RESEARCH PAPER | Medical Science | Volume : 5 | Issue : 4 | April 2015 | ISSN - 2249-555X

Asymptomatic Bacteriuria in Non-Hospitalized Patients With Liver Cirrhosis : is C-Reactive Protein Helpful?

KEYWORDS: Asymptomatic; Bacteriuria; Liver cirrhosis.

Yahia Z. Gad*
Assistant professor of Internal Medicine, Hepato-Gastroenterology Unit, Mansoura Specialized Medical Hospital, Mansoura, Egypt

Amany M. Hassan
Hepato-Gastroenterology*, Clinical Pathology, Mansoura University, Mansoura, Egypt

ABSTRACT *Background/aim: Bacteriuria has been implicated as a source of infection with a substantial risk of morbidity and mortality in cirrhotic patients. In this work, we aimed to screen for asymptomatic bacteriuria in non-hospitalized Egyptian patients with cirrhotic liver disease.*

Patients and methods: A total of eligible 397 consecutive follow-up cirrhotic patients attending our outpatient clinic, during 2013, were enrolled. All patients were subjected to history taking, clinical examination, traditional laboratory investigations, urine culture, and C-reactive protein (CRP) measurement. Ultrasonography assessed the prostate volume (PV) and post-void residual volume (PVRV) in males.

Results: Cirrhotic females (P < 0.001 with Diabetes Mellitus (D.M.)(P < 0.05) and a positive past history of hepatic encephalopathy (HE) (P < 0.001) and gut bleeding(P < 0.001), are significantly associated with asymptomatic bacteriuria On multivariate logistic regression analysis, female gender (P = 0.013), D.M. (P = 0.007), Child-Pugh class C (P = 0.014) are independent predictors for development of asymptomatic bacteriuria. CRP levels are significantly elevated (P < 0.001) in patients with asymptomatic bacteriuria when compared with the corresponding group without bacteriuria.

Conclusions: Our data revealed a significant prevalence of asymptomatic bacteriuria in non-hospitalized cirrhotic patients. Considering its potential hazards and resources availability, asymptomatic bacteriuria should be systematically screened on regular outpatient basis and not to miss moderate CRP rises in cirrhotic patients to initiate norfloxacin therapy.

Introduction

Bacterial infections are a common cause of morbidity and mortality in patients with liver cirrhosis. In about 30% patients, infections are present at admission or develop during hospitalization.[1] Impaired host defense mechanism due to reticuloendothelial system dysfunction, is responsible for increased susceptibility to infections.[2] Spontaneous bacterial peritonitis, pneumonia, bacteremia, cellulitis and urinary tract infections (UTIs) are the most commonly encountered infectious complications.[3]

UTIs account for 12% to 29% of infectious complications found in patients with decompensated cirrhosis.[4] Gram-negative bacteria constitute approximately 70-80% of the isolated organisms. The use of prophylactic antibiotics has lately resulted in the appearance of Gram-positive bacteria in a considerable proportion of patients.[1,5]

In cirrhotic patients, UTIs may be asymptomatic or oligosymptomatic. Asymptomatic bacteriuria is a recognized form present in a high frequency. [6,7] The responsible factors for the increased prevalence of bacteriuria in cirrhotics are numerous. The role of liver failure is suggested. [8,9] The increased bladder post-void urine volume and possibly associated vesical dysfunction could favor the occurrence of bacteriuria in cirrhotic ascitic patients.[10]

The aim of this work was to screen for asymptomatic bacteriuria in a cohort of non-hospitalized Egyptian cirrhotic patients.

Patients and methods

A total of 397 consecutive chronic liver disease follow-up patients attending the outpatient clinic of the Hepato-Gastroenterology unit, Mansoura Specialized Medical Hospital, during 2013, were enrolled in this study after ethical approval and giving a well-informed consent.

Exclusion criteria: 1- Recent or ongoing intake of antibiotics, corticosteroids, or other immunosuppressive agents. 2 -Patients with prostatic disease, kidney graft, urolithiasis, or anatomical defects of the urinary system. 3- Comatose patients or those with urinary catheters. 4- Hospitalized patients and those with a history of hospitalization during the last 6 months. 5- HIV positive serology. 6- Recent alcohol intake. 7- Symptomatic UTI. 8- Pregnancy or ongoing pelvic inflammatory disease in females.

Data collection was performed through a structured questionnaire including; age, sex, presence of diabetes mellitus (D.M.). Presence of orthostatic hypotension, Child-Pugh score, presence of hepatocellular carcinoma (HCC) and other hepatic parameters, were studied in all enrolled patients. The traditional laboratory investigations were carried out for each patient including liver, renal function tests, full blood count, serum electrolytes, random blood glucose, the coagulation profile, complete urine analysis and urine culture. A clean-catch midstream urine sample was obtained from each patient and delivered to the clinical laboratory within 30 min. of collection for standard analysis. Commercial kits from Bio-Merrieux (Lyon, France) were used for urine culture. Each specimen was cultured under aerobic and anaerobic conditions.

Significant bacteriuria was defined as the growth of $\geq 10^5$/ml while negative urine cultures showed no bacterial growth.[9] Pyuria was defined as >10 leucocytes/mm^3 in non-centrifuged urine sample.[11] The presence of numer-

Volume : 5 | Issue : 4 | April 2015 | ISSN - 2249-555X

ous bacteria in urine with no symptoms is considered as a asymptomatic bacteriuria Bacteriuria was considered to be symptomatic if it was associated with urinary symptoms as dysuria and asymptomatic if not and fever was not considered as a urinary symptom.[12,13] UTI is defined as an association between bacteriuria and pyuria.[9]. In this work, all cases with pyuria were symptomatic and thus, ultimately excluded.

C-reactive protein (CRP) was measured by immunoturbidimetry using Toshiba 200 FR Chemistry analyzer (Japan). The CRP reference range in this study is <0.5 mg/dl.

PVRV and prostate volume (PV) were calculated using the ellipsoid formula (PVRV and PV= 0.52 x maximum height x maximum length x maximum width by trans-parietal pre- and post-micturition ultasonographies.[14]

The diagnosis of liver cirrhosis was based on clinical, biochemical, ultrasonographic or liver histological data obtained from the out-patients' records. The Child-Pugh scoring was used to determine disease severity in each case.

Statistical analyses were made using SPSS 15.0 (SPSS, Chicago, IL, USA)

Comparisons between groups were performed using Student's *t*- test and the Chi-square test. Univariate analysis was used to test differences between bacteriuria-positive and bacteriuria –negative groups while the multivariate analysis, by stepwise logistic regression, was used to determine the independent predictors of asymptomatic bacteriuria. $P < 0.05$ was considered statistically significant.

Results

A total of 397 cirrhotic patients (247 males, 150 females), with a mean age of 55.1±1.1 years, recruited at our outpatient clinic, Mansoura Specialized Medical Hospital, for follow up were enrolled in this study. The clinical, demographic and laboratory data of the studied participants are shown in Tables (1, 2).

Differences between bacteriuria-positive and bacteriuria-negative groups are displayed in Table 2. Asymptomatic bacteriuria is significantly encountered among diabetic, Child-C, HCV-positive, female participants. On univariate analysis, cirrhotic females ($P< 0.001$ with D.M.($P < 0.05$) and a positive past history of hepatic encephalopathy(HE) ($P < 0.001$) and gut bleeding ($P < 0.001$), are significantly associated with asymptomatic bacteriuria (Table 2).

On multivariate logistic regression analysis, female gender ($P = 0.013$), D.M. ($P =0.007$), Child-Pugh class C ($p =0.014$) are independent predictors for development of asymptomatic bacteriuria as shown in Table 3.

CRP levels are significantly elevated ($P < 0.001$ in each group) in patients with asymptomatic bacteriuria when compared with the corresponding group without bacteriuria (Class A, Class B, Class C; respectively). Comparing the same groups with Child A cirrhotic patients without bacteriuria, CRP levels are significantly elevated ($P < 0.001$, <0.01, <0.05; respectively) as shown in Table 4.

However, the CRP levels, in class C patients, is elevated to a lesser degree ($P <0.05$) than class A and B with bacteriuria when compared with Child A without bacteriuria ($P < 0.001$, <0.01, <0.05; respectively). CRP levels are significantly elevated but with a lesser degree as shown in Table 4.

Our patients with asymptomatic bacteriuria have a significantly elevated CRP levels ($P < 0.001$ in each group) when compared with the corresponding group without bacteriuria (Child A, Child B, Child C, respectively). Patient groups when compared with Child A class group, without bacteriuria, CRP levels are significantly elevated but with a lesser degree ($P< 0.001$, <0.01, <0.05; respectively) as shown in Table 4.

A total of 12 uropathogens have been identified as a cause of asymptomatic bacteriuria where E. coli is the commonest 63 (73.25%) and norfloxacin clears infection in 83/86(96.51%) of our cirrhotic participants (Table 5).

Discussion

Bacterial infections are important factors for decompensation of cirrhotic patients, and are associated with worsening of prognosis and increased mortality rates.[8] In such patients, the prevalence of bacteriuria ranges on admission, from 15% to 27 %.[8,9] In retrospective studies, bacteriuria was found to represent about half of infections found decompensated cirrhotics.[8,15] Hence, the importance of our work in screening for asymptomatic bacteriuria among ambulant, non-hospitalized, cirrhotics.

In our study, the prevalence of asymptomatic bacteriuria is (21.66%) where we included patients coming for follow-up from the outpatient clinic with a rather stable feature. Different inclusion criteria with consequently different patients' characteristics would have probably explained the wide range of prevalence in different studies.

Bacterial infections are known to be a potential trigger factor for many complications of liver cirrhosis including; coagulopathy, hepatic encephalopathy, and variceal bleeding.[16] In these patients, bacteriuria has been implicated as a source of infection in up to 50% of bacteremia, and 20% of episodes of spontaneous bacterial peritonitis as well as in cases of infective endocarditis.[15,17]

It has been reported that liver cirrhosis is associated with decreased number and function of Kupffer cells, decreased bactericidal and phagocytic activity, as well as decreased chemotaxis to bacteria.[2,17-19] Moreover, hepatic failure, when develops, further increases the susceptibility to infections because of its associated reticuloendothalial dysfunction[19] and reduced complement levels.[21]

It has been suggested that liver failure, tense ascites, and bladder post void urine could be involved in the high prevalence of bacteriuria in cirrhotic patients.[8,9,10] On the other hand, Cadranel and colleagues found a significant implication of liver insufficiency only against the other studied variables.[13]

Yoneyama et al. [22], found that severe, class C cirrhosis accounted for 48.6% of patients in infection-positive group and 22.4% of patients in infection-negative group and suggested that suggested the more severe cirrhosis is associated significantly higher increased risk of development of infections. Also, Kuo et al suggests that the severity of cirrhosis is a risk factor for infections.[23]

In this work, diabetic ($P < 0.05$), Child C ($P < 0.001$), female cirrhotic patients ($P < 0.001$) with a positive past history of HE ($P < 0.001$) and gut bleeding ($p < 0.001$) are associated with asymptomatic bacteriuria on univariate analysis.

Volume : 5 | Issue : 4 | April 2015 | ISSN - 2249-555X

Female gender is a universal, well-known risk factor associated with bacteriuria, irrespective of cirrhosis. In this work, asymptomatic bacteriuria affects females more than males. [(13.35%) females vs (8.31%) males]; a data supported by Rabinowidz et al[11] and Cadranel et al[13] earlier findings regarding dominant female affection.

Increased bladder post-void residual volume and a possible vesical dysfunction have been suggested as a risk factor for bacteriuria in cirrhotic patients.[10] However, data related to these variables were not significant in our work.

Deschesnes and Villeneneuve[24] considered hospitalization for gut bleeding as a risk factor of infections in their series. Belliache et al[9] found a high prevalence of UTI in Child-Pugh C patients. Cadranel et al[13] reported that deterioration of the liver reserve is associated with an increased risk of bacteriuria.

In our work, it has been found that female gender (P = 0.013), D.M. (P = 0.007), and Child-Pugh class C (P = 0.014) are independent predictors for development of asymptomatic bacteriuria on multivariate regression analysis.

Fever is a well-known cardinal sign of infection that tends to be frequent in patients with bacteriuria than non-infected patients. However; cirrhotic patients may develop infections without fever, thus hampering the diagnosis of infections.[21] Hence, the importance of systematic screening for bacteriuria in asymptomatic cases and non reliability on fever in this setting.

CRP is an acute phase human serum protein produced mainly by the hepatocytes, Kupffer cells and to a lesser extent from extrahepatic sources as monocytes and some subsets of lymphocytes that seems to function in an autocrine fashion.[26- 28] CRP is a sensitive but non specific systemic marker of inflammation and its measurement is widely used to monitor various clinical infectious states.[29] Le Moine and coworkers suggested that CRP response to infection may be attenuated in patients with liver dysfunction [30] but its predictive value is similar to patients without liver cirrhosis.[31]

Our patients with asymptomatic bacteriuria have a significantly elevated CRP levels (P < 0.001 in each group) when compared with the corresponding group without bacteriuria (Child A, Child B, Child C, respectively). However, the CRP levels, in class C patients, is elevated to a lesser degree (P < 0.05) than class A and B with bacteriuria (P < 0.001, <0.01; respectively) when compared with Child A cirrhotic patients without bacteriuria. Thus, in this work, the CRP response to uropathogens is significantly elevated in Child A and B patients and moderately increased in advanced hepatocelluar dysfunction (Child C) and not completely abolished as postulated; a data observed by park et al[32] and support the speculation of Pieri and coworkers[33] to consider moderate CRP rises in such patients to initiate appropriate antibiotic therapy according to the local prevalent susceptibility patterns.

UTIs accounts for 12% to 29% of infectious complications found in decompensated cirrhotic patients where asymptomatic bacteriuria alone is found in a high percentage and Gram-negative bacteria constitute the majority of the isolated organisms.[4-7] Cadranel and colleague[21] reported that norfloxacin could be a first line therapy for asymptomatic bacteriuria in cirrhotic patients when urine culture become sterile in [21/22 (95.2%)] of their patients after 72 h of norfloxaoxcin administration.

In this work, norfloxacin was used successfully to eradicate bacteriuria (96.51%) in our asymptomatic cases with cirrhotic liver disease and *E.coli* [63(73.25%)] was the commonest offending uropathogen.

In conclusion, our data revealed a significant prevalence of asymptomatic isolated bacteriuria in non-hospitalized cirrhotic patients where female gender, DM, and advanced Child-Pugh class C are the independent predictors for its occurrence.

Table 1: Patients' characteristics

Parameter	Patients' data
Age (years)	55.1±1.1
Gender:	
Male/Female	247/150
Aetiology :	
HCV/ HBV/ Others	330/42/27
Ongoing diuretics	213
Past history :	
Gut bleeding	109
H.E.	108
D.M.	112
HCC	83
Orthostatic hypotension	14
Ascites	230
Child-Pugh class:	
A/B/C	60/208/124

Table 2: Demographic, clinical and laboratory characteristics of the studied patients:

Parameter	Without bacteriuria (n=311)	With bacteriuria (n=86)
Age (years)	55.3±1.9	54.7±2.1
Gender:		
Male	214(68.82%)	33(38.38%)
Female	97(31.81%)	(53)(61.62%)**
Aetiology :		
HCV	257(82.63%)	73(84.88%)
HBV	33(10.61%)	9(10.71%)
Others	21(6.76%)	6(7.4%)
Ongoing diuretics	183(58.84%)	54(62.8%)
Past history :		
Gut bleeding	65(20.9%)	44(51.62%)**
H.E.	67(21.54%)	41(47.67%)**
Ascites	179(57.55%)	51(59.3%)
Orthostatic hypotension	11(4.18%)	3 (3.48%)
D.M.	73(23.47%)	39(45.34%)*
HCC	64(20.67%)	

Volume : 5 | Issue : 4 | April 2015 | ISSN - 2249-555X

Albumin (gm/dl)	32.5±0.9	30.2±1.2*
PT%	67±7	69±9*
Bilirubin (mg %)	76±85	81±79
Child-Pugh class:	49(15.5%	11(12.78%)
A	179(57.55%)	24(27.9%)
B	83(26.6%)	51(59.3%)**
C	8.9±2.1	9.1±4.2*
Child-Pugh score	107±26	109±33
Blood glucose level	199±121	159±132
Urinary urea conc.(mmol/L)	6.1±0.9	6.3±0.8
Urinary pH	22.79	23.77
PV (cm^{3})	30.33	31.77
PVRV(ml)		

*P value < 0.05; **P value < 0.001

Table 3: Independent risk factors for asymptomatic bactiruria

Risk factor	Odds ratio	(95%)Confidence interval	*P* value
Female gender	3.71	(1.49-9.29)	0.013
Diabetes mel-litus	0.775	(1.37.4.11)	0.007
Child-Pugh class C	1.189	(1.31-9.76)	0.014

Table 4: C-reactive protein levels and Child- Pugh class

Param-eter	Without bacteriuria [median(range)]	With bacteriuria [median(range)]
Child A	0.45(0.12-0.49)	13.7(7.1-16.8) *
Child B	0.97(0.3-0.87)	8.4(6.3-11.7) *
Child C	0.4(0.3-1.1)	6.1(5.7-9.2) *

**P* value < 0.001

Table 5: Isolated Uropathogens:

Isolated bacteria	No. of samples (%)
Escherichia coli	63(73.25%)
Enterobacter spp	5(5.81%)
Klebsiella pneumoniae	3(3.48%)
Klebsiella azaenae	2(2.32%)
Serratia spp	1(1.16%)
Staphylococcus aureus	1(1.16%)
Proteus mirabilis	5(5.81%)
Streptococcus pneumoniae	1(1.16%)
Cedecea davisae	1(1.16%)
Escherichia fergusonii	1(1.16%)
Staphylococcus epidemidis	1(1.16%)
Citrobacter	2(2.32%)
Sterilization after Norfloxacin	83/86(96.51%)

REFERENCE

1- Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 2002; 35:140-8. | 2- Lahnborg G, Friman L, Berghem L. Reticuloendothelial function in patients with alcoholic liver cirrhosis. Scand J Gastroenterol 1981; 16: 481- 9. | 3- Gustot T, Durand F, Lebrec D, Vincent IL, Moreau R. Severe sepsis in cirrhosis. Hepatology 2009; 50: 2022-2033. | 4- Navasa M, Fernandez J, Rodes J. Bacterial infections in liver disease. Semin Liver Dis 1997; 17: 323-33. | 5-Rosa H, Silverio AO, Pireni RF. Bcterial infections in cirrhotic patients and its relationship to alcohol. Am J Gastroenterol 2000; 95:1290- 3. | 6. Burroughs AK, Rosenstein O, et al. Bacteriuria and primary biliary cirrhosis. Gut 1984; 25: 133-7. | 7-Lipsky BA. Urinary tract infections in men: Epidemiology, pathophysiology, diagnosis, and treatment. Ann Intern Med 1989; 110: 138-50. | 8- Clay WR, Strauss E. Prospective study of bacterial infections in patients with liver cirrhosis. J Hepatol 1993; 18: 353-8. | 9-Bellaiche G, Pauls A, Levy M, Tondjmann T, Levy VG. L'infection urinaire asyptomatique est frequente chez le attaint de cirrhose malade hospitalize. Gastroenterol Clin Biol 1994; 18: 69-7. | 10-Bercoff E, Dechelotte P, Weber j, Morcamp P, Denis P, Boureille J. Urinary trct infections in cirrhotic patients, an urodynamic explanation. Lancet 1985;i: 987. | 11-Rabinovitz M, Prieto M, Gavaler JS, Van Theil DH, Bacteriuria in patients with cirrhosis. J Hepatol 1992; 16: 73-6. | 12-Toledo C, Flores C, Saenz M. Infecciones bacterianas en la cirrosis hepatica. Rev Med Chile 1994; 122: 788-94. | 13- Cadranel JF, Denis J, Pauwels A, Barbare JC, Eugene C, diMartino V, et al. Prevalence and risk factors of bacteriuria in cirrhotic patients: a prospective case-control multicenter study in 244 patients J Hepatol 1999; 31: 464-468. | | 14- Dana A. Atlas d' Echographie de la Prostate. Parris: Masson 1992:15-7. | 15-Wyke RJ. Problems of bacterial infection in patients with liver disease. Gut; 1987; 28:623-41. | 16-Wong F, Bernadi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the international ascites club. Gut 2005; 54: 718- 725. | 17- Manifold IH, Trigger DR, Underwood JC. Kupffer-cell depletion in chronic liver disease: Implications for hepatic carcinogenesis. Lancet II 1983; 431-3. | 18- Rimola A, Soto R, Bory F, Arroyo, Piera C, Rodes J. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. Hepatology 1984;4:53-8. | 19-Holdstock G, Leslie B, Hill S, Tanner A, Wright R. Monocyte function in cirrhosis. J Clin Pathol 1982; 35: 972-9. | 20- Ronaldo N, Philpott-Howard J, William R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis 1996; 16: 389-402. | 21- Homann C, Vaming K, Hogasen K, Mollnes TE, Graudal N, Thomsen AC, Garred P. Acquired C3 deficiency in patients with alcoholic cirrhosis predisposes to infection and increased mortality. Gut 1979; 40: 433-9. | 22- Yoneyama K, Miyamagishi K, Kiuchi Y, Shibata M, Mitamura K. Risk factors for infections in cirrhotic patients with and without hepatocellular carcinoma. J Gastroenterol 2002, 2002; 37: 1028-1034. | 23- Kuo CH, Changchein CS, Yang CY, Sheen IS, Liaw YF. Bacteriuria in cirrhotic patients with cirrhosis of the liver. Liver 1991; 11: 334-9. | 24- Deschenes M, Villeneuve JP. Risk factors for development of bacterial infections in hospitalized patients with cirrhosis. Am J Gasteroenterol 1999; 94: 2193-7. | 25- Hurlimann J, Thorbecke GJ, Hockwald GM. The liver as the site for C-reactive protein formation Exp Med 1966; 123: 365: 378. | 26- Egenhofier C, Alsdorff K, Kolb-Bachofen V. Membrane-associates C-reactive protein on rat liver macrophages is synthesized within the macrophages, expressed as neo-C- reactive protein and bound through a C-reactive protein-membrane receptor . Hepatology 1993; 18: 1216-1223. | 27- Murphy TM, Baun LL, Bearman KD. Extrahepatic transcription of C-reactive protein. J Exp Med 1991; 173: 495-498. | 28- Dong Q, Wright JR. Expression of C-reactive protein by alveolar macrophages. J Immunol 1996 ; 156: 4815-4820. | 29- Gabay C, Kushner R. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340: 448-378. | 30- Le Moine O, Deviere J, Devaster JM, Crusiaux A, Durand F, Bernuau J, Goldman M, Benhammou JP. Interleukin-6: an early marker of bacterial infection in decompansated cirrhosis. J Hepatol 1994; 20: 819-824. | 31- Papp M, Vitalis Z, Altorjay I, Tornai I, Udvardy M, Harsvaly J, Vida A, et al. Acute phase proteins in the diagnosis in the prediction cirrhosis associated bacterial infections . Liver Int 2011; 32: 603-611. | 32- Park WB, Lee KD, Lee CS, Lee CJ, Kim HB, Lee HS, Oh M, Choe KW. Production of C-reactive protein in Escherechia coli-infected patients with liver dysfunction due to liver cirrhosis. Diagnostic Microbiology and Infectious Disease 2005; 51: 227-230. | 33- Pieri G, Agarwal B, Burroughs AK. C-reactive protein and bacterial infection in cirrhosis. Annals of Gasteroenterology 2014; 27: 1-7.