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Prevalence of Bacterial Infection in Patients with Chronic Hepatitis C Treated and not Treated with Interferon

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TREATMENT with interferon and ribavirin in patients with chronic hepatitis C (CHC) is the most common therapy although it is accompanied by multiple side effects. Bacterial infection represents the most common side effect. The present study aims to analyze relation between bacterial infection in patients with CHC, interferon treatment and virulence factors of isolated bacteria. Out of 212 immunocompromised patients with hepatitis C hospitalized were studied for bacterial infection, the median age of patients was 50 years (range 23-83 y) of which 132 male (62.3%) and 80 females (37.7%). 149 patients have bacterial infection while 63 patients are negative for bacterial infection. The collected data obtained from patients showed that 92 patients (43.5 %) not treated with interferon and 120 (56.6%) treated with different doses of the interferon and ribavirin,. Our results showed that the bacterial infection represents 90.8 % of patients who were treated with interferon while patients who were not treated with the combined therapy showed signs of infections of 43.5 %. *E. coli* being the most frequent pathogen (25%) followed by *Acinetobacter baumannii* (13.8 %). The strains were confirmed by Biolog Microlog 34.20 system. The development of bacterial infection in patients treated with interferon associated with hematological complications as anemia (85.4 %), neutropenia (94.5 %) and thrombocytopenia (100 %). Patients with CHC undergoing treatment with interferon and ribavirin have increased risk of develping bacterial infection as a result of bone marrow suppression.

Keywords: HCV, Interferon treatment, Bacterial infection, Hematological complications.

Hepatitis C virus is a major cause of chronic liver disease, infecting 200 Million individuals worldwide (Mc Hutchison *et al.*, 2004). Egypt has a very high prevalence of HCV rates in several populations reached up to 20% (Mohamed *et al.*, 2005 and Seif El- Nasr *et al.*, 2006), a high morbidity and mortality from chronic liver diseases, cirrhosis and hepatocellular carcinoma, and the highest prevalence of HCV-4 (67 %) with a predominance of subtype 4a (55 %) (Elkady *et al.*, 2009 and Khattab *et al.*, 2011).

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Treatment with interferon and ribavirin in patients with chronic CHC represent current standard therapy, although it is accompanied by multiple side effects (Marincu *et al.,* 2010). Leads to long-term resolution of infection in 45%–80% of individuals, depending on viral genotype (Fried, 2002*).* The mechanism of action is not completely understood, but both drugs have a wide-range effects on the immune system (Barnes *et al.,* 2004) The most common side effects of interferon and ribavirin are the hematological and immunological ones, as the most common side effect of interferon therapy is bone marrow suppression that results in a decrease of the leukocyte count(Dieterich and Spivak, 2002). Bacterial infection is a frequent and severe complication of cirrhosis that may be present on admission or developed during hospitalization in 30–60% of hospitalized cirrhotic patients (Borzio *et al.,* 2001). The most frequent infective complications include spontaneous bacterial peritonitis, urinary tract infections, respiratory infections, and bacteraemia, mostly due to the concomitant presence of various facilitating mechanisms such as immunological abnormalities as neutrophil dysfunction and reduction in serum bactericidal account for the increased susceptibility of chronic liver diseases patients for bacterial seeding (Runyon, 2004). Also, changes in the reticulo- endothelial system decreases the opsonic activity of the ascetic fluid, and iatrogenic factors. In fact, up to 25% of death cases in cirrhotic patients are believed to be related to bacterial infections (Yang and Lin, 2005).

Recent studies reported that multi drug resistant *Enterobacteriaceae* and non – fermentable bacilli *e.g. Pseudomonas aeruginosa* (pathogens resistant to the main antibiotics, including b-lactams) are the most common infection in patients with cirrhosis showing high prevalence in different geographic areas (Fernandez *et al.,* 2012 and Fernandez and Arroyo, 2013). *Staphylococcus aureus* is increasingly recognized as an important pathogen in cirrhotic patients (Chang *et al.,* 1998). It has been shown that this organism is ranked second in frequency among causative agents of bacteremia in patients who have end-stage liver disease and are awaiting transplantation (Mccashland *et al.,* 1994 and Singh *et al.,* 1997). Some studies have described the distribution of the most frequent types of infection, but few studies have tried to assess whether the frequency of infection is related to interferon treatment.

Materials and Methods

Clinical examination and Laboratory data

Two hundred and twelve hospitalized patients were included in this study suffering from HCV within cirrhosis (stage Ⅱ) at Ain Shams hospitals, Cairo, Egypt in the period from January 2012 till November 2012, 132 males and 80 females their ages ranged from 23 years to 83 years. The data were extracted from medical records (blood counts, alanine aminotransferase, aspartate aminotransferase, unconjugated bilirubin, conjugated bilirubin, total bilirubin, gamma-glutamyl transpeptidase, alkaline phosphatase and antibodies against the hepatitis C virus (anti-HCV), HCV RNA PCR & Interferon doses).

Sampling and isolation

A total number of two hundred and twelve (212) samples were collected according to (Cheesbrough, 2006) from different sites whenever signs of infections become apparent and transported to laboratory immediately. The samples are sputum , pus , urine , ascitic fluids , bile and blood samples . The strains had been isolated on different media as Nutrient agar, MacConkey agar, Mannitol salt agar and blood culture bottles (Bactec 9240).

Identification of isolated bacteria

Identification at least to genus level by MicroScan® microbiology, cultural characteristics , biochemical activities and API 20E system (bioMe´rieux, France) as well as; Confirmation of our presumptive identification by Biolog Microlog 34.20 System.

Antimicrobial susceptibility test

Antimicrobial susceptibility of the isolates was studied by the disk diffusion technique on Muller Hinton agar medium (Jorgensen *et al*., 1999). The interpretive criteria followed the latest National Committee for Clinical Laboratory Standards (NCCLS) recommendations NCCLS (2003).

Phenotypic detection of Virulence factors of isolated bacterial species

Proteolytic activity done by well diffusion method using skimmed- milk agar plates (10%); while sheep blood (5%) agar plates were used to detect hemolysis. The binding activity with Congo red dye indicating the invasion capability using Congo red agar was tested. Lipolytic activity was assessed on tween 80 agar medium and incubated for 3 days.

Statistical analysis

The collected data were tabulated and graphed by Excel program 2007 and analyzed by SPSS statistics (V.20.0, IBM Corp).

Results

Among the patients under study, a total of 132 males (62.3%) and 80 females (37.7%), 149 patients have bacterial infection while 63 patients are negative from total 212 hospitalized patients, 92 patients (43.3 %) did not receive interferon and ribavirin treatment, 120 patients (56.6%) received treatment in different doses of interferon (Table 1). Bacterial infection represents 90.8 % in patients treated with interferon, but infections recorded 43.5 % in those not treated with the combined therapy. The results showed that the prevalence of bacterial infection increase with the increasing in interferon and ribavirin doses as 100 % of patients who received 22 – 32 doses having positive bacterial culture. 52 from 63 patients who are negative for bacterial infection are not treated with interferon, but only 11 patients from 120 patients treated with interferon and ribavirin are not have bacterial infection. That show positive correlation

between interferon treatment and incidence of bacterial infection and high significance (P value < 0.05) (Table 2).

TABLE 1. Frequency of Interferon doses and bacterial infection among the study Population.

Interferon dose intervals	Total	Infected		Non-infected	
		Count	%	Count	%
0	92	40	43.4%	52	56.6%
1-12	44	35	79.5%	9	20.5%
12-22	36	34	94.4%	2	5.6%
22-32	40	40	100%	0	0
Total	212	149	70.3%	63	29.7%

TABLE 2. Prevalence of infection among the study population according to interferon treatment .

Patient	Total	Infected	Non-infected
Treated with interferon	120	109 (90.8%)	11(9.2%)
Not treated with interferon	92	40 (43.5%)	52 (56.5%)

Hematological complications

According to laboratory data of complete blood count (CBC), patients who had bacterial infection (N= 149) suffered from hematological complications as anemia, Thrombocytopenia and Neutropenia. The results of CBC of our patients revealed that interferon and ribavirin combined treatment had suppressive effect on bone marrow and caused reduction in the production of platelets and leukocytes.

Our results showed that the high reducing effect of interferon was on neutrophil production as the incidence of neutropenia in patients who were treated with interferon compared to those who were not treated showed that the high reducing effect on neutrophil production followed by platelets production.

M*anifestation of Bacterial infection*

The most common site of pathogen isolation was urinary tract as all urine samples give positive culture (100 %), followed by ascetic fluid samples as 12/14 of samples are positive upon culturing. Infections of blood, bile, pus and sputum samples represent 75, 60, 57.8 and 55.4 % respectively of the total samples collected from each site (Table 3). Among the bacterial infections, the most common isolated and identified species were *E.coli* (40 isolate) as it represent 25 % of all isolates followed by *Acinetobacter baumanni* (13.8 %), *Pseudomonas*

aeruginosa and *Klebsiella pneumonia* represents (12.6 %) for each one. Other bacterial species were isolated the *Klebsiella terrigina* (10.7%), *Staphylococcus aureus (10.7%), staphylococcus coagulase –ve* (8.2%), *Proteus mirabilis* (3.1%), *Enterobacter aerogens* (2.5%) and *Citrobacter sp.* (0.6%) (Table 4). Confirmation of identification by Biolog Microlog system divided *Klebsiella sp*. to *K. pneumonia* and *K. terrigina*.

TABLE 3. Prevalence of positive bacterial cultures among collected samples from different sites.

Clinical specimens	Total	Positive	% of Positive Samples	Negative	% of Negative samples
Urine	48	48	100	0	0
Blood	24	18	75	6	25
Ascitic fluid	14	12	85.7	2	14.3
Bile	5	3	60	2	40
Pus	38	22	57.8	16	42.1
Sputum	83	46	55.4	37	44.5
Total	212	149	70.3	63	29.7

TABLE 4. Prevalence of Bacterial species in respective to infection sites.

Isolated Species	Clinical Presentation						Total	%
	RI	Bacterimia	SBP	Dis	PTI	Cutaneous		
E.coli	29	1	3	1	2	4	40	25.2
Pseudomonas aeruginosa	5	1	2	1	7	3	20	12.6
Staphylococcus aureus	0	5	1	0	9	2	17	10.7
Staphylococcus coaggulase -ve	3	7	0	0	3	0	13	8.2
Acinetobacter baumannii	3	1	2	1	13	2	22	13.8
Proteus mirabilis	0	0	0	0	0	5	5	3.1
Klebsiella pneumonia	6	0	2	0	12	2	20	12.6
Klebsiella terrigina	2	4	2	0	3	4	17	10.7
Enterobacter aerogens	0	0	0	0	2	3	4	2.5
Citrobacter	1	0	0	0	0	0	1	0.6
Total	49	19	12	3	51	25	159	100

RI = Renal infection, SBP= Spontaneous bacterial peritonitis,
PTI= Pulmonary tract infection , Dis= Disseminated infection

Suscibtibility of identified bacterial species to antibiotics

The antibiotics suscebtibility patterns of isolated bacteria were listed in Table 5. It is important to notice that all isolated bacterial species are Multi- drug resistant (MDR) , especially *Acinetobacter baumannii* which is resistant to all antibiotics followed by *E.coli* and *Pseudomonas aeroginosa*. Impenam is considered the most effective antibiotic to isolated species.

TABLE 5. Antibiotic susceptibility profiles of isolated bacterial species.

Bacterial species	Antibiotics							
	IPM	AMC	AK	P	CAZ	GM	LEV	TZP
E.coli	++	-	-	-	-	++	-	-
Klebsiella spp.	+++	-	+	-	-	++	-	+
Enterobacter aerogens	++	+	+	-	++	-	-	+
Citrobacter sp.	++	+	-	-	-	-	-	+
Pseudomonas aeroginosa	-	-	+	-	-	-	+	-
Acinetobacter baumannii	-	-	-	-	-	-	-	-
Proteus mirabilis	+	++	-	-	-	-	-	+
Staphylococcus spp.	-	-	++	-	-	++	-	+

Impenam (IPM) , Augmentin (AMC) , Amikacin (AK), Penicillin (P), Ceftazidim (CAZ) , Gentamycin (GM) , Levofloxacin (LEV) ,Tazocin (TZP)
(++) = highly sensitive. (+) = sensitive. (-) = resistant

Phenotypic detection of virulence factors

All isolates were subjected to simplified phenotypic tests as described in Table 6. The three pattern of blood heamolysis α, β and γ were detected by the identified species . β heamolysis represents the most common pattern of α-heamolysis. Proteolytic activity of all isolated bacterial species was expressed by mean diameter of clearing zone. All bacterial species were able to hydrolyze protiens (produce proteases enzymes). All isolates have the ability to produce lipase enzyme ecxept *E.coli, Acinetobacter baumannii and Entrobacter aerogens.* The results of congo red binding activity taken after 24 hr of incubation revealed that *Acinetobacter baumannii*, *Klebsiella pneumonia* and *Staphylococcus aureus* have strong binding activity.

TABLE 6. Phenotypic characteristics of bacterial isolates.

Parameter	***E.coli* N= 40**	***Klebsiella spp*.N=37**	***Entrobacter aerogens* N=4**	***Citrobacter sp* N=1**	***Pseudomonas aeroginosa* N=20**	***Acinetobacter baumannii* N=22**	***Proteus mirabilis* N=5**	***Staph. Spp*.N=30**
Heamolysis	β	α	α	B	B	Γ	β	β
Lipase	-	+	-	+	+	-	+	+
Proteolytic	+	+	+	+	+	+	-	+
Catalase	+	+	+	+	+	+	+	+
Congo red	-	+	-	-	-	+	-	+

N= number of isolates.

Discussion

Chronic liver diseases (CLDs) are defined as the continuity of clinical and biochemical evidence of hepatic dysfunction for longer than six months (Suchy, 1996). Egypt has a very high prevalence of HCV as well as high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma (WHO 2013**).** Bacterial infection is a frequent complication in patients with chronic liver diseases mainly during the advanced stages. There is evidence that the main factors that contribute to a predisposition to infection in patients are related to hepatic failure with consequent immunodeficiency (Delvone *et al.*, 2001). 149 out of 212 patients are positive for bacterial infection (70.3%) while 63 are negative of patients (29.7%). The results showed that the prevalence of bacterial infection increases with the increasing of interferon and ribavirin doses (Soza *et al.*, 2002), and they also show relation between bacterial infection, incidence of thrombocytopenia (100%) and anemia (85.8%). Marincu *et al.* (2010) reported that 77.3% of acute bacterial infection occurred during therapy with interferon and ribavirin was associated with neutropenia .In our study, neutropenia represented 94.5 % of patients who were treated with interferon and rabavirin (IR) and they are having bacterial infection. Ferreira *et al.* (2012) and Mattos *et al.* (2003) reported that urinary tract infection represented 31.8% between cirrhotic patients .This was in agreement with our results which showed that urinary tract infection was 32.2% among the study population.

Our data showed that *E. coli* was the predominant pathogen that implicated in incidence of urinary tract infection followed by *Klebsiella sp. (Klebsiella pneumonia and Klebsiella terrigina).* These findings were supported by Fatima *et al.* (2012). Respiratory tract infection was represented by 30.8 % (46 out of 149 cases) among our study population. These finding were closely in agreement with that reported by Fried (2002). On the contrary, Ferreira *et al.* (2012) reported that respiratory tract infection represent 15 % among his study population .Our study and other studies provided evidence that gram negative bacilli and *staphylococci* were the most common bacterial species implicated in respiratory tract infection (Cheruvattath and Balan 2007). Spontaneous bacterial peritonitis (SBP) was a frequent and a serious complication that occurs in 10-30% of patients with cirrhosis and ascites (Garcia-Tsao, 2005 and Navasa *et al.*,1997) which mainly was caused by enteric bacteria particularly *Escherichia coli* (Bert *et al.*, 2005 and Park *et al.*, 2007) while in our study SBP represent only 8 % (12 of 149 cases) of bacterial infections.

Proteus was a common cause of wound infections in West Africa. Orrett (1999) and Resliniski *et al.* (2005) they showed *Proteus* species to be more commonly encountered in urine than in other clinical specimens. In our study *Proteus mirabilis* was the most predominant isolated bacterial species implicated in cutaneous infection, these finding was supported by Mansy (2001) and

Bahashwan and El-shafey (2013) who reported *P. mirabilis* to have been implicated in nosocomial infections of the surgical wounds and lower respiratory tract.

In our study, through identification by (Biolog Microlog 34.20 system) it appeared that *Klebsiella sp*. was divided into *K. pneumonia* and *K. terrigina*. *K. terrigina* is considered a new species for us to be isolated from clinical samples expressing virulence factors and showing pathogenicity closure, to some extent, to that expressed by *K. pneumonia* about of 20 years ago after its first description. The reports on the isolation of *K. terrigena* from human clinical specimens were considered remarkably rare (Podschun *et al.,* 2000).

Staphylococcus aureus was an important pathogen in cirrhotic patients (Chang *et al.,* 1998), most common causative agents of bacteremia in patients who have end-stage of liver disease and are awaiting transplantation (Mccashland *et al.,* 1994 and Singh, 1997). In our results, gram positive cocci (mainly *Staphylococcus aureus*) represented 18.8 % of bacterial infections and is considered the main cause of bacterimia as well as showing high prevalence in respiratory infection. Staphylococcal infection can also occur in other sites as ascetic fluid and cutaneous infection. Nasal carriage of *S. aureus* played an important role in the epidemiology and pathogenesis of infection and may account for the recurrence of infections at multiple sites (Kluytmans *et al.,* 1997 and Voss & Doebbeling 1995). *Acinetobacter baumannii* was the most prevalent pathogen among our isolation sites. It is considered the most prevalent pathogen in sputum samples and implicated in respiratory tract infection. This observation was in agreement with Henwood *et al.* (2002) who found high isolation rate of *Acinetobacter buamanni* from sputum samples that was associated with lower respiratory tract infection. Our results showed that members of *Enterobacteriaceae* have different patterns of susceptibility to different antibiotics. *E.coli* and *Klebsiella sp.* show high degree of sensitivity to group of carbapenems members (Impenam IPM and Meropenem MEM) and high resistance was recorded to Cephalosporins generation 4 (Maxipime FEP) and Cephalosporine generation 3 (Cefotaxime CTX). The highest sensitivity was been showed by *Enterobacter aerogens* to most antibiotics with degree more than 50 %. On the other hand, *Proteus mirabilis* showed high resistance pattern to majority of antibiotics . *Pseudomona aeroginosa* lay between 30% to 70% against to the investigated antibiotics and complete resistance to Augmentin (AMC) and Doxycylin (DO) . These results are in agreement with Fernandez *et al.* (2012)who demonstrated that the data from different geographical areas show an increased prevalence of infections caused by multiresistant bacteria in cirrhosis (pathogens resistant to the main antibiotics, including b-lactams). The most common organisms, *Enterobacteriaceae,* nonfermentable gram negative bacilli (e.g., *Pseudomonas aeruginosa***),** produced spectrum b-lactamase.

Acinetobacter baumannii was considered the most resistant bacterial species in our study whose sensitivity to different antibiotics does not exceeds 23 %, this percentage of sensitivity appears with Ceftazidime, Amikacin and Sulperazon. *Henwood et al.* (2002) in United kingdom demonstrated that *Acinetobacter*

baumannii clinical isolates show less resistance to amikacin than other used antibiotics , but over 75 % of isolates were resistant to Ceftazidime . They also reported that the only established drugs active against 90 % of isolates are Carbapenems. In our study, *Acinetobacter baummanni* isolates showed high sensitivity to combination of two antibiotics not to Carbapenems only. On the other hand a recent study done by Fouad *et al.* (2013) in Egypt who demonstrated that 74% of *Acinetobacter baummanni* isolated from different hospitals were resistant to Carbapenems. *Staphylococcus aureus* isolates were sensitive to Vancomycin followed by Tiecoplanin and showed low sensitivity to Penicillin and Tetracyclin. These results were in agreement with that reported by Trkyilmaz & Eskuuzmurler (2006), they found all isolated *Staphylococcus aureus* were sensitive to Vancomycin and have 49 % resistance to Penicillin. We found that all isolates studied of bacterial species showed positive proteolytic activity with different diameters of the clearing zones. *Staphylococcus coagulase -ve* and *E.coli* have the highest proteolytic activity as Castro *et al.* (2003) stated that protease production was prevalent in clinical isolates than environmental since protease is important to colonization in host cell. They stated that protease is a major virulence enzyme in the isolates. Our results of Congo red test showed that all isolated bacterial spp as (*E.coli, Pseudomonas aeroginosa, Acinetobacter baumanii, Klebsiella spp. Staphylococcus spp.* and *Enterobacter aerogens*) were both able slim production and invasion, while *Proteus mirabilis* and *Citrobacter spp* were lost this ability. The high potency of slim production appeared by *Acinetobacter baumanni* (77%) followed by *Staphylococcus coagulase -ve* isolates (76%) in agreement with Cevahir *et al.* (2008) who found that most isolates had the ability for biofilm production and considered that to be one of the reasons for the multi-drug resistance showed by *A.baumannii*. Trkyilmaz and Eskuuzmurler (2006) reported that slim production detected by Congo red agar represented 77% between *Staphylococcus aureus* isolates**.** It was noticed that all abcterial species were multi drug resistant (MDR). Most of our bacterial species were resistant to three antibiotics or more. This is in accordance with Mulla and Jethwani (2012*)* who were recorded that percentage of resistance was 100% in *Acinetobacter baumannii* and 37.5% in *Enterobacter aerogens* **.** The current results of phenotypic virulence factors indicated that there is a relation between biofilm formation and the resistance to antibiotics. *Acinetobacter baumannii* represented the most resistant species to antibiotics and had the highest ability for slim production.

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تواجد الالتهاب البكتيرى فى مرضى الالتهاب الكبدى الوبائى المزمن سى المعالجين والغير معالجين بالإنترفيرون

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يُعد العلاج بالانترفيرون وريبا فيرين فى المرض الذين يعانون من التهاب الكبد المزمن سى من أوسع طرق العلاج انتشاراً، على الرغم من ارتباطهم بالعديد من الآثار الجانبية.

وقد وجُد أن العدوى البكترية تمثل الجانب الأكبر والأكثر شيوعاً فى الآثار الجانبية وتهدف هذه الدراسة إلى تحليل العلاقة بين العدوى البكترية فى مرض الإلتهاب الكبدى سى والعلاج بالإنترفيرون وكذلك تحديد العوامل الممرضة فى البكتريا المعزولة من هؤلاء المرضى. لقد تمت الدراسة على ٢١٢ حالة من مرض الإلتهاب الكبدى سى ذوى نقص فى المناعة والمقيمون بالمستشفى لتحديد مدى إصاباتهم بإلتهابات بكتيرية وكان متوسط عمر المرضى ٥٠ عاماً (يتراوح عمرهم ما بين ٢٣ -٨٣ سنة) منها ١٣٢ من الذكور بنسبة ٦٢,٣) و ٨٠ من الإناث بنسبة (٣٧,٧٪) تم جمع العينات السريرية من المرضى وزرعها على البيئة الخاصة بنمو البكتريا، وأظهرت النتائج التى تم جمعها أن ٩٢ مريضاً (٤٣,٥٪) لم يتم التعامل معهم بمضاد الفيروسات، و١٢٠ مريضاً (٥٦,٦٪) تم التعامل معهم بجرعات مختلفة من العلاج بالريبافيرين والإنترفيرون وأن ١٤٩ من المرضى وجد لديهم عدوى بكترية فى حين ٦٣ مريضاً سلبياً للعدوى البكترية كما أظهرت النتائج أن العدوى البكترية تمثل ٩٠,٨٪ فى المرض الذين عولجوا بالانترفيرون والريبا فيرين، ٤٣,٥٪ فى تلك المرضى الذين لم يعالجوا بالانترفيرون والريبا فيرين، ولقد وجد أن الايشيريشيا كولاى هى الأكثر شيوعاً فى العدوى البكتيرية حيث تمثل ٢٥٪ ، يليها الاسنيتوباكتر بامانبى بنسبة ١٣,٨٪ وتم تأكيد النتائج بإستخدام Bioiog Mic Rolog 34. 20 . وقد ظهرت أعراض ومضاعفات مصاحبة للعدوى البكتيرية مثل فقر الدم بنسبة ٨٥,٤٪، قلة كرات الدم البيضاء بنسبة ٩٤,٥٪ وقلة الصفائح الدموية بنسبة ١٠٠٪ . ولقد اتضح أن المرضى الذين يعانون بالالتهاب الكبدى المزمن سى ويتم علاجهم بالانترفيرون والريبا فيرين هم الأكثر عرضه للإصابة بالالتهابات البكيترية وذلك نتجية كحدوث تثبيط بالنخاع العظمى الناتج من العلاج بمضادات الفيروسية.