

# Hepatitis C and blood transfusion among children attending the Sickle Cell Clinic at Mulago Hospital, Uganda

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## Abstract

**Background:** Hepatitis C virus (HCV) accounts for 90% of post-transfusion hepatitis. In Uganda, there has been limited research of prevalence of HCV among sickle cell anaemia (SS) patients, a group at risk for multiple transfusions.

**Objectives:** To establish prevalence of HCV infection and determine whether blood transfusion increases risk among SS patients.

**Methods** 244 SS patients aged 1-18 years were recruited by consecutive sampling. Socio-demographic, clinical and transfusion history was collected. Clinical examination done and blood tested for HCV by MEIA.

**Results:** 244 children were recruited. Of these, 159 (65%) had a history of blood transfusion. Among the transfused, five patients were HCV positive. Four of these were over 12 years of age. Among patients with no history of transfusion, one patient aged 14 years was HCV positive. Risk of HCV was higher among the transfused OR 2.7(CI 0.31-24). Patients who received more than two units were more likely to be HCV positive ( $p=0.03$ ).

**Conclusions:** HCV prevalence of 2.5% was low but higher than that reported by other investigators in Uganda. Blood transfusion was a major contributing factor in occurrence of HCV. Children who get repeated transfusions should be screened for Hepatitis C and screening of blood for HCV prior to transfusion would help reduce occurrence of the disease.

**Keywords:** Hepatitis C, Blood transfusion, Sickle cell

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## Introduction

HCV is one of the agents transmissible by blood transfusion and is now known to be the major cause of HCV post-transfusion hepatitis<sup>1</sup> accounting for about 90%. Patients at risk of HCV infection includes, transfusion dependent patients<sup>2,3</sup> like patients with sickle cell anaemia (SS), beta Thalassemia major and myelodysplastic syndromes. The prevalence of HCV in the general population and among SS patients in Uganda is not known. Secondary analysis on blood among SS patients at Mulago Hospital found a prevalence of 4% using antibody test<sup>4</sup>. among blood donors<sup>5</sup> the prevalence is 0.5%.

Several studies have shown that blood transfusion increases the risk of acquiring HCV<sup>1, 6</sup>. In Uganda; donor blood is not routinely screened for HCV. It is against this background that this study was designed to establish the prevalence of HCV infection and to establish if blood transfusion

increases the risk of HCV among SS patients. HCV is among major threats to public health because there is no protective immunity against re-infection with HCV<sup>7, 8, 9</sup> and no vaccine has been developed. The World Health Organisation (WHO) estimates that about 170 million (3%) people worldwide are infected with HCV<sup>10,11</sup>, and that three to four million new infections occur each year<sup>11</sup>.

The risk of acquiring HCV from blood transfusion varies between 20-40% in countries where donor blood is not routinely screened for HCV<sup>12</sup>, depending on prevalence of infection, number of transfusions and screening programmes there are in a particular area. Surveys for hepatitis C infection indicate that this infection is related to transfusion practice and geographic endemicity<sup>13</sup>. Studies done on the prevalence of Hepatitis C among SS patients have shown varying results. Some studies indicate direct relationship with blood transfusion among SS patients<sup>14, 15, 16, 17, 18</sup>. On the contrary, some studies have shown no relationship with blood transfusion<sup>19, 20</sup>. There is evidence of consistent increase in HCV prevalence with age of the general population across all regions and all countries<sup>21</sup>.

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## Methods

This was a cross-sectional descriptive study at Mulago Hospital sickle cell clinic which has about 3500 registered patients with SS disease confirmed by Hb electrophoresis. Mulago Hospital is the National Referral and teaching Hospital for Makerere University.

The study population were children attending the SCC aged 1 to 18 years. The sample size was estimated using the formula developed by Kish and Leslie<sup>22</sup>. Standard normal variant corresponding to the 95% confidence interval and prevalence of HCV in children with SCC was estimated at 17% 14 and the required precision of the estimate (0.05).

Children were recruited by consecutive sampling. Informed written consent was sought from caretakers and assent obtained from children 8 years and above. Exclusion Criteria was if caretaker was not able to give all the required information especially with regards to transfusion and age and those with insufficient blood samples. The children were subjected to further evaluation by the principal investigator or research assistant, which included a detailed history concerning socio-demographic and clinical characteristics. Further information was sought from patient's file, discharge forms, and referral note or by using history recall by the caretaker.

A pretested and pre-coded standardized questionnaire was used. Physical examination was done noting a general examination, axillary temperature, weight, height, jaundice, and pallor, cardiovascular, respiratory and abdominal examination for liver and spleen size and tenderness. Weight and height/length were measured. 4mls of venous blood was drawn in an EDTA bottle then centrifuged. The serum was used for HCV antibody test by micro-particle enzyme immunoassay (MEIA) using the Abbott IMX immuno-analyser. The cryotubes were put in order of the numbers in a box rack and they were properly sealed. The samples were then stored at -200 c for 6 months. The stored serum was used for measurement of HCV using MEIA. Internal validity of the study was ensured by pre-testing questionnaires and MEIA was done at Mulago Hospital Clinical chemistry laboratory by a senior laboratory technologist. Another senior laboratory technologist checked the samples/results. Data obtained was entered using EPI-INFO version 6.4 computer software package.

Analysis was done using SPSS Version 11, Bio-medical package statistical software (BMDP)

with assistance of a statistician. Data was summarized using frequency tables, Pie charts and bar charts for categorical data. Means, standard deviation and histograms were used to summarize continuous variables. Confidence interval of 95% was obtained and Chi-squared test and Fishers exact test was used to ascertain statistical significance of association between categorical variables and unpaired t-test was used for significance of association between continuous variables and HCV. Odd's ratio was used to determine the relative risk. P-values of below 0.05 were considered significant.

The study underwent a full review by Makerere University School of Medicine Research Committee, Mulago hospital Ethics committee and Uganda National Council for Science and Technology.

## Results

From July to November 2003, two hundred and seventy one children were screened for recruitment in Mulago hospital Sickle cell clinic. It was not possible to establish whether 13 patients had received blood transfusion, so they were excluded from the study. Of the 258 recruited, 14 had insufficient blood samples for analysis and so were excluded. 244 children were studied of whom 159 had a positive history of blood transfusion and 85 had no transfusion. (figure 1).

### Baseline demographic characteristics

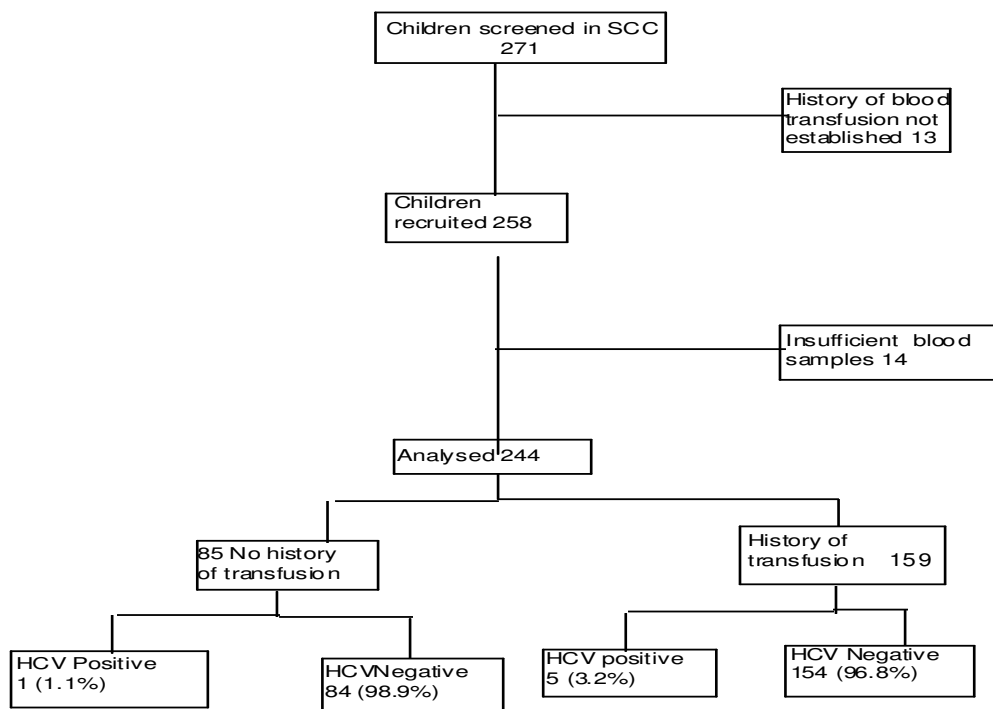
There were 114 (46.7%) males and 79 of these had history of blood transfusion. There were 80 females among the transfused. The difference was not statistically significant ( $p=0.204$ )

The mean age of study patients was 10 years (SD 4.8) (range 1 -18 years). Mean age of transfused children was 10 years (SD $\pm$  4.7) while that of the non-transfused children was 9.6 years (SD 4.9).

Mean age of HCV positive patients was 14 (SD 2.3)  $p=0.033$  years and age range was 10-17 years. Mean age of HCV negative patients was 10 years (SD 4.8) range 1-18 years.

Among those transfused, the average number of units transfused was three and average number of transfusions was two times in a lifetime. The majority of the patients were Baganda 72.8% and the others included Basoga 6.5%, Itesot 3.9%, Acholi and Langi 3.1% each, Samia 2.7%. Other tribes included Gwere and Gishu.

**Figure 1. Study profile for children enrolled in the Hepatitis C and blood transfusion study among SS patients who attended the SCC Mulago Hospital July to November 2003**



### Presenting clinical features of the 244 children

Abdominal pain was found among 31.6%, yellow eyes 55.3% and pain in the limbs 42.6% were more common among the transfused but these were not statistically significant. Forty three percent had a history of fever at recruitment. Most of the patients 185 (71.6%) had mild to moderate pallor, fourteen patients (5.4%) had severe pallor there was however no statistical significance. One hundred and sixty six patients (63.8%) had mild to moderate pallor and five (1.9%) had severe jaundice. About 89 (37%) had hepatomegaly and 12.6% of these were tender. Splenomegaly was present in 57 (21.8%) and of these, 17.5% were tender. These were not related to HCV sero-status.

### Clinical characteristics among the HCV sero-status groups

Among HCV patients, 2(33.3%) were males and 4(66.7%) were females. Considering history and clinical examination, history of transfusion was the only significant difference between HCV positive and HCV negative patients. Those who were transfused were more likely to be HCV positive though not statistically significant ( $p=0.34$ ). Four (66.7%) of the HCV patients had received more than two units of blood. Those who received over 2 units of blood were more likely to be HCV positive and this was statistically significant ( $p= 0.03$ ) (table 1). Those who were in a good general condition were more likely to be HCV negative ( $p=0.02$ ), which was statistically significant. Four (66.7%) of the HCV positive patients were jaundiced compared to 65.5% of the HCV negative patients.

**Table 1: Blood transfusion and HCV sero status**

Factors	HCV +ve n (%)	HCV -ve n (%)	OR	95% CI	P-value
<b>History of blood transfusion</b>					
Yes n=159	5 (3.1)	154 (96.9)	2.73	0.31-23.73	0.34
No n=85	1 (1.2)	84 (98.8)			
<b>Number of units transfused</b>					
<2 units n= 179 (%)	2 (1.1)	177(98.9)	0.17	0.03-0.96	<b>0.03*</b>
>2 units n=65 (%)	4 (6.2)	61 (93.3)			
<b>Mean number of units transfused (SD)</b>	3.0 (2.2)	1.9 (2.4)			0.27

OR = Odds ratio CI = Confidence intervals ¶ Fishers' exact test \* Statistically significant if  $p < 0.05$

n= Number of children SD Standard deviation

### Prevalence of HCV

The prevalence of HCV infection among the 244 children aged 1 to 18 years who attended SCC from July to November 2003 was 2.5% (6/244). The prevalence increased with age and this was statistically significant ( $p=0.03$ ). When the children were categorized in age groups, those above 12 years, 5 (83.3%) were more likely to be HCV positive and this was statistically significant ( $p=0.02$ ). Only one child was below 12 years as shown in figure 2.

The numbers of HCV positive patients was small six. Among patients positive for HCV, five (83.3%) had history of blood transfusion while 1(16.7%) had no history of transfusion. This was clinically important but was not statistically significant ( $p=0.34$ ). However, when categorized according to number of units transfused, those who received over two units of blood were more likely to be HCV positive and this was statistically significant. ( $p=0.03$ ) (table 1).

Prevalence of HCV infection among transfused children and non-transfused children The children with HCV were few however, the

prevalence of HCV was 3.1 %(five) among those transfused and 1.2 %(one) among the non-transfused. The Odds ratio was 2.7 (CI 0.3-23.7) but there was no statistical significance ( $p=0.34$ ). When the patients were categorized into those who received up to 2 units and those who received over 2 units of blood in a lifetime, those who received over two units were more likely to be HCV positive and this was statistically significant ( $p=0.03$ ).

Table 2 shows a summary of the transfusion history and liver function tests of the HCV positive patients. ALT was within the normal range for all the 6 patients. Only 2 patients had slightly elevated AST 56 and 58 U/l. Five (83.3%) patients had elevated GGT.

All patients but one had elevated total bilirubin. Five (83.3%) of the patients had elevated alkaline phosphate and this was not related to transfusion history. (Mean 520, SD 366 U/l, Range 347-1243 U/l).

Figure 2: Age distribution of children by HCV sero-status

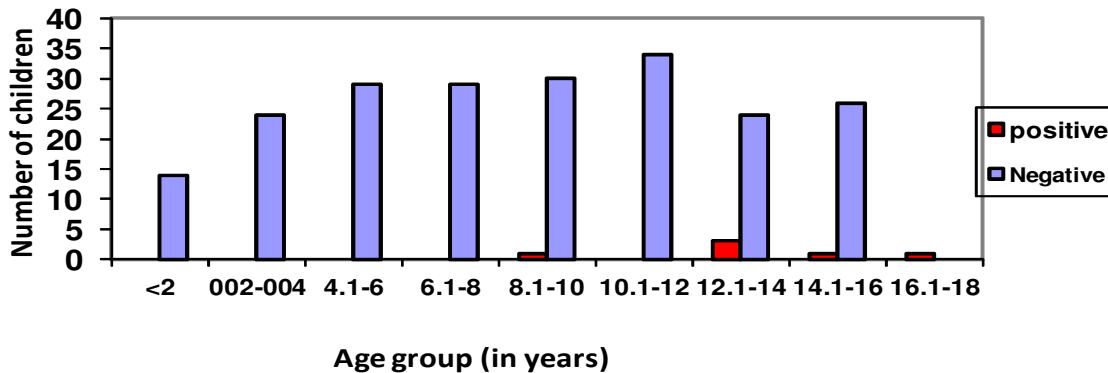


Table 2: Summary of the 6 HCV positive patients

Serial No.	Age	Sex	Transfusion	No. of units	ALT	AST	GGT	T Bil	T prot	ALP
HCS002	16	Female	Yes	1	17	28	84	101	76	347
HCS092	13.3	Female	Yes	4	27	28	64	40.6	72	210
HCS103	14	Male	Yes	3	21	58	117	10.6	106	402
HCS105	16.7	Female	Yes	6	23	49	49	68.4	76	1243
HCS216	14	Female	No	0	13	22	71	29.6	75	478
HCS246	10	Male	Yes	4	26	56	64	47.5	76	441
Mean					21	20	74.8	47.5		520
± SD					5.38	16	23.6	31.6		366

Age in years ± SD Standard deviation

ALT = Alanine aminotransferase (0-40 U/l)

AST = Aspartate aminotransferase (0-50 U/l) GGT = Gamma glutamyl aminotransferase (0-55 U/l)

Tbil = Total bilirubin (0-20 mmol/l) Tprot Total protein (76 g/l) ALP Alkaline phosphatase (89-279 U/l)

## Discussion

### Prevalence of HCV

The prevalence of HCV among SS patients was 2.5%, which is higher than the 0.5% reported by Wolfgang<sup>5</sup> among blood donors in Uganda and it is lower than that of 4% using antibody test (and 0.4 using PCR) that was reported by Biggar<sup>4</sup> following secondary analysis of blood among SS patients. However, the 2.5% is within the estimated prevalence range<sup>6</sup> of 0.0-14.2 but lower than the prevalence reported from other African studies<sup>14,15,16</sup>. For example the prevalence among SS patients was, 31% in Cameroon<sup>15</sup>, 20% in Nigeria<sup>16</sup> and 17% in Benin<sup>14</sup>. The low prevalence (0.5%) among blood donors could be another possible explanation for the low prevalence of HCV in the current study. A similar situation has been observed in Cameroon<sup>15,21</sup>. The low prevalence in this study could also be due to the fact that we used a method with a high specificity (99.9%)<sup>23</sup>. In a similar study in Nigeria, Adewuyi<sup>19</sup> using a less specific method (first generation ELISA) found a prevalence of 5%. The prevalence of 2.5% among sicklers in this study is 5 times higher than among blood donors and this was not unexpected. This is similar to findings of a study in Jamaica that found prevalence, which was 7 times higher than among blood donors<sup>18</sup>. This could be due to the repeated exposure to blood that has not been screened for HCV. The low prevalence of 2.5% could also be due to low risk of mother to child transmission. In Uganda, the risk of mother to child transmission is negligible (0%) using confirmatory assays<sup>24</sup>. Secondly, the study patients were less than 18 years yet other studies<sup>15</sup> have shown that prevalence of HCV increases with age.<sup>21</sup>

### Prevalence of HCV in relation to age and blood transfusion

In this study, the prevalence of HCV increased with age this is possibly because of increasing number of transfusions. This is consistent with studies from other African countries.<sup>10</sup>

Similarly, in a study in Nigeria, the median age of Western blots positive patients (including sicklers and controls) was 17 years (range 6-44), and only one child under the age of 10 was confirmed anti-HCV positive<sup>16</sup>. In this study, the oldest patient was 18 years. The highest number of transfusions received was 14 units which are both much lower than other studies except for the study in Nigeria and Tanzania which studied children aged 3-21 years and less than five years respectively.<sup>19,20</sup>

### Clinical presentation of the HCV positive patients

None of the clinical features or symptoms was associated with HCV sero-status in keeping with other studies<sup>8,20</sup>. In this study, jaundice, hepatomegaly, abdominal pain and fever were more common among the HCV positive patients though not statistically significant. The jaundice could be due to chronic hemolysis, cholecystitis, cholestasis and cholelithiasis associated with SS disease<sup>9</sup> or due to hepatitis caused by HCV. Hepatomegaly could be due to hepatitis. Abdominal pain could be explained by acute cholecystitis, hepatitis, hepatic sequestration, and cholelithiasis<sup>9</sup>. Epodoi<sup>25</sup> found a prevalence of 41.5 % of gallstones among SS patients attending the SCC in Mulago Hospital.

### Limitations of this study

We relied on the caretaker's history for the number of transfusions and there could have been a recall bias with under reporting. A study among Mulago Hospital SS patients in 2002 with regards to transfusion history using validated chart abstracts and review of the hospital record found a correlation between the caretakers' history and the hospital records<sup>26</sup>.

### Conclusion

The HCV prevalence of 2.5% was low but higher than that reported by other investigators in Uganda. Blood transfusion was a major contributing factor in the occurrence of the disease. Screening of blood for HCV prior to transfusion would help reduce the occurrence of the disease among sickle cell disease patients. The clinical application is that clinicians should ensure that children who get repeated transfusions get screened for Hepatitis C

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