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# Emerging bacterial resistance patterns in febrile neutropenic patients: experience at a tertiary care hospital in Pakistan

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# Etiology of Chronic Liver Disease in Children

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## Abstract

**Objective:** To review the clinical spectrum and etiology of chronic liver disease in children at National Institute of Child Health, Karachi.

**Methods:** Prospective study in children aged 1 to 14 years with suspected chronic liver disease. Complete blood count, LFT's, prothrombin time, serum albumin and ultrasound of abdomen were done in all patients. Liver biopsy was done in majority of the cases. Viral markers included HBsAg, anti HCV and ANA to determine etiology. Those who were negative for hepatitis B, C and autoimmune disease, were subjected to slit lamp examination of eyes and 24 hours urinary copper estimation for Wilson's disease. Alpha-1-antitrypsin levels were done in selected patients.

**Results:** A total of 55 cases were studied. The common presenting features were edema, ascites (44 patients), jaundice (27), variceal bleeding (23) and fever (22). On examination anemia was present in 52 patients, edema in 46, jaundice in 37, splenomegaly in 42 and hepatomegaly in 35 patients. Fortynine patients had hypoalbuminemia (<2.5 gm%), 45 raised ALT (>80 IU/L) and 49 prolonged PT (>4 sec of control). Ultrasonography showed a dilated portal vein in 34 patients and esophageal varices were seen in 46 patients on endoscopy. Thirteen (24%) had chronic hepatitis B, 9(16%) autoimmune disease, 9 (16%) Wilson's disease and all were anti HCV negative. Etiology remained uncertain in 24 (44%) cases.

**Conclusion:** Hepatitis B was the leading cause of chronic liver disease in children followed by Wilson's disease and autoimmune liver disease. None of the patients had hepatitis C in this study (JPMA 54:119;2004).

## Introduction

The common causes for chronic liver disease (CLD) in children are hepatitis B, hepatitis C, hepatitis D, autoimmune hepatitis and metabolic disorders like Wilson's disease and  $\alpha$ -1 antitrypsin deficiency.<sup>1</sup> In majority of the patients the etiology remains uncertain.<sup>1-3</sup> Literature from West suggests that autoimmune hepatitis leads the list of causes while infections are among the lowest; the biggest chunk is however idiopathic.<sup>4,5</sup> Few studies have looked at the etiology of chronic liver disease in children in Pakistan

and one such study has reported hepatitis B as the leading cause.<sup>6</sup> We undertook the present study to further define the etiology of CLD in children.

## Patients and Methods

All children aged 1 year to 14 years who were admitted at National Institute of Child Health Karachi (NICH) between February 1998 to December 1999 with clinical stigmata of chronic liver disease were included in the study. The signs of chronic liver disease included

deranged liver function tests (LFTs) for more than 3 months<sup>7</sup>, enlarged or shrunken liver, splenomegaly, edema, ascites, bleeding from varices and cutaneous features like spider angiomas/palmar erythema. A detailed history and physical examination was done in all the cases and findings recorded on a proforma.

Children below 1 year and over 15 years having chronic liver disease with malignancy, those with hemolytic anemia and recurrent blood transfusions, patients with storage disorders like glycogen and lipid storage disease and those with congenital malformation of biliary tract like congenital biliary atresia or choledochal cyst were excluded.

Investigations included complete blood picture with reticulocyte count, liver function test, prothrombin time, serum albumin, ultrasound abdomen, hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti HCV) and antinuclear antigen (ANA). Slit lamp examination of the eyes for Keyser-Fleischer (K.F.) rings were done in patients negative for HBsAg, anti HCV and ANA. Children with positive K.F. rings, underwent 24 hours urinary copper estimation with and without D-Penicillamine challenge to confirm Wilson's disease. Alpha-1-antitrypsin levels were done in patients in whom no etiology was found. Liver biopsy was done with Menghini's needle or Tru-cut needle in those cases where there was no contraindication and where parental consent was obtained. Severity of chronic liver disease was defined using Child's grading.<sup>3</sup>

## Results

A total of 55 children were included in the study. There were 32 (58%) males and 23 (42%) females, whose ages ranged from 3½ years to 14 years (Mean 8.28 years ± 2.75 SD). The common presenting symptoms were edema and ascites in 44 (80%) patients followed by jaundice in 27 (49%) patients. Bleeding from varices in the form of haematemesis or malena or both was seen in 23 cases (42%) (Table 1).

**Table 1. Clinical presentation.**

Symptoms	Signs		
Edema/ascites	44 (80%)	Anemia	52 (95%)
Jaundice	27 (49%)	Jaundice	37 (67%)
Variceal bleed	23 (42%)	Edema/ascites	46 (84%)
Fever	22 (40%)	Splenomegaly	42 (76%)
		Hepatomegaly	35 (64%)
		Palmar erythema	02 (3.6%)
		Spider haemangioma	02 (3.6%)

On examination anemia was seen in 52 (94%) patients, jaundice in 37 (67%) and edema and ascites in 46

(84%) patients. Splenomegaly was found in 42 (76%), hepatomegaly in 35 (64%). Other signs are shown in Table 1.

Out of 52 patients with anemia 14 (25%) were severely anemic (hemoglobin less than 7 gm%) and 29 (53%) moderately anemic (hemoglobin level between 7-10 gm%). In the remaining children hemoglobin was more than 10 gm%. Serum bilirubin was between 1-3mg% in 33 (60%) patients, >3 mg% in 22 (40%) cases. In majority of the patients bilirubin was conjugated. ALT was raised (>80 i.u/L) in 45 (82%). Hypoalbuminemia (serum albumin < 2.5 gm%) was seen in 49 (90%). Prothrombin time was prolonged (>4 seconds of control) in 49 (90%) patients. (Table 2). According to Child's grade 49 (90%) patients

**Table 2. Laboratory results.**

LABS	
Hemoglobin	< 7 Gm% 14 (25%) > 7 Gm% 41 (75%)
Serum bilirubin	1-3 mg% 33 (60%) > 3 mg% 22 (40%)
SGPT > 80 i.u/L	45 (82%)
Serum albumin < 2.5Gm%	49 (90%)
PT > 4seconds of control	49 (90%)
Portal vein diameter > 1cm	34 (64%)
Endoscopy done in (n=50)	Esophageal varices seen in 46pts (92%)
Liver biopsy done in (n=39)	CAH 32 (82%) Cirrhosis 7 (18%)

CAH = Chronic active hepatitis.

were in grade C, 6 (10%) in grade B and none in grade A.

Ultrasound of the abdomen showed a normal sized liver in 16 (29%) cases, enlarged in 21 (38%) and shrunken in 18 (33%) cases. Portal vein was dilated (more than 1 cms) in 34 (62%) cases. Upper GI Endoscopy was done in 50 (91%) cases, 46 (92%) patients had grade II esophageal varices while 4 (8%) patients had no varices.

Liver biopsy was performed in 39 (71%) patients and in 16 (29%) cases it could not be done due to child's condition or refusal by the parent. In 32 (82%) patients liver biopsy revealed chronic active hepatitis while in 7 (18%) cirrhotic changes. were reported.

HBsAg was positive in 13 (24%) patients and Wilson's disease was the etiology in 9 (16%) patients. A positive ANA indicating autoimmune hepatitis was found in 9 (16%) patients. None of the patients were positive for Alpha-1-antitrypsin deficiency or anti HCV. No etiology could be found in 24 (44%) patients, therefore they were labeled as idiopathic.

**Table 3. Comparison of clinical presentation.**

Symptoms	No. (%)	No. (%)	No. (%)
	Present study	Malik <sup>8</sup>	Mehnaz <sup>9</sup>
	n = 55	n = 30	n = 80
Edema	44 (80%)	9 (30%)	59 (75%)
Abd. Distension	44 (80%)	9 (30%)	59 (75%)
Jaundice	27 (49%)	22 (73%)	40 (50%)
Variceal bleed	23 (42%)	4 (13%)	12 (15%)
Fever	22 (40%)	15 (50%)	53 (67%)
Signs			
Anemia	52 (95%)	17 (56%)	60 (75%)
Jaundice	37 (67%)	22 (73%)	40 (50%)
Edema/ascites	46 (84%)	9 (30%)	50 (62%)
Splenomegaly	42 (76%)	19 (63%)	40 (50%)
Hepatomegaly	35 (64%)	20 (66%)	44 (55%)
Palmar erythema	02 (3.6%)	Not mentioned	2 (2.5%)
Spider haemangioma	02 (3.6%)	Not mentioned	2 (2.5%)

## Discussion

This study shows that chronic liver disease (CLD) is not a major disease in children. Slight male predominance (58%) seen in this study is similar to that reported both locally and internationally.<sup>8-10</sup> A higher mean age of 8.2 years was seen in our study, while it was 4.5 years in another local study<sup>9</sup> and 6.1 years in a study done abroad.<sup>6</sup>

Edema and ascites were the major presenting symptoms in the present study, being 80% as opposed to 30% reported from Lahore<sup>6</sup> and 50% reported in another study from Karachi.<sup>9</sup> (Table 3) This high incidence of edema and ascites in our study indicates fairly advanced disease with decompensation. Incidence of jaundice, bleeding varices, fever, hepatosplenomegaly, spider nevi and palmar erythema in the present study was similar to that reported in other studies from Pakistan<sup>6,9</sup> and India.<sup>10</sup>

Anemia was seen in 94% cases in this study, which is similar to what has been reported earlier.<sup>9</sup> This high incidence of anemia in CLD may be due to a number of factors like, GIT bleed due to varices, sequestration of blood in enlarged spleen, increased red cells vulnerability to osmotic haemolysis, oxidant injury to R.B.C. due to vitamin E and glutathione deficiency. Anemia can also be immunologically mediated due to antibodies, injury to RBC by toxic material like excessive copper and due to nutritional deficiencies like iron, vitamin B12 and folic acid.<sup>11</sup>

In chronic liver disease serum bilirubin, serum albumin and prothrombin time are the markers of

progression of the liver disease. Rising bilirubin and prothrombin time and lowering of albumin are bad prognostic signs. In the present study hyperbilirubinemia (>1mg%) was seen in 75% cases, which is slightly lower than 90% reported in two other local studies.<sup>6,9</sup> Serum albumin was low (<2.5gm%) in 89% cases and, prolonged prothrombin time (>2 times of normal) in 65%. Similar results were reported by others.<sup>6</sup> Transaminase levels (SGPT/ALT) are not a marker for advanced liver disease because they return to baseline once decompensation sets in; they are useful only in assessing the chronic liver disease where they are raised. In the present study ALT was raised (>1½ times of normal) in 82% cases which is higher than 70% and 42% reported in other studies.<sup>6,9</sup>

Ultrasound is a useful imaging technique, which can provide essential information in all forms of chronic liver disease. In our study ultrasonographic hepatomegaly was seen in 31% cases and it was shrunken in 33%, signifying that in CLD one may have an enlarged to a fibrosed liver depending upon severity and chronicity of underlying disorder. Ultrasonographic splenomegaly was seen in 80% cases and portal vein was dilated in 62% cases, denoting portal hypertension.

In the present study endoscopic examination of upper GIT was performed in 50 patients, and it revealed esophageal varices in 46 patients (92%) a sign of portal hypertension. Only 42% cases had history of haematemesis, indicating that patients with CLD have esophageal varices without history of upper GIT bleed. These varices are a potential site of bleeding and an early endoscopic examination can identify these high-risk children who can be controlled by prophylactic β blockers.

Percutaneous liver biopsy is an excellent investigation to evaluate the exact pattern and extent of liver disease. In our series liver biopsy was performed in 71% cases whereas in other studies it was performed in 60% and 45% cases respectively.<sup>6,9</sup> On histology 32 (82%) cases had chronic active hepatitis (CAH) and 7 (18%) had cirrhotic changes; when compared to another local study, CAH was reported in 55.5% and cirrhosis in 39% cases<sup>6</sup> indicating that there were more chronic and cirrhotic cases in the previous study.

In this study HBV infection was the commonest etiologic factor causing CLD in 13 patients (24%), as compared to 18% in a local study from Karachi<sup>9</sup>, 47% from Lahore<sup>6</sup> and 80% from Italy.<sup>8</sup> Vertical or horizontal transmission of the HBsAg is probably the cause of high antigenemia in our study. A high HBsAg carrier rate of 10% in general population<sup>12-14</sup> and 15% HBe antigen positivity in mothers also indicates a high chance of transmission of the disease to the new borns.<sup>5</sup> It is therefore recommended

by WHO that all pregnant females should be screened for HBsAg and HBeAg. The newborns of those found positive for 'e' antigen, should be vaccinated with hepatitis B hyper immunoglobulin 0.50ml within 12 hours of birth along with 1st dose of hepatitis B vaccine at a different sites.<sup>11</sup> The overall incidence of HBV infection can be reduced by vaccination against hepatitis B on mass level, imparting health education, limiting the use of blood transfusion, use of screened blood and blood products and use of disposable syringes. Reuse of needles and syringes should be discouraged at all levels.

In none of our patients hepatitis C was found as causative agent for CLD. Local as well as international literature also has not shown hepatitis C as etiology of CLD in children<sup>6,8,9</sup> reflecting that although hepatitis C is one of the major cause of CLD in adults, its prevalence is not that high in pediatric age group.

In 9 patients (16%) of the present study, the cause of CLD was identified as Wilson's disease. Similar results were reported in another local study.<sup>6</sup> But in an Italian study<sup>8</sup> of 196 patients of CLD was identified as Wilson's disease in only 3 patients (1.53%). The high incidence of Wilson's disease in our study is alarming, as this disorder is not commonly reported in local literature as a cause of CLD and has probably remained under diagnosed. It is recommended that the entity should always be anticipated and evaluated in children with CLD. This not only has the beneficial effect on the patient, but can also identify asymptomatic carriers in family.

Another autosomal recessive disorder that may cause CLD is  $\alpha$ -1-antitrypsin deficiency but it was not found in our study. Bortolotti<sup>8</sup> had reported 1 patient, reflecting that  $\alpha$ -1 antitrypsin deficiency is a rare cause of CLD in children. There is no specific treatment for this disorder except liver transplantation.<sup>15</sup>

In our study autoimmune hepatitis was established as etiology for CLD in 9 patients (16%), whereas in other local study<sup>9</sup> it was seen in one patient only (1.2%) autoimmune hepatitis is a common cause of CLD in the West<sup>16</sup> but in our country this disorder is reported very infrequently, either because this entity is undetermined or serological tests to confirm this disorder are expensive.

Twenty patients (44%) in our study remained idiopathic because we were unable to establish the etiology of CLD as compared to 26.7% in a local and 4.9% in an Italian study.<sup>6,8</sup> This high frequency of idiopathic CLD in our study reflects our financial constraints as well as non-

availability of advanced and specific diagnostic tools to find out other underlying causes of CLD. The frequency of idiopathic CLD also varies in different parts of world. In United Kingdom it is about 5-10%, whereas other areas such as France and urban parts of United States of America where alcoholism is prevalent, the proportion of idiopathic CLD is lower. As specific diagnostic facilities appear, the percentage of idiopathic CLD falls, like advent of HBsAg and anti HCV transferred many previously designated idiopathic CLD to post-hepatitis group.<sup>3</sup> Still there remains significant percentage of patients with CLD as idiopathic and etiological diagnosis in these patients awaits further development of specific diagnostic tools.

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