
3) Screening for and prophylaxis of esophageal varices to reduce the risk of gastrointestinal hemorrhage are also recommended.
4) Porto-caval shunts and TIPS (transjugular intrahepatic portosystemic shunt) for digestive hemorrhage or ascites risk reduction, reducing indirectly SBP risk
5) Abstinence from alcohol in case of alcoholic cirrhosis.

Patients surviving an episode of SBP should be considered for liver transplantation if acceptable candidates.[42] Regardless, antibiotic prophylaxis should be restricted to high-risk patients; namely those with gastrointestinal hemorrhage (short-term), a prior episode of SBP (long-term), or those with ascitic fluid total protein levels < 1 g/dl.[35] Whether the latter group should receive long-term or inpatient-only prophylaxis needs careful assessment of the risks and benefits on a case-by-case basis.

FOLLOW-UP PARACENTESIS

A follow-up ascitic fluid analysis is not needed in many patients with infected ascites.[70] Repeat paracentesis can be performed to document sterility of culture and dramatic decrease in PMN count in patients with SBP; however, it is not necessary. The majority of patients have SBP in the typical setting (i.e., advanced cirrhosis) with typical symptoms, typical ascitic fluid analysis (total protein of 1 g/dL, LDH less than the upper limit of normal for serum, and glucose of 50 mg/dL), a single organism, and a dramatic clinical response.[30,70]

In contrast, if the setting, symptoms, analysis, organism(s), or response are atypical, repeat paracentesis can be helpful in raising the suspicion of secondary peritonitis and prompting further evaluation and surgical intervention when appropriate.[31]

PROGNOSIS

In the past, 48% to 95% of patients with a spontaneous ascitic fluid infection died during the hospitalization in which the diagnosis was made, despite antibiotic treatment.[28, 35] The most recent series report the lowest mortality rates (less than 5% if antibiotics are administered in a timely fashion), probably because of earlier detection and treatment of infection, as well as the avoidance of nephrotoxic antibiotics.[71] In order

to maximize survival, it is important that paracentesis be performed in all patients with ascites at the time of hospitalization, so that infection can be detected and treated promptly.

The trial in which cefotaxime plus albumin was studied reported the lowest hospitalization mortality rate yet—10%.[50] Even now, however, some patients are cured of their infection but die of liver failure or gastrointestinal bleeding, because of the severity of the underlying liver disease. In fact, spontaneous ascitic fluid infection is a good marker of end-stage liver disease and has been proposed as an indication for liver transplantation in a patient who is otherwise a candidate.

Paracentesis should be repeated during the hospitalization if any manifestation of clinical deterioration develops, including abdominal pain, fever, change in mental status, renal failure, acidosis, peripheral leukocytosis, or gastrointestinal bleeding. No survivors of spontaneous bacterial peritonitis have been reported when the diagnosis is made after the serum creatinine level has risen above 4 mg/dL (350 μmol/L) or after shock has developed.

MATERIALS AND METHODS

It was a prospective study between January 2008 and December 2009 where consecutive asymptomatic outpatients with cirrhosis undergoing therapeutic paracentesis for tense ascites were included. The same patient undergoing paracentesis on more than one occasion was also included. All patients had a baseline ascitic fluid analysis. Cirrhosis was diagnosed by clinical, imaging and biochemical values. Baseline demographic details including age, gender, literacy and socioeconomic status were collected. A detailed work up for the etiology of cirrhosis was done. The severity of liver disease was graded according to Child Pugh scoring.

Ascitic fluid paracentesis was performed in the standard fashion by means of an 18-Fr catheter connected to a line and draining by gravity. The ascitic fluid was collected under strict aseptic precautions for analysis. Ascitic fluid total white cell count along with the differential count was performed using standard laboratory techniques. Laboratory analysis for estimation of total protein and albumin levels was done. Bacterial cultures were obtained by bedside inoculation of 10 mL of ascitic fluid into aerobic and anaerobic blood culture bottles under strict aseptic precautions.

The diagnosis of ***Spontaneous bacterial peritonitis*** was made when there was a positive ascitic fluid culture and an elevated ascitic fluid absolute PMN count (i.e., at least 250 cells/mm^3 [0.25×10^9/L]) without evidence of an intra-abdominal surgically treatable source of infection.[16]

The criteria for diagnosis of ***Monomicrobial nonneutrocytic bacterascites*** (MNB) included (1) a positive ascitic fluid culture for a single organism, (2) an ascitic fluid PMN count lower than 250 cells/mm^3 (0.25×10^9/L), and (3) no evidence of an intra-abdominal surgically treatable source of infection.[17]

Culture-negative neutrocytic ascites (CNNA) was diagnosed when (1) the ascitic fluid culture grows no bacteria, (2) the ascitic fluid PMN count is 250 cells/mm^3 (0.25×10^9/L) or greater, (3) no antibiotics have been given (not even a single dose), and (4) no other explanation for an elevated ascitic PMN count (e.g., hemorrhage into ascites, peritoneal carcinomatosis, tuberculosis, or pancreatitis)

Exclusion criteria:

Patients excluded were those with

1) Fever
2) Abdominal pain
3) Hepatic encephalopathy

4) Gastrointestinal bleeding within the last month
5) Impaired renal function
6) Previous history of SBP and
7) Antibiotic treatment within 2 weeks
8) Antibiotic prophylaxis for SBP
9) Noncirrhotic ascites

Patients with diagnosis of SBP were hospitalized for treatment while those with neutrocytic ascites and monomicrobial bacterascites were treated with oral antibiotics Ofloxacin 400 mg twice a day for 5 days.[18] A follow up paracentesis was done to confirm the resolution of the infection.

All patients who participated in the study gave a written informed consent. The study was approved by the institutional ethical committee.

Statistical analysis:

Quantitative data were expressed in Mean & SD. Qualitative data were given in frequencies with their percentage. The association between various factors like age, gender, alcohol consumption, etiology of cirrhosis, Child's score, serum albumin and mean ascitic fluid total protein study and the occurrence of ascitic fluid infection was analyzed

using Pearson Chi square test/ student independent test/2 sample proportion test as appropriate. $P<0.05$ was taken as statistically significant.

RESULTS

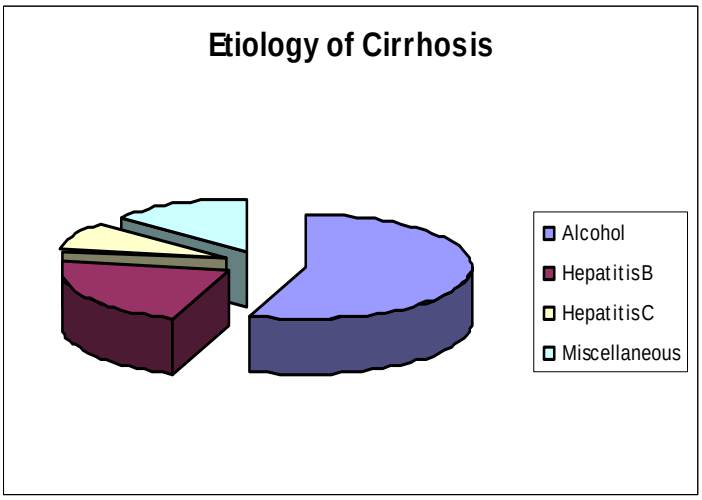
A total of 110 patients with cirrhosis underwent therapeutic paracentesis in the outpatient setting during the study period. The mean age of the study population was 47.1±9.6 years. Cirrhosis was predominantly observed in men (Male: Female - 2.7:1). The etiology of cirrhosis was:

1) Alcohol in 55.5%.

2) Hepatitis B in 21.8%

3) Hepatitis C in 9.1% and

4) Miscellaneous in 13.6%.



The severity of liver disease as assessed by Child Pugh scoring was: Child's B and C in 70% and 30% respectively. Total number of paracentesis performed during the study period was 278 with a range between one and four. The average number of paracentesis was 2.5±1.1. The characteristics of the study population are summarized in Table 1.

Table 1: Demographic characteristics of the study population

Characteristics	No (%)
Total No of cases	110
Mean age (years)	47.1±9.6
Gender distribution	
Male	80 (72.7)
Female	30 (27.3)
Literacy status	
Yes	36 (32.7)
No	74 (67.3)
Etiology of cirrhosis	
Alcohol	61 (55.5)
Hepatitis B	24 (21.8)
Hepatitis C	10 (9.1)
Miscellaneous	15 (13.6)
Child Turcotte Pugh staging (CTP)	
CTP B	77 (70)
CTP C	33 (30)
Total No of paracentesis	278
Average paracentesis	2.5±1.1

The prevalence of spontaneous ascitic fluid infection in asymptomatic cirrhotic patients undergoing therapeutic paracentesis was 2.5% (7/278 paracentesis). The variants of ascitic fluid infection observed were:

1) Spontaneous bacterial peritonitis in one (0.4%),

2) Monomicrobial nonneutrocytic bacterascites in two (0.7%) and

3) Culture-negative neutrocytic ascites in four patients (1.4%).

The characteristic of patients with ascitic fluid infection is shown in Table 2. The bacterial culture showed Escherichia coli in one patient with spontaneous bacterial peritonitis. Klebsiella and Staphylococcus aureus were grown in patients with bacterascites. All patients had evidence of spontaneous infection at the time of their first therapeutic paracentesis.

There was no significant difference between outpatient cirrhosis with and without infection with regards to age (p=0.73), gender (p=0.93), alcohol consumotion (p=1), etiology of cirrhosis (p=0.93), Child Pugh score (p=0.93), serum albumin (p=1) and ascitic fluid total protein (p=0.19). [Table 3]

Table 2: Characteristics of patients with ascitic fluid infection

Cases	Age	Sex	Etiology	Childs staging	Alcohol	Total no of paracentesis	Cell count >250 cells/ mm^3	Culture	Serum albumin (gm/dl)	Ascitic protein (gm/dl)
1	52	M	Alcohol	B	Yes	1	No	Positive	2.6	1
2	49	M	HBV	C	No	4	No	Positive	3.1	1.3
3	48	F	HCV	C	No	3	Yes	Negative	2.3	1.1
4	47	M	Alcohol	B	Yes	3	Yes	Negative	3	1.2
5	48	M	Alcohol	B	Yes	3	Yes	Negative	3	1.2
6	47	M	Alcohol	B	Yes	2	Yes	Negative	2.8	1
7	47	F	Others	B	No	2	Yes	Positive	2.9	1

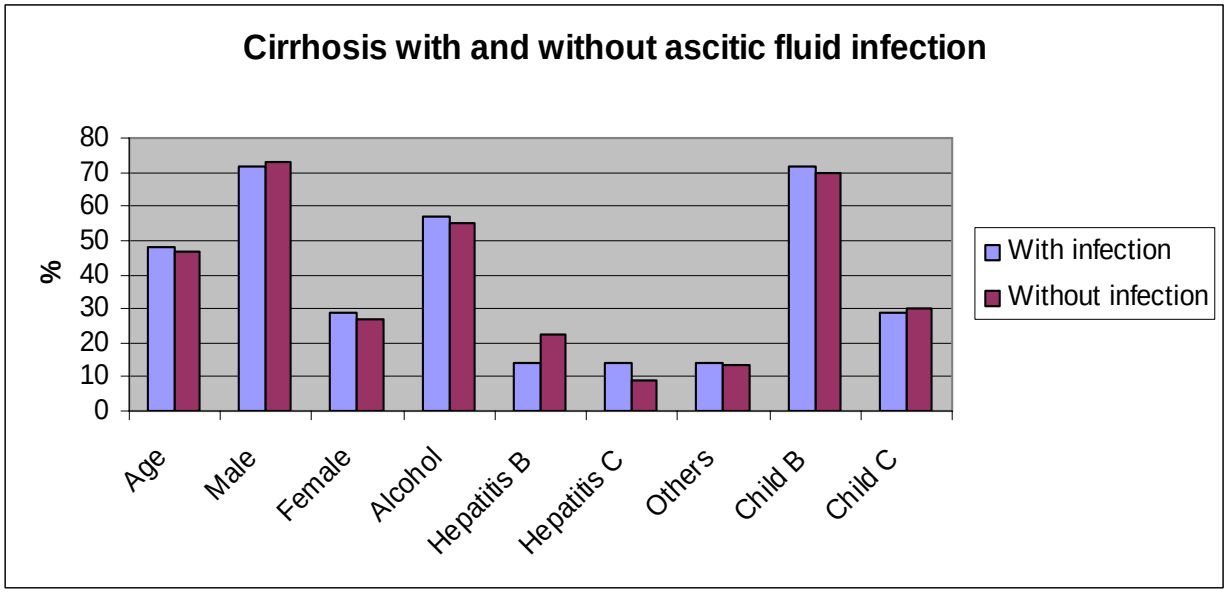


Table 3: Cirrhosis with and without spontaneous ascitic fluid infection

		Outpatients with Ascitic Fluid infection		P value
		Yes N=7 (2.5%)	No N=103 (97.5%)	
Mean Age (years)		48.3±1.8	47±9.9	0.73
Gender	Male	5 (71.4)	75 (72.8)	0.93
	Female	2 (28.6)	28 (27.2)	
Alcohol		4 (57.1)	57 (55.3)	1
Etiology	Alcohol	4 (57.1)	57 (55.3)	0.93
	Hepatitis B	1 (14.3)	23 (22.3)	
	Hepatitis C	1 (14.3)	9 (8.7)	
	Miscellaneous	1 (14.3)	14 (13.6)	
Child's score	B	5 (71.4)	72 (69.9)	0.93
	C	2 (28.6)	31 (30.1)	
Serum albumin		2.8±0.3	2..8±0.4	1
Mean ascitic fluid protein		1.1±0.1	1.2±0.2	0.19

DISCUSSION

SBP in asymptomatic outpatients has distinguishing features from SBP in hospitalized patients and may be a separate entity. The organisms cultured are predominantly gram positive in outpatients as compared with gram negative in hospitalized patients. Survival is better, and type I hepatorenal syndrome as a complication of SBP in outpatients is infrequent, whereas type I hepatorenal syndrome occurs in as many as 30% of inpatients with SBP.[50] Finally, recurrence of SBP is unusual in outpatients even when they are not on antibiotic prophylaxis. Only one third of the outpatients diagnosed with SBP died within 1 year of the outpatient paracentesis as compared with a 1-year mortality of 50% to 70% in historically hospitalized patients with SBP.[72]

Several retrospective studies of inpatients have demonstrated poor performance of clinical signs in the diagnosis of spontaneous bacterial peritonitis. Fever, abdominal pain, and encephalopathy were present in 32% - 54%, 41% - 57%, and 9% - 74% of spontaneous bacterial peritonitis patients, respectively.[73-75] In clinical practice, patients requiring therapeutic LVP may present with less ominous but concerning symptoms of vague abdominal discomfort, mild tenderness on exam, or subtle changes in affect that may be suggestive of occult infection. The

pain related to the abdominal wall distention of large volume ascites in the non–spontaneous bacterial peritonitis patient may be difficult to differentiate from peritoneal irritation in the spontaneous bacterial peritonitis.

Brian Chinnock et al [76] concluded that clinical signs, symptoms, and physician impression were poor in ruling out spontaneous bacterial peritonitis. Abdominal pain or tenderness was unreliable in the diagnosis of spontaneous bacterial peritonitis in patients undergoing diagnostic or therapeutic paracentesis in the emergency department.

It would be reasonable in such instances of clinical uncertainty to obtain ascitic fluid cell count with differential. This approach would rapidly screen for SBP and CNNA, which require immediate intervention without the additional expense of cultures. However, if the ascitic fluid were cloudy at the time of therapeutic paracentesis, it would be prudent to obtain not only cell counts but a bacterial culture as well.

The incidence of SBP in cirrhotic outpatients undergoing large volume paracentesis (LVP) with low risk of infection is very low. Evans *et al.*[12] found the prevalence of SBP to be 1.4% and neutrocytic ascites to be 2.1% in 427 paracenteses in 427 cirrhotic patients seen at a single

outpatient clinic without symptoms of SBP and without high risk of SBP. The prevalence of bacterascites was 3% which was frequent in patients on selective intestinal decontamination. Mark A. Jeffries et al[11] prospectively studied ascitic fluid cell counts and cultures in outpatients with refractory ascites undergoing large volume paracentesis. 2.5% had monomicrobial bacteriascites. None had spontaneous bacterial peritonitis.

In our study, the prevalence of spontaneous bacterial peritonitis in asymptomatic cirrhotics undergoing therapeutic paracentesis was 0.4%. Monomicrobial nonneutrocytic bacterascites and Culture-negative neutrocytic ascites were observed in 0.7% and 1.4% respectively.

Two other studies have addressed the issue of whether ascitic fluid should be analyzed at the time of therapeutic paracentesis in asymptomatic outpatients. In a retrospective study of 37 outpatient LVPs performed at Emory University, ascitic fluid cell counts and cultures revealed no evidence of peritoneal fluid infection.[77] Similarly, in a prospective study from Barcelona, 173 ascitic fluid samples were analyzed from 51 asymptomatic stable cirrhotics with Refractory ascites (RA).[78]All ascitic fluid cell counts were < 250 PMN/mm3 and only four cultures (2.3%) grew bacterial microorganisms and were classified as asymptomatic MNB.

Runyon recently reported a 2% prevalence of spontaneous bacterial peritonitis in a series of 400 paracenteses performed in two years in an outpatient setting.[35] A retrospective review of 916 outpatient AF samples from the United States showed that abnormal AF appearance had a sensitivity of 98.1% [(95% confidence interval (CI): 95.3%-99.5%] and a specificity of 22.7% (95% CI: 19.4%-26.3%) in the detection of SBP.[79] For out- and inpatients, laboratory abnormalities such as leukocytosis, metabolic acidosis and azotemia, should prompt investigations for SBP, even in the absence of other clinical features.

The organisms cultured were unusual and did not include *Escherichia coli* and *Klebsiella pneumoniae*, which are usually seen in hospitalized patients with cirrhosis. They were mostly gram-positive cocci. The organisms grown in our study were Escherichia coli, Klebsiella and Staphylococcus. A study by Fernandez et al., [53] confirmed the changing patterns of organisms cultured from patients with SBP. It was explained on the basis of norfloxacin prophylaxis or interventions previously carried out.

While patients with ascitic fluid positive for Escherichia coli developed clinical SBP after 24 h, those secondary to gram-positive cocci did not

develop an overt clinical or analytical SBP. Moreover, a second ascitic fluid analysis performed some days after the index episode proved normal in all cases.

In our study, the bacterial culture showed Escherichia coli in one patient with spontaneous bacterial peritonitis. Klebsiella and Staphylococcus aureus were grown in patients with bacterascites.

Patients with neutrocytic ascites did not suffer decreasing liver or renal function, or clinical features of SBP despite no treatment suggesting that they might represent a false positive of the total PMN count for diagnoses of SBP. Several studies have confirmed spontaneous clearance of bacterascites on close monitoring of subjects with MNB. [17, 78, 80] As many as 62% of episodes of bacterascites resolve without development of neutrocytic ascites.[17] Because the outcome of patients with asymptomatic MNB was favorable, minimal risk would be incurred if ascitic fluid cultures were not routinely performed. Also such patients do not require antibiotic therapy.

It is unclear whether bacterascites represents true pathogenic growth or simple transient colonization of peritoneal fluid with intestinal flora. However, another study demonstrated that about one third of

bacterascites progressed to spontaneous bacterial peritonitis.[17] Studies have shown similar in hospital mortality in patients with normal ascitic fluid and those with asymptomatic bacterascites, and consensus recommendations do not indicate the need for immediate antimicrobial treatment of these patients.[42, 80]

Although further studies are needed, the routine culture of ascitic fluid in asymptomatic outpatients frequently receiving prophylactic antibiotics may not be necessary when there is a low index of suspicion for occult infection. In circumstances of clinical uncertainty, however, obtaining an ascitic fluid cell count with differential is recommended to ensure patient safety.

SUMMARY

In the present study,

1) The prevalence of Spontaneous bacterial peritonitis in cirrhotic outpatients undergoing therapeutic paracentesis is 0.4%.
2) The prevalence of Monomicrobial nonneutrocytic bacterascites in cirrhotic outpatients undergoing therapeutic paracentesis is 0.7%
3) The prevalence of Culture-negative neutrocytic ascites in cirrhotic outpatients undergoing therapeutic paracentesis is 1.4%
4) There was no significant difference between outpatient cirrhosis with and without infection with regards to age, gender, alcohol consumption, and etiology of cirrhosis, Child Pugh score, serum albumin and ascitic fluid total protein.

CONCLUSION

In conclusion, the results of our study confirm that the prevalence of spontaneous bacterial peritonitis, monomicrobial bacterascites and culture negative non neutrocytic ascites in asymptomatic cirrhotic outpatients undergoing therapeutic paracentesis was very low. There were no significant risk factors predicting the occurrence of spontaneous infection of the ascitic fluid in outpatients.

In our opinion, routine ascitic fluid analysis may be unnecessary in this clinical setting as it may not be cost effective. However testing the ascitic fluid only for cell count and differential in outpatient therapeutic paracenteses will ensure the clinician not to miss spontaneous ascitic fluid infection in the absence of clinical signs and symptoms.

The criteria for diagnosis of spontaneous ascitic fluid infection as well as risk factors associated with it in outpatients without clinical or biological signs of infection need to be reassessed in larger randomized trials.

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S.No	*MGE NO*	Age	Sex	Etiology	Literacy	Alcohol	Smoking	Albumin	No of paracentesis	Childs	Infection	Cell count	Culture	Ascitic protein
1	6379/09	55	1	1	1	1	2	2.4	1	B	2	2	2	1.2
2	6528/09	53	1	1	1	1	1	2.3	1	B	2	2	2	1.2
3	3765/09	22	2	4	2	2	2	2.8	1	B	2	2	2	1.1
4	3638/09	52	1	1	1	1	1	2.6	1	B	1	2	1	1
5	3768/06	38	2	4	2	2	2	2.7	1	B	2	2	2	1.3
6	5103/09	51	2	2	2	2	2	3	4	C	2	2	2	1.4
7	3063/09	47	1	1	2	1	1	3.1	4	C	2	2	2	1.2
8	4941/09	45	1	1	2	1	1	2.8	4	C	2	2	2	1
9	2192/06	38	1	2	2	2	1	2.4	4	B	2	2	2	1.2
10	1166/05	48	2	4	2	2	2	3	4	B	2	2	2	1.1
11	912/09	56	2	2	2	2	2	2.6	4	B	2	2	2	1.5
12	3295/08	43	2	1	2	1	2	2.9	4	C	2	2	2	1.2
13	650/07	49	1	1	1	1	1	3.4	4	B	2	2	2	1.1
14	3954/09	24	1	1	1	1	2	2.1	4	C	2	2	2	1
15	5989/06	49	2	3	2	2	2	2.4	4	C	2	2	2	1.3
16	3942/09	45	1	1	1	1	1	3	1	B	2	2	2	1.4
17	1517/08	22	1	1	2	1	1	2.4	1	B	2	2	2	1
18	21334	38	1	1	2	1	2	2.4	1	B	2	2	2	1
19	1723/09	24	1	4	2	2	2	3.1	1	B	2	2	2	1.2
20	1558/06	56	1	2	2	2	1	3	1	B	2	2	2	1.1
21	6048/09	50	2	4	2	2	2	3.2	3	B	2	2	2	1
22	2716/07	24	1	1	1	1	2	2.9	3	B	2	2	2	1.4
23	1011/08	32	2	1	1	1	2	2.8	3	C	2	2	2	1
24	6572/09	49	1	4	2	2	2	3.1	3	C	2	2	2	1.3
25	4955/07	52	1	3	2	2	1	3.2	3	C	2	2	2	1
26	4613/09	48	1	2	2	2	2	3	3	B	2	2	2	1.2
27	4302/09	58	1	1	1	1	1	2.3	3	C	2	2	2	1.5
28	5944/09	54	2	2	2	2	2	2.7	3	C	2	2	2	1
29	5458/09	50	2	1	2	1	2	3.1	3	B	2	2	2	1.3
30	5450/09	31	1	1	2	1	1	2.5	3	C	2	2	2	1.4

31	3726/05	52	1	1	2	1	1	2.2	1	B	2	2	2	1
32	5889/09	49	1	2	2	2	1	2.4	1	B	2	2	2	1.1
33	3118/09	51	1	1	1	1	2	2	1	B	2	2	2	1
34	5753/09	28	1	4	2	2	1	2.2	1	B	2	2	2	1.4
35	5550/09	51	1	1	1	1	1	3	1	B	2	2	2	1.3
36	4584/06	54	1	1	1	1	2	2.3	4	C	2	2	2	1
37	6642/09	49	1	2	2	2	2	3.1	4	C	1	2	1	1.3
38	3700/08	60	1	1	2	1	1	3.2	4	C	2	2	2	1.2
39	5999/09	51	1	1	1	1	2	2.9	4	B	2	2	2	1.2
40	5335/09	42	2	2	2	2	2	3.5	4	B	2	2	2	1.1
41	5000/09	36	2	1	1	1	2	3.3	3	B	2	2	2	1
42	5394/03	53	1	2	2	2	1	3.4	3	C	2	2	2	1.4
43	1145/08	47	2	2	2	2	2	2.3	3	C	2	2	2	1
44	736/04	48	2	3	2	2	2	2.3	3	C	1	1	2	1.1
45	3464/08	45	2	2	2	2	2	2.6	3	C	2	2	2	1
46	5901/09	20	1	4	2	2	2	2.9	3	C	2	2	2	1.3
47	7065/07	47	1	1	1	1	1	3	3	B	1	1	2	1.2
48	6349/09	59	1	1	1	1	1	3.2	3	B	2	2	2	1
49	5189/09	45	1	2	2	2	2	2.6	3	B	2	2	2	1.3
50	1421/06	48	1	1	2	1	2	3	3	B	1	1	2	1.2
51	4566/09	56	1	1	1	1	1	3.4	2	B	2	2	2	1.2
52	3224/06	49	1	3	2	2	2	2.6	2	B	2	2	2	1.5
53	5344/09	51	1	1	1	1	1	3	2	B	2	2	2	1.6
54	4888/07	26	1	1	2	1	2	3	2	B	2	2	2	1.3
55	28/08	48	1	2	2	2	1	2.3	2	B	2	2	2	1.4
56	3638/09	52	1	1	1	1	2	2.9	2	B	2	2	2	1
57	215/08	51	2	2	2	2	2	3.3	2	B	2	2	2	1
58	4479/09	54	1	1	2	1	1	2.8	2	C	2	2	2	1.2
59	1468/06	40	1	1	1	1	1	1.9	2	B	2	2	2	1.5
60	3768/06	36	2	4	2	2	2	2.7	2	B	2	2	2	1.2
61	4784/09	55	1	1	2	1	2	2.6	3	C	2	2	2	1

62	4752/09	50	1	1	1	1	1	2.4	3	C	2	2	2	1.1
63	476/06	56	1	1	2	1	1	2.5	3	B	2	2	2	1
64	4080/07	37	1	2	2	2	2	2	3	C	2	2	2	1
65	6185/08	50	1	1	1	1	1	3.1	3	C	2	2	2	1.3
66	1398/09	40	1	2	2	2	1	2.9	3	C	2	2	2	1.2
67	6417/09	52	1	1	2	1	2	3.2	3	B	2	2	2	1
68	796/08	45	1	2	2	2	2	3.4	3	B	2	2	2	1.3
69	1022/05	39	2	2	1	2	2	3.3	3	B	2	2	2	1.2
70	6665/07	57	1	1	1	1	2	3.4	3	B	2	2	2	1.1
71	4054/06	49	2	4	2	2	2	2.3	3	C	2	2	2	1
72	4362/09	56	1	2	2	2	1	3.4	3	B	2	2	2	1.2
73	6557/07	30	1	1	2	1	2	2.7	3	B	2	2	2	1.1
74	801/07	20	1	3	2	2	2	2.8	3	C	2	2	2	1
75	4744/09	51	1	1	1	1	2	2.5	3	C	2	2	2	1.3
76	5092/09	45	1	1	2	1	2	2.6	3	C	2	2	2	1.4
77	5534/07	59	1	3	2	2	2	3.2	3	B	2	2	2	1
78	4036/06	54	1	3	2	2	1	3.4	3	B	2	2	2	1
79	2980/07	53	1	1	1	1	2	2.2	4	C	2	2	2	1.3
80	5971/08	57	1	1	2	1	2	3	4	B	2	2	2	1.4
81	4688/04	53	1	1	1	1	2	2	2	B	2	2	2	1
82	4566/07	50	2	2	2	2	2	3.2	2	B	2	2	2	1.3
83	3412/09	52	1	1	1	1	2	3.1	2	B	2	2	2	1.2
84	1965/05	50	2	3	2	2	2	2.2	2	B	2	2	2	1.5
85	6241/09	35	1	1	2	1	2	2.8	2	B	2	2	2	1
86	4770/08	57	1	1	1	1	2	2.5	2	B	2	2	2	1.3
87	546/09	45	1	2	2	2	2	3.2	2	B	2	2	2	1.4
88	5169/06	52	1	1	2	1	2	3	2	B	2	2	2	1
89	2798/09	37	1	1	1	1	2	2.6	2	B	2	2	2	1.4
90	6744/03	53	2	1	2	1	2	2.4	2	C	2	2	2	1.2
91	2590/06	57	2	4	2	2	2	3	2	B	2	2	2	1.1
92	6320/08	60	1	1	1	1	2	2.4	2	B	2	2	2	1.3

93	6210/09	49	1	1	2	1	2	2.4	2	B	2	2	2	1.5
94	5883/07	45	1	3	1	2	2	3	2	B	2	2	2	1.2
95	2647/09	54	2	4	2	2	2	2.6	2	B	2	2	2	1.1
96	6355/09	47	1	1	2	1	2	2.8	2	B	1	1	2	1
97	5965/07	54	1	1	1	1	1	2.9	2	B	2	2	2	1.3
98	486/08	59	2	2	2	2	2	2.7	2	B	2	2	2	1.4
99	6360/05	55	1	1	2	1	2	2.2	2	B	2	2	2	1.4
100	1103/06	49	2	4	2	2	2	3.1	2	B	2	2	2	1.2
101	3653/06	53	1	1	2	1	2	3.4	2	B	2	2	2	1.2
102	4196/09	55	1	3	2	2	1	2.8	2	B	2	2	2	1.3
103	4108/07	51	1	1	1	1	2	3	2	B	2	2	2	1
104	4545/08	49	2	4	2	2	2	3.1	2	B	2	2	2	1.4
105	5860/07	37	2	2	2	2	2	3.2	2	B	2	2	2	1.4
106	1332/06	52	1	1	1	1	2	2.7	2	B	2	2	2	1
107	2822/07	47	2	4	2	2	2	2.9	2	B	1	1	1	1
108	2248/07	53	1	1	1	1	1	2.5	2	B	2	2	2	1.2
109	1401/09	54	1	1	2	1	1	2.7	2	B	2	2	2	1.3
110	2514/09	56	1	1	2	1	2	2.3	3	C	2	2	2	1

Sex

Male	1
Female	2

Etiology

Alcohol	1
Hepatitis B	2
Hepatitis C	3
Others	4

Literacy

Yes	1
No	2

Alcohol

Yes	1
No	2

Smoking

Yes	1
No	2

Infection

Yes	1
No	2

Cell count >250 cells/mm3

Yes	1
No	2

Culture

Positive	1
Negative	2

ABBREVIATIONS

SBP	Spontaneous bacterial peritonitis
LVP	Large-volume paracentesis
MNB	Monomicrobial non-neutrocytic bacterascites
CNNA	Culture-negative neutrocytic ascites
PMN	Polymorphonuclear
BT	Bacterial translocation
GALT	Gut-associated lymphoid tissue
APC	Antigen presenting cells
PAMP	Pathogen-associated molecular pattern
PRR	Pattern recognition receptor
TLR	Toll like receptor

Proforma

Name	Age	Sex
MGE No:		
Resident	Occupation (Unoccupied [U], specify)	
Literacy	Per capita income	No of family members
Adults	Children	Religion
Type of house (Pucca, Semi, Kutcha)		Veg/NV
Alcohol:Y/N	Duration:	Quantity: (180/360/720)
Frequency: (daily; alternate; once a week; festival)		
Brand: (Whiskey/Brandy/Country liquor)		Abstainence:
Height	Weight	BMI
Diagnosis: (Cirrhosis – Child's scoring: B	C	
Etiology :(Alcohol; HBV; HCV; Miscellaneous)		Duration:

Co morbid:

HT/Duration:	DM/Duration:	Treatment :(OHA/Insulin)
Diagnosed before CLD:	CAD:	Past H/O surgery:
Blood transfusion:		

Complications:

Ascites:	Pedal edema:	UGI bleed:
SBP:	HE:	Jaundice:
HCC:	Oliguria:	

Duration of symptoms:

Ascites:	Pedal edema:	UGI bleed:
SBP:	HE:	Jaundice:

Investigation:

Hb:	TC:	Platelet:	PCV:
MCV:	MCH:	MCHC:	PT:
INR:	APTT:	Bl group:	Sugar:
Urea:	Creatinine:	Bilirubin: (T)	Direct:
AST:	ALT:	GGT:	SAP:
Total protein:	Albumin:	Globulin:	HBsAg:
Anti HCV:	AntiHIV:		

Ascitic Fluid:

Protein:	Albumin:	Cell count:	Culture:
Amylase:			
SAAG:	AFP:		

USG:

Liver (Shrunken;Coarse/Altered/↑echoes;Irregular):

Spleen:

PV diameter:	PV thrombosis:	Collaterals:
Flow: (Hepatopedal/Hepatofugal)	Ascites:	GSD: