

ABSTRACT:

Key words: Acute hepatitis B, extrahepatic abnormalities, anemia, thrombocytopenia, leukopenia, neutropenia, leucocytosis, neutrophilia, macrocytosis, microcytosis, lymphocytosis, pancytopenia, hepatocellular

Deleted: in routine diagnosis investigations [2]

Hepatitis is a term used to describe inflammation of one of the vital organs, the liver, which performs many critical functions pivotal to metabolism throughout the body in addition to synthesis of erythropoietin, thrombopoietin, plasma proteins and clotting factors.

Deleted: an

Deleted: that affect

Deleted:

Liver disease is associated with a wide range of haematological alterations. Anemia arises through multiple mechanisms, where haem metabolism is disturbed, and liver disease causes alterations in red cell lipid metabolism. Defects in platelet number and function arise due to the effects of liver disease. (1)

Deleted: of

There are different causes of hepatitis some of which are infectious while others are not. The infectious agents include virus, bacteria, fungi, and parasite. However, the foremost primary hepatic infections are the viral hepatitis. (2) Viruses (A, B, C, D, E, and G)

are common causes of hepatitis, they affect many millions of people throughout the world with considerable morbidity and mortality.(3) The symptoms of hepatitis A usually appear suddenly, but are not followed by the chronic (long-lasting) problems that hepatitis B and C

Deleted: is

Deleted: H

Deleted: symptoms

viruses can cause.(4) although HCV is the most common cause of cirrhosis and is responsible for >50% of liver transplants performed currently (3, 5, 6), Studies of hepatitis C virus

showed a low seroprevalence of 2.2%–4.8%. Hepatitis B virus is the commonest cause of chronic liver disease and hepatocellular carcinoma and is the second commonest cause of acute liver failure in the Sudan.(7) Sudan is classified among countries with a high hepatitis B

Deleted: and

Deleted: was

Deleted: was

surface antigen (HBsAg) endemicity of more than 8%.(8) Primarily we have to distinguish between acute and chronic hepatitis, hepatitis is acute when it lasts less than six months

Deleted: So this article was focused on hepatitis B, particularly acute hepatitis B and its haematological complications.

and chronic when it persists longer with symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease. Acute hepatitis can be divided into four phases: (A) an incubation period, (B) a symptomatic pre-icteric phase (C) a symptomatic icteric phase (with jaundice and sclera icterus) and (D) convalescence. It heals on its own or can progress

Deleted: healing

to chronic hepatitis. (2) Hepatitis B is mostly spread through blood and blood products (9, 10) and when hepatocytes are damaged by virus, a healthy liver cells begin to compensate and with fewer healthy cells, symptoms begin to appear. The most common symptoms include loss of Appetite, Nausea, Vomiting, Fever, Weakness, and Tiredness. These unspecific symptoms may mimic other infections that are common in the, sub Saharan Africa like malaria and typhoid fever. Moreover, it has been shown that, in cases with viral hepatitis, bone marrow hypoplasia and pancytopenia are frequently encountered in the setting of acute hepatitis B infection, where they were attributed to immunological causes.(11) For the previous causes we wanted to determine the rates of hematological abnormalities (leukopenia, leukocytosis, neutropenia, anemia, thrombocytopenia, and pancytopenia) in cases diagnosed as acute hepatitis B. This will not only help in diagnosis of these patients, further more it can assist in there follow-up and treatment. So this article was focused on hepatitis B, particularly acute hepatitis B and its haematological complications.

Patient and method

The current study is, a descriptive cross-sectional study. The limitation of this study was one month, During the period of 15th of January up to 16th of February 2016, Forty nine patients with clinical and laboratory evidence of acute hepatitis B viral infection seen at the medical out-patient hepatology clinics of Ibensina, Dr Fatima Farah private clinic and military hospital, were recruited into the study. The diagnosis of acute hepatitis B was made by measuring elevated liver function tests (including elevated transaminases), HBsAg and HBeAg positivity determined by Enzyme-Linked Immuno Sorbent Assay (ELISA). Cases with hepatitis B positivity (>6 months) were excluded from the study as well as patients with IFN-based treatment, renal disease, other liver disease.

Deleted: including

Deleted: spreads

Deleted: in

Deleted: More ever

Deleted: was

Deleted: had developed

Deleted: It was

Deleted: during

Deleted: Diagnosis

Deleted: done

Deleted: ...etc

Acute hepatitis is defined as hepatitis lasting less than six months and while it is considered to be chronic when it persists longer with symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease.

Anemia is defined as values of hemoglobin, hematocrit or red cell counts that are less than two standard deviation of the norm.

Pancytopenia is defined as a decrease in at least two out of three blood lineages.

On the day of clinical attendance, 2ml of venous blood was collected from each patient into a bottle containing potassium Ethylene Diamine Tetra Acetate [K2-EDTA]. The blood samples were then mixed with their anticoagulant for immediate analysis.

Complete blood analyzer (Sysmex) in addition to thin blood film were used to determine the red cell count, packed cell volume (PCV), mean cell hemoglobin (MCH), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), white blood cells (WBCs) counts, differentials of WBC and absolute platelet count. Such parameters are not routinely checked in the setting of acute hepatitis B in the country.

Ethical Approval

Ethical approval was obtained from Alneelain University ethical committee. Each patient signed an informed written ethical consent. Statistical analysis was done using SPSS for proportions, frequency, means and standard deviations. Statistical significance was specified at ($P>0.05$).

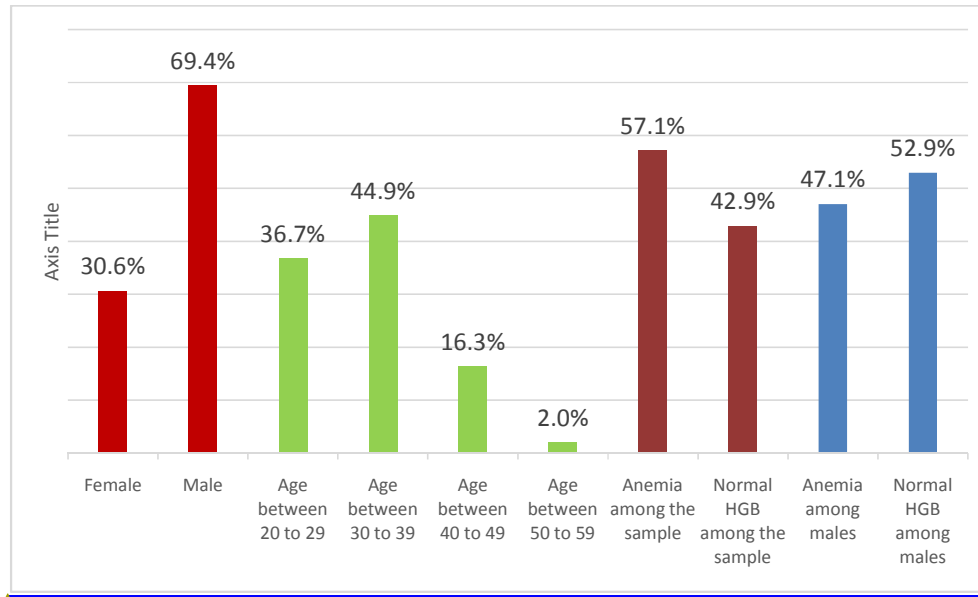
Deleted: instrument

Deleted: ¶

Formatted: Underline

RESULTS:

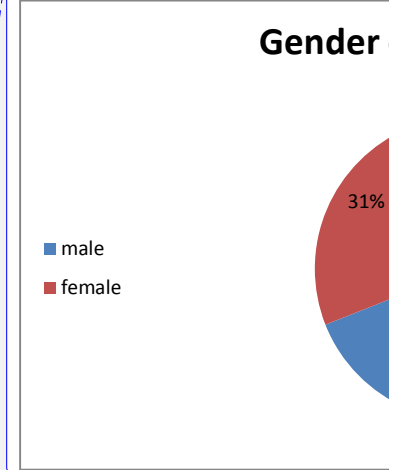
figure 1 : MAIN FINDING OF THE STUDY 1



Formatted: Justified, Keep with next

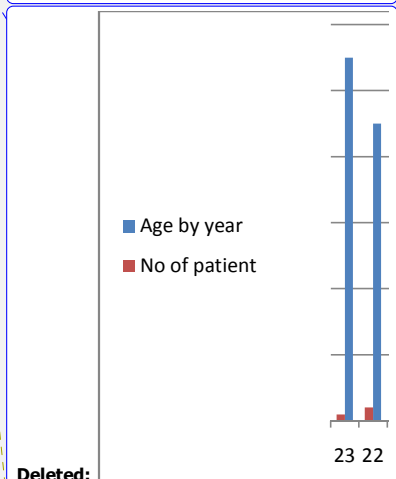
Formatted: Font: 14 pt, Font color: Auto

Deleted: FIGURE 1:PERCENTAGE OF MALE AND FEMALE POPULATION



Formatted: Font: 14 pt, Font color: Auto

FIGURE 2: PATIENS NO IN RELATION TO AGE Deleted AGE



Deleted:

Formatted: Font: 14 pt, Font color: Auto

Deleted: (Figure 2).

Deleted: (Figures3&4).

Deleted: in

Our patient's population consisted of 49 patients, 34 male (69.4%), 15 female (31.6%) (Figure1), age of patients ranged between 22-55 with mean age 38.5 years old. Anemia was detected in (12 female patients ,80%) (HBG<11.5g/dl) and (16 male, 47.06%) of male) (HBG<13.5g/dl). MCV was normal in(37 patients ,75.51%), Microcytosis (MCV<80 fl) in(11 patients ,22.45%) and Macrocytosis (MCV>95 fl) in (one patient, 2.04%). WBC counts were detected to be leucopenia (<4.000/mm3) in(6 patients ,12.24%), normal (4.000-11.000/mm3) in (39 patients ,79.59%) and leucocytosis (>11.000/mm3) in (4 patients ,8.16%) of all the cases). The differential WBC showed Neutropenia (Neutrophils < 40%) was detected in (9 cases ,18.37%) , Neutrophilia (Neutrophils >70%) in (5 patients ,10.20%),

lymphocytosis in (20 patients, 40.72%). Table 1 shows haematological parameters comparing between male and female gender. Mean WBCs count were $7.13 \pm 3.35 \times 10^3/\text{mm}^3$ and $6.55 \pm 2.53 \times 10^3/\text{mm}^3$ for female and male respectively with no statistically significant ($P > 0.05$). Mean RBCs count were $4.23 \pm .78 \times 10^3/\text{mm}^3$ and $4.93 \pm .87 \times 10^3/\text{mm}^3$ for female and male respectively with significant P value=.010. HBG was significantly lower among females(mean 10.45 $\pm$ 1.28 g/l) compared to males(mean 13.57 $\pm$ 2.21g/l) with a significant P value =.000.Similarly, haematocrit was also lower among females(mean 34.62 $\pm$ 4.4%) when compared to males(mean 39.87 $\pm$ 7.72%)with P value 0.018.The duration of disease was divided in to twocategories, early (from first month up to third month of infection) and late (from forth month up to sixth month of infection), the higher frequency of patients' number was obtained in the second month (34.69%) but none the less the difference was not significant in terms of overall duration (P -value=.023)

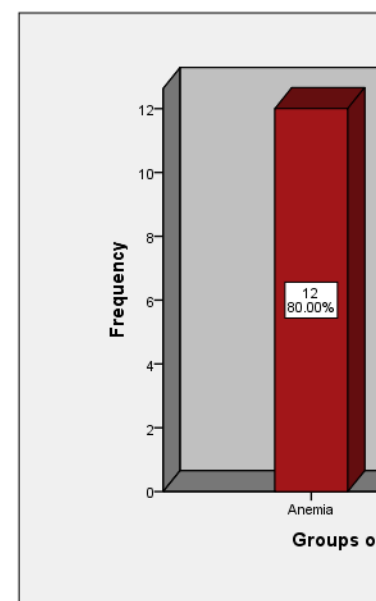
Thrombocytopenia was detected in(5 patients ,10.20%) of all cases, and no case of pancytopenia was determined in our study.

TABLE 1: Difference between mean haemtological parameters in male and female groups

	Gender	Mean	Std. Deviation	P-value
Age	Female	31.67	4.81	.539
	Male	33.03	7.88	
WBCs	Female	7.13	3.35	.502
	Male	6.55	2.53	
RBC	Female	4.23	.78	.010
	Male	4.93	.87	
HBG	Female	10.45	1.28	.000
	Male	13.57	2.21	
HCT	Female	34.62	4.40	.018
	Male	39.87	7.72	

Deleted: HBG was decreased significantly in female cases (mean 10.45 $\pm$ 1.28 g/l) compared to male HBG (mean 13.57 $\pm$ 2.21 g/l) with significant P value =.000. Haematocrit also decreased in female (mean 34.62 $\pm$ 4.4%) when compared to male group (mean 39.87 $\pm$ 7.72%) with P value 0.018. Duration of disease divided in to tow categories, early (from first month up to third month of infection) and late (from forth month up to sixth month of infection), the higher frequency of patient number obtained in second month (34.69%) but no significant value in duration overall (P -value=.023) (Figure5)

FIGURE 3: GROUP OF ANAEMIA AMONG :Deleted FEMALE CASES WITH ACUTE HEPATITIS B



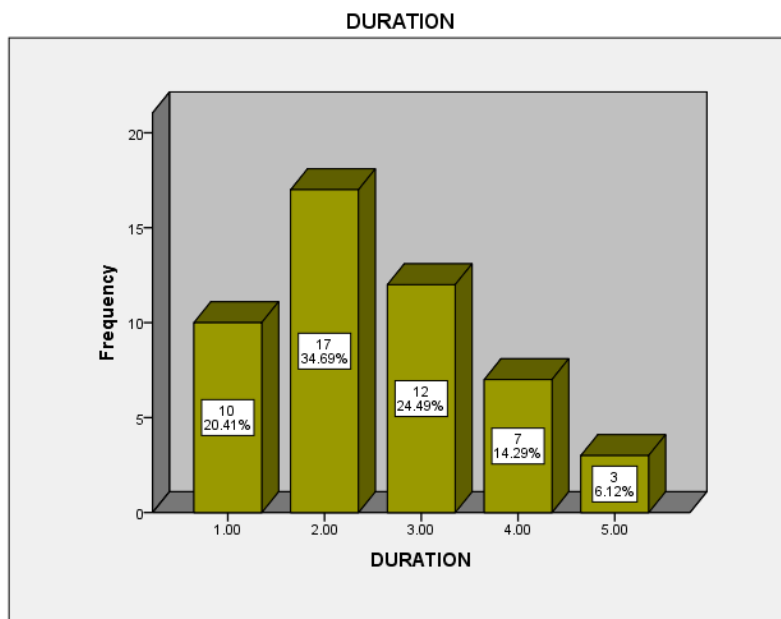
Formatted: Font: 12 pt, Not Bold, Font color: Auto

FIGURE 4:GROUP OF ANAEMIA AMONG :Deleted MALE CASES WITH ACUTE HEP(... [3]

Formatted: Font: 12 pt, Not Bold, Font color: Auto

MCV	Female	83.69	12.13	.965
	Male	83.54	5.91	
MCH	Female	26.46	6.43	.368
	Male	28.07	3.14	
MCHC	Female	30.89	3.79	.009
	Male	33.62	2.94	
PLT	Female	215.87	91.27	.300
	Male	241.79	74.49	
LYM	Female	14.43	14.43	.478
	Male	38.41	14.38	
EOS	Female	3.17	2.58	.833
	Male	3.04	1.70	
MONO	Female	3.73	2.49	.889
	Male	3.83	2.18	
NEUTRO	Female	51.44	13.94	.633

FIGURE 5: RELATION BETWEEN FREQUENCY OF CASES AND DURATION OF DISEASE IN MONTH



DISCUSSION

Liver has many critical functions that affect general body metabolism, it forms and stores many of the elements and proteins needed in blood production, and therefore liver disease is associated with a broad spectrum of haematological abnormalities.

Deleted: throughout the body

Deleted: necessary

This study aims to assess the haematological alterations accompanying acute hepatitis B viral infection.

Deleted: aimed

Deleted: in

Deleted: viral

In the current study, prominently higher (57.1%) rates of anemia was detected, this percentage is markedly increased when compared with other studies. (11-13) Not

Deleted: our cases

Deleted: no

surprisingly as acute infections, either viral or bacterial, can cause anaemia through different mechanisms, such as mild idiopathic hemolysis and marrow inhibition(14). and more ever the burden of anemia remains highest in sub-Saharan Africa (15) In our cases, anaemia was detected in 80% of female and (47.06%) in male. RBCs count; HBG and HCT were found to be decreased in female patients when compared to male groups with significant P values 0.010, 0.00 and 0.018 respectively. Acute viral infection is not the unique cause of anaemia in our cases; it may also be due to nutritional or infectious reasons, in order to know the real cause further chemical and haematological investigations were needed. In mean corpuscular volume (MCV) Macrocytosis is detected in 2.04% while Microcytosis tended to be 22.45%, although there was no significant value between male and female (P value=.965), a significant haematological alteration in MCV overall (micro and macrocytosis) was detected with P-value =.000. In inflammation interleukin 6 and other cytokines increase hepcidin hormone the major hormonal regulator of iron homeostasis , lead to reduce iron absorption and iron release from macrophages and finally result in iron deficiency anemia(16), this may explain other mechanism causing anemia in our finding above ,since there was microcytosis had been observed. Furthermore dilution anemia is another possible explanation for this observation, as plasma volume is frequently increased in active hepatic disease (17).

Deleted: A

Deleted: some

Among WBCs group, Leucopenia was observed in 12.24% of cases it was relatively high when compared with previous studies (11-13) , while leukocytosis was detected in 8.16% and this percentage can comparable with Chinese study(12),but relatively high when compared with Nigerian one.(13) Leucopenia rather than leukocytosis is a more frequent finding in acute viral hepatitis, though leukocytosis is often associated with fulminant viral hepatitis(18) , in recent years they discovered that HB virus directly invade the marrow interfering with leucopoiesis supports the more frequent finding of leucopaenia rather than leukocytosis(19),and this agrees with our finding in this study. Other alteration in WBCs was detected in neutrophil group, in which neutropenia was observed in 18.37% of cases, it was high percentage compared to that observed elsewhere(13) , neutrophilia also observed with high percent (10.20%). Lymphocytosis is another abnormality of WBCs differential, it is usually observes in viral infection, in our study, it was detected in 40.82% of all cases with P-value =.199. Acute and chronic hepatitis are characterized with marked infiltration of lymphocytes into the liver(20), this will result in liver injury in addition to elevated cytokine levels such as interleukin 6 (IL6) from such a response.

Deleted: 16

Deleted: 17

Deleted: 18

Deleted: In inflammation interleukin 6 and other cytokines increase hepcidin hormone the major hormonal regulator of iron homeostasis , lead to reduce iron absorption and iron release from macrophages and finally result in iron deficiency anemia(19), this may explain other mechanism causing anemia in our finding above ,since there was microcytosis had been observed. Furthermore dilution anemia is another possible explanation for this observation, as plasma volume is frequently increased in active hepatic disease (20).

Deleted: p

Liver disease is one of major causes of thrombocytopenia. Previous study conducted in London 2013 reported that liver disease is the cause of thrombocytopenia in 58% of outpatients(21).In our study thrombocytopenia was detected in 10.20% of cases, this finding is completely differ from Nigerian study(13), in which no case of thrombocytopenia had been observed, but agrees with other studies (11, 12) as thrombocytopenia had been reported. Agrees with previous studies (11, 13) no case of pancytopenia was detected in our study. One of the limitations of the current study is the small sample size, another limitation is the reliance on the patients recall to the onset of symptoms a thing that might lead recall bias.

Conclusion

✓ In summary, the present study suggested that Sudanese patients have more haematological abnormalities following acute hepatitis B viral infection, Such an observation reflects an important public health problems in our country. Haematology tests should be included in routine diagnostic investigations as well as follow up diagnosis, in order to avoid fatal complications.

Deleted: Hepatitis B virus was the commonest cause of chronic liver disease and hepatocellular carcinoma in Sudan

Deleted: ed

Deleted: which

Deleted: constitute

Deleted: diagnosis

References:

1. [Mehta AB, McIntyre N, editors. Haematological disorders in liver disease. Forum \(Genoa, Italy\); 1997.](#)
2. [Cotran RS, Kumar V, Robbins basic pathology. 7th ed; Saunders; 2004.](#)
3. [Mitruka K. Global Snapshot of Viral Hepatitis Morbidity and Mortality 4th International Conference on Viral Hepatitis March 17, 2014.](#)
4. [American Sexual Health Association <http://www.washasexualhealth.org/>](#)
5. [Strader DB, Seeff LB. Hepatitis C: a brief clinical overview. ILAR Journal. 2001;42\(2\):107-16.](#)
6. [This N. National Institutes of Health consensus development conference statement: management of hepatitis C: 2002—June 10-12, 2002. Management. 2002;2002.](#)
7. [Mudawi H. Epidemiology of viral hepatitis in Sudan. Clin Exp Gastroenterol. 2008;1:9-13.](#)
8. [Immunization WHOEPo. Hepatitis B vaccine: Making global progress: World Health Organization; 1996.](#)
9. [Service UPH. Updated US Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports/Centers for Disease Control. 2001;50\(RR-11\):1.](#)
10. [Fejza H, Telaku S. Prevalence of HBV and HCV among blood donors in Kosovo. Virol J. 2009;6:21.](#)
11. [Akarsu S, Erensoy A, Elkran Ö, Kurt A, Kurt A, Aygün AD. Hematological Abnormalities in Patients With Acute Viral Hepatitis A and B. Journal of Pediatric Infection/Cocuk Enfeksiyon Dergisi. 2008;2\(3.\(/](#)
12. [Lin S, Chu C, Shih L, Liaw Y. \[Hematological abnormalities in acute viral hepatitis and acute hepatitis in HBsAg carrier\]. Changgeng yi xue za zhi/Changgeng ji nian yi yuan= Chang Gung medical journal/Chang Gung Memorial Hospital. 1991;14\(4\):253-8.](#)
13. [Fasola F, Otegbayo J, Abjah U, Ola S. Haematological Parameters in Nigerians with Acute Viral Hepatitis. Nigerian Journal of Gastroenterology and Hepatology. 2009;1\(1\):27-31.](#)
14. [Viana MB. Anemia and infection: a complex relationship. Revista brasileira de hematologia e hemoterapia. 2011;33\(2\):90-2.](#)
15. [Pasricha S-R. Anemia: a comprehensive global estimate. Blood. 2014;123\(5\):611-2](#)
16. [Hoffbrand V, Moss PA. Essential haematology. 6th ed; John Wiley & Sons; 2011](#)
17. [Conrad ME, Schwartz FD, Young AA. Infectious hepatitis—a generalized disease: a study of renal, gastrointestinal and hematologic abnormalities .The American journal of medicine. 1964;37\(5\):789-801.](#)

18. Pontisso P, Poon M, Tiollais P, Brechot C. Detection of hepatitis B virus DNA in mononuclear blood cells. *Br Med J (Clin Res Ed)*. 1984;288(6430):1563-6.
19. Jones GP, Evans EG. Thrombocytopenic purpura in infective hepatitis. *British medical journal*. 1951;2(4729):451.
20. Dienes HP, Hüttersoth T, Hess G, Meuer SC. Immunoelectron microscopic observations on the inflammatory infiltrates and HLA antigens in hepatitis B and non-A, Non-B. *Hepatology*. 1987;7(6):1317-25.
21. Hancox S, Smith B. Liver disease as a cause of thrombocytopenia. *QJM*. 2013;106(5):425-31.

Deleted: <#> . Mehta AB, McIntyre N, editors. Haematological disorders in liver disease. Forum (Genoa, Italy); 1997. ¶

<#> . Cotran RS, Kumar V. Robbins basic pathology. 7th ed: Saunders; 2004. ¶

<#> . Mitruka K. Global Snapshot of Viral Hepatitis Morbidity and Mortality 4th International Conference on Viral Hepatitis March 17, 2014 ¶

<#> . American Sexual Health Association <http://www.shasexualhealth.org/>. ¶

<#> . Strader DB, Seeff LB. Hepatitis C: a brief clinical overview. *ILAR Journal*. 2001;42(2):107-16. ¶

<#> . This N. National Institutes of Health consensus development conference statement: management of hepatitis C: 2002—June 10-12, 2002. Management. 2002;2002. ¶

<#> . Mudawi H. Epidemiology of viral hepatitis in Sudan. *Clin Exp Gastroenterol*. 2008;1:9-13. ¶

<#> . Immunization WHOEPo. Hepatitis B vaccine: Making global progress: World Health Organization; 1996. ¶

<#> . Service UPH. Updated US Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports/Centers for Disease Control*. 2001;50(RR-11):1. ¶

<#> . Fejza H, Telaku S. Prevalence of HBV and HCV among blood donors in Kosovo. *Virol J*. 2009;6:21. ¶

<#> . Akarsu S, Erensoy A, Elkiran Ö, Kurt A, Kurt A, Aygün AD. Hematological Abnormalities in Patients With Acute Viral Hepatitis A and B. *Journal of Pediatric Infection/Cocuk Enfeksiyon Dergisi*. 2008;2(3). ¶

<#> . Lin S, Chu C, Shih L, Liaw Y. [Hematological abnormalities in acute viral hepatitis and acute hepatitis in HBsAg carrier]. *Changgeng yi xue za zhi/Changgeng ji nian yi yuan= Chang Gung medical journal/Chang Gung Memorial Hospital*. 1991;14(4):253-8. ¶

<#> . Fasola F, Otegbayo J, Abjah U, Ola S. Haematological Parameters in Nigerians with Acute Viral Hepatitis. *Nigerian Journal of Gastroenterology and Hepatology*. 2009;1(1):27-31. ¶

<#> . Viana MB. Anemia and infection: a complex relationship. *Revista brasileira de hematologia e hemoterapia*. 2011;33(2):90-2. ¶

<#> . Pasricha S-R. Anemia: a comprehensive global estimate. *Blood*. 2014;123(5):611-2. ¶

<#> . Pontisso P, Poon M, Tiollais P, Brechot C. Detection of hepatitis B virus DNA in mononuclear blood cells. *Br Med J (Clin Res Ed)*. 1984;288(6430):1563-6. ¶

... [4]

23-Oct-16 2:03:00 PM

disorders in liver disease. Forum

ed: Saunders; 2004.

itis Morbidity and Mortality 4th

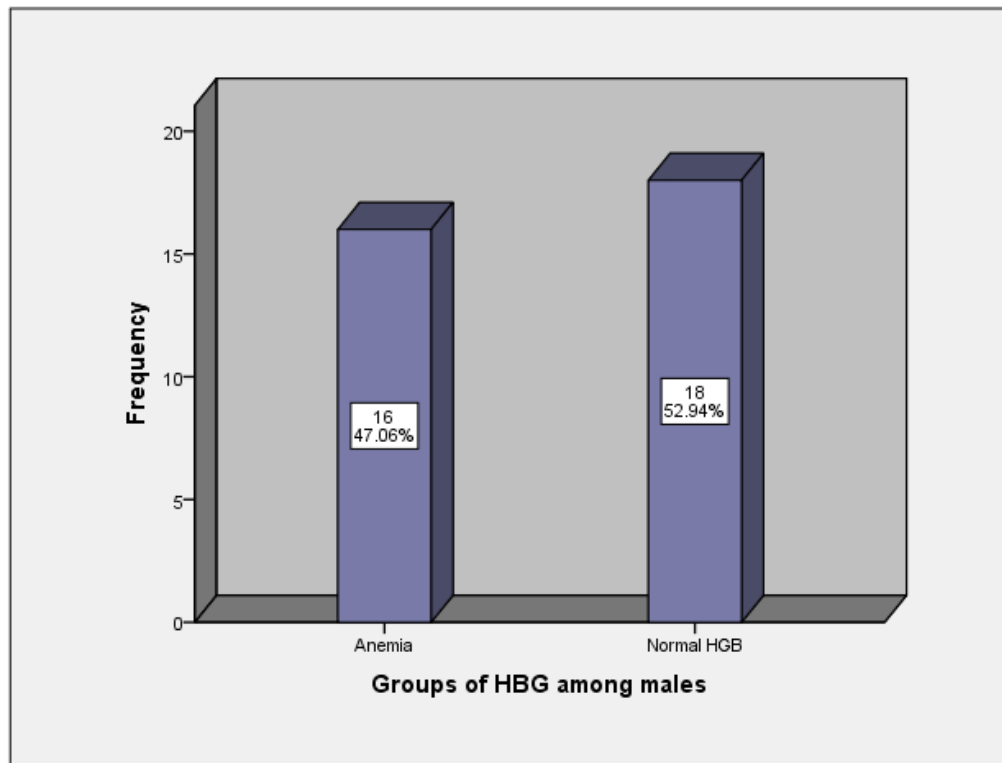
14

[ashasexualhealt](#)

clinical overvi

development coi

management. 2002



antigens in hepatitis B and non-A,
ed: John Wiley & Sons; 2011.
hepatitis—a generalized disease: a
malities .The American journal of
ause of thrombocytopenia. QJM.