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Frequency of Acute Hepatitis in Children with Enteric Fever of Age 1 to 10 Years Presenting to Ayub Teaching Hospital Abbottabad

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ABSTRACT

Background: Acute hepatitis in children with enteric fever remains a significant public health concern, with varying prevalence across different populations. The association between demographic factors and the prevalence of acute hepatitis in children with enteric fever has yet to be fully explored. **Objective:** To determine the frequency of acute hepatitis in children with enteric fever of age 1 to 10 years presenting to Ayub Teaching Hospital Abbottabad. **Study Design:** Cross-sectional observational study. **Duration and Place of Study:** The study was conducted from May 2024 to November 2024 at the Department of Pediatrics, Ayub Teaching Hospital, Abbottabad. **Methodology:** A total of 102 children aged 1–10 years, diagnosed with enteric fever (fever ≥101°F for 4 days with positive blood culture for *S. Typhi*), were included. Children with a history of malaria, pneumonia, liver disorders, or immunocompromised states were excluded. Blood samples were analyzed for liver enzyme levels and real-time PCR to confirm viral hepatitis (HBV, HCV, HAV, HEV). **Results:** The mean age of participants was 5.84 ± 2.16 years, with a mean weight of 8.27 ± 3.51 kg. Acute hepatitis was diagnosed in 16 patients (15.7%), with the types being HBV (2%), HCV (5.9%), HAV (4.9%), and HEV (2.9%). Rural residence was associated with a higher prevalence of acute hepatitis (27.5% vs. 8.1% in urban areas, p = 0.012). **Conclusion:** This study highlights acute hepatitis as a major health concern in children, with Hepatitis A as the leading cause. Elevated liver enzymes contribute to acute liver failure. Public health interventions, including improved sanitation and accessible care, are essential to mitigate the disease's impact on children.

INTRODUCTION

Enteric fever due to Salmonella typhi or Salmonella Paratyphi is generally characterized by fever, abdominal pain, diarrhea, or constipation, while in a few cases it may be associated with liver involvement.[1] Hepatitis in such conditions can present with elevated liver enzymes, jaundice, or pain in the right upper quadrant which are indicative of hepatic inflammation.[2] The pathophysiology of liver involvement in enteric fever is unclear but is suspected to be due to direct infection of the hepatocytes by the etiologic bacteria or an immune response to the infection.[3]

The clinical presentation in pediatric patients with enteric fever may range from mild, asymptomatic transaminase elevations to more prominent symptoms such as jaundice, hepatomegaly, and acute liver failure.[4] Laboratory tests are typically associated with elevated transaminases (AST and ALT), alkaline phosphatase, and bilirubin. Coagulopathy and prolonged prothrombin time may be present in severe disease, indicating severe liver dysfunction. The child may present with nonspecific symptoms, so it is important to include acute hepatitis in the differential diagnosis in the treatment of enteric fever.[5]

The etiology of acute hepatitis in the context of enteric fever in children is most likely to be multifactorial with the contribution of both direct bacterial invasion and immune-mediated mechanisms. Salmonella typhi and Salmonella paratyphi have been shown to invade various organs, including the liver, which may be the site of the localized infection or may be responsible for the inflammatory response at a distance.[6] Hepatic damage may also be the result of the dysregulated immune response to the pathogen with the production of excessive cytokine generation and damage to the hepatocytes.[7] Moreover, impairment of the normally effective gut-liver axis in enteric fever, by bacterial endotoxins or intestinal permeability alterations, may be the factor of the worsening of the hepatic damage. Based on the studies, it seems in some children, especially in those with severe enteric fever, the liver becomes a secondary infection center, with the inflammatory cascade being more vigorous resulting in clinically significant hepatitis.[8] The pathophysiology of the

association of enteric fever with hepatitis in children is complex with this interaction between the pathogen and the patient's immune response.[9]

Diagnosis of acute hepatitis in the setting of enteric fever is established by the combination of clinical presentation, lab findings, and radiological examinations.[10] Routine monitoring of liver function tests (LFTs) in the child with enteric fever should be performed in the setting of jaundice or worsening illness.[11] In suspected severe cases of hepatitis, other tests in the form of ultrasound of the liver or liver biopsy in exceptional cases may be required to assess the extent of liver impairment.[12] Blood cultures and stool cultures remain the gold standard for the diagnosis of enteric fever, whereas serologic tests for Salmonella species may be used as confirmatory evidence for the infection.[13] A study by Waris R et al. demonstrated that the frequency of acute hepatitis in children with enteric fever was 21.53%.[14]

Acute hepatitis in pediatric patients with enteric fever remains a matter of concern in the age group of 1-10 years. While it can potentially affect the pediatric patient's health, the relationship between acute hepatitis and enteric fever in this age group remains unclear. Since the incidence of enteric fever in most regions is high, it becomes necessary to investigate the frequency, clinical presentation, and prognosis of acute hepatitis in such pediatric patients. The current study will be able to provide valuable information about the co-existence of the conditions, resulting in easier diagnosis, effective treatment, and satisfactory clinical outcomes for the pediatric patients.

METHODOLOGY

This cross-sectional study was conducted between May and November 2024 at the Department of Pediatrics, Ayub Teaching Hospital, Abbottabad. A sample of 102 children was selected using the WHO sample size calculator, based on a 95% confidence level, an 8% margin of error, and an expected frequency of acute hepatitis of 21.53% in children with enteric fever.[14]

Inclusion criteria consisted of children aged 1 to 10 years, of either gender, who presented with enteric fever, defined as fever ≥101°F for 4 days with a positive blood culture for *S. Typhi*. Exclusion criteria included a history of malaria, pneumonia, inherited liver disorders (such as Wilson's disease or alpha-1 antitrypsin deficiency), or an immunocompromised state (e.g., chemotherapy or HIV/AIDS).

After obtaining ethical approval, informed consent was acquired from the guardians of all participants. Demographic details such as age, gender, weight, duration of fever, socioeconomic status, and family history of HBV/HCV were recorded. A detailed history and comprehensive physical examination were performed on each participant. Blood samples (5 mL) were collected via venipuncture at the back of the hand or heel, following standard procedures. These samples were sent to the hospital laboratory for analysis.

Acute hepatitis was diagnosed in children presenting with elevated ALT levels greater than twice the normal limit of 40 IU/L, along with symptoms including abdominal pain (VAS >3), nausea, and fatigue. The presence of viral hepatitis (HBV, HCV, HEV, or HAV) was confirmed by real-time PCR, where persistent RNA levels above 50 IU/ml for each virus were considered indicative of infection. Specifically, HBV was confirmed by HBV RNA levels >50 IU/ml, HCV by HCV RNA >50 IU/ml, HEV by HEV RNA >50 IU/ml, and HAV by HAV RNA >50 IU/ml.

The data were analyzed using IBM SPSS version 26. Continuous variables such as age, weight, and duration of fever were summarized as mean ± standard deviation or median (IQR) for non-normally distributed data. Categorical variables, including gender, residential status, socioeconomic status, family history of HBV/HCV, and the presence of acute hepatitis, were presented as frequencies and percentages. Stratified analysis was performed for age, gender, weight, residential status, socioeconomic status, and duration of fever. Chi-square or Fisher's exact test was applied for statistical significance, with $p \leq 0.05$ considered significant.

RESULTS

The demographic analysis of patients revealed a mean age of 5.84 years (±2.16), an average weight of 8.27 kg (±3.51), and a duration of fever averaging 7.95 days (±2.36), with a distribution of 55 males (53.9%) and 47 females (46.1%). Residentially, 40 patients (39.2%) resided in rural areas, while 62 (60.8%) were from urban settings. Socioeconomic status was categorized into low (39.2%), middle (39.2%), and high (21.6%) statuses, with a history of HBV/HCV noted in 15 patients (14.7%) (as shown in Table 1).

Table 1

Patient Demographics

Demographics		Mean ± SD / n (%)
Age (years)		5.843±2.16
Weight (kg)		8.274±3.51
Duration of Fever (days)		7.951±2.36
Gender	Male	55 (53.9%)
	Female	47 (46.1%)
Residential Status	Rural	40 (39.2%)
	Urban	62 (60.8%)
Socioeconomic Status	Low	40 (39 %)
	Middle	40 (39.2%)
	High	22 (21.6%)
History of HBV/HCV	Yes	15 (14.7%)
	No	87 (85.3%)

Figure 1

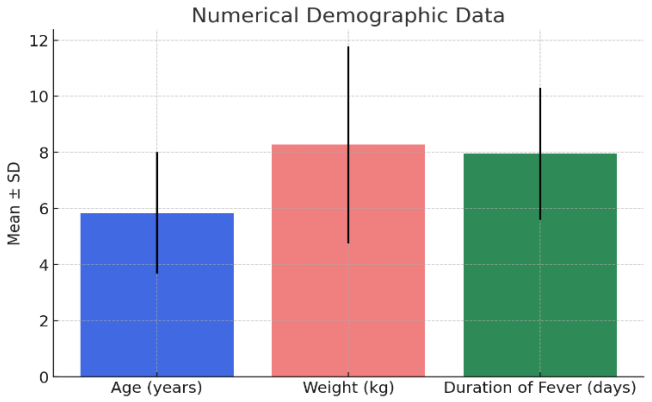
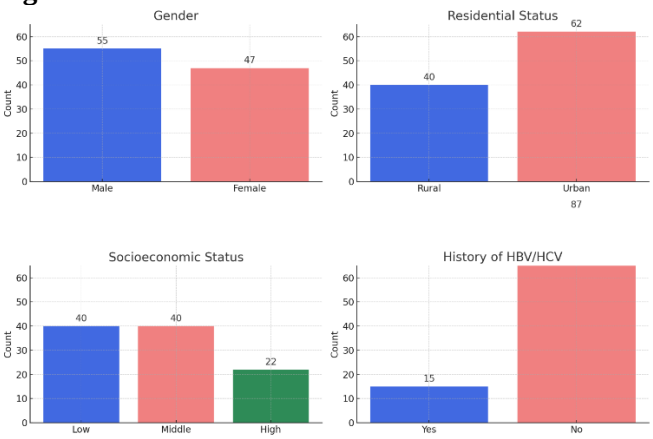


Figure 2



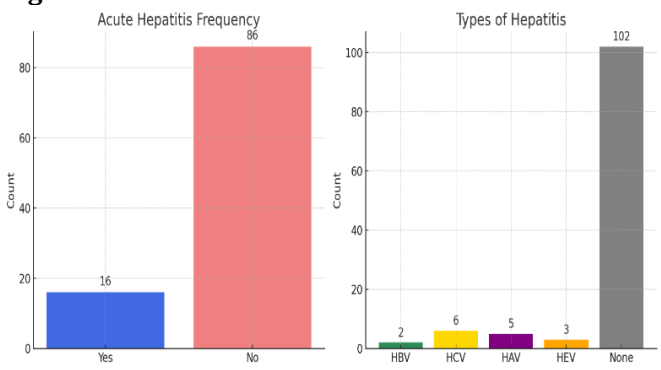
Regarding acute hepatitis, 16 patients (15.7%) were diagnosed with the condition, while 86 (84.3%) were not. The types of hepatitis included HBV (2 patients, 2%), HCV (6 patients, 5.9%), HAV (5 patients, 4.9%), and HEV (3 patients, 2.9%), with 102 patients (84.3%) having none (as shown in Table 2).

Table 2

Acute hepatitis and its types

Acute Hepatitis	Frequency	%age
Yes	16	15.7%
No	86	84.3%
Types		
HBV	2	2%
HCV	6	5.9%
HAV	5	4.9%
HEV	3	2.9%
None	102	84.3%

Figure 3



The association of acute hepatitis with demographic factors indicated that among children aged ≤5 years, 8 (18.2%) had acute hepatitis compared to 8 (13.8%) over the age of 5, with a p-value of 0.546. Gender-wise, 8 males (14.5%) and 8 females (17%) had the condition, yielding a p-value of 0.732. Evaluating fever duration, 7 patients (13.5%) with ≤7 days of fever and 9 (18%) with >7 days were affected, with a p-value of 0.529. Notably, rural residents showed a higher prevalence with 11 (27.5%) affected compared to 5 (8.1%) in urban areas (p-value = 0.012). Socioeconomic status revealed 5 patients (12.5%) from low status and 7 (17.5%) from middle status, while 4 (18.2%) were from high status, with a p-value of 0.827. A significant association was found regarding the history of HBV/HCV in parents, where 14 patients (92.3%) with a positive history had acute hepatitis compared to 2 (2.3%) without, with a highly significant p-value of <0.001 (as shown in Table 3).

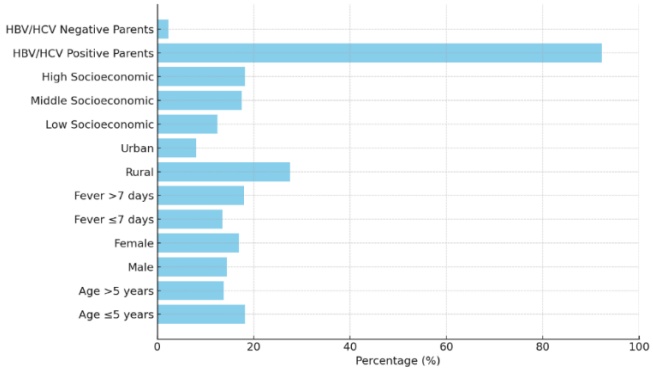
Table 3

Association of Acute Hepatitis with Demographic Factors

Demographic Factors		Acute hepatitis		p-value
		YES n (%)	NO n (%)	
Age (years)	≤5	8 (18.2%)	36 (81.8%)	0.546
	>5	8 (13.8%)	50 (86.2%)	
Gender	Male	8 (14.5%)	47 (85.5%)	0.732
	Female	8 (17%)	39 (83%)	
Duration of Fever (days)	≤7	7 (13.5%)	45 (86.5%)	0.529
	>7	9 (18%)	41 (82%)	
Residential Status	Rural	11 (27.5%)	29 (72.5%)	0.012*
	Urban	5 (8.1%)	57 (91.9%)	
Socioeconomic Status	Low	5 (12.5%)	35 (87.5%)	0.827*
	Middle	7 (17.5%)	33 (82.5%)	
	High	4 (18.2%)	18 (81.8%)	
History of HBV/HCV in Parents	Yes	14 (92.3%)	1 (6.7%)	<0.001*
	No	2 (2.3%)	85 (97.7%)	

Fisher Exact Test*

Graph 1: *Stratification of Acute Hepatitis Prevalence by Demographic Factors in Children*



DISCUSSION

The demographic profile with a mean age of 5.84 years and balanced sex distribution is consistent with the overall demographic profile of children with enteric fever. The fact that no strong association exists between the prevalence of acute hepatitis and the group's age (p = 0.546) shows that within the provided range the risk for

developing hepatitis is not significantly related to the age. This could be attributed to the uniform exposure patterns towards the hepatotropic viruses within the different age groups, although further studies with increased sample sizes might better clarify this.

One of the most noteworthy findings was the higher prevalence of acute hepatitis in rural children (27.5%) compared with urban children (8.1%) with a statistically significant p-value of 0.012. This suggests the potential for environmental and accessibility issues related to hygiene habits and sanitation to be the causative factor behind the increased prevalence of hepatitis in rural communities. It is probable that rural children would have higher exposure to contaminated water or food sources by which the hepatotropic viruses HAV and HEV are transmitted.

A very high correlation was found between parents with a past history of HBV/HCV and the risk of acute hepatitis among their offspring ($p < 0.001$). This reflects the strong role of genetics and family in the transmission of viral hepatitis. The offspring were significantly susceptible to developing acute hepatitis when their parents had a past history of HBV or HCV infection, reflecting the strong environmental and genetic factors behind the spread of the virus.

Our results revealed a mean age of 5.84 (±2.16), with the weight averaging 8.27 kg (±3.51), and the fever's duration averaging 7.95 (±2.36) days. The gender distribution was slightly dominated by the male gender with 55 (53.9%) men and 47 (46.1%) women. Of note was the rural residence of 39.2% and the urban residence of 60.8%. The socioeconomic status was low (39.2%) and middle (39.2%) with 15 patients (14.7%) with a history of HBV/HCV.[14]

A reverse demographic pattern was described by Wani K. et al., where the prevalence of jaundice was seen in all the patients who were tested and where the leading cause of ALF was identified as infections with Hepatitis A taking the lead. Their findings also identified a predominantly male population with the prevalence towards the older children aged 6-10 years.[14] This is also the pattern seen with our results as our population also had prominent cases of acute hepatitis in children ≤5 years.

Furthermore, Ganesh V. et al. identified the most common clinical presentation as abdominal pain, fever, and icterus in children with acute hepatitis, consistent with our findings where abdominal pain was found in all patients and fever was found in 95%.[15] Liver enzyme elevation, predominantly SGOT and SGPT, were identified with high prevalence in the two studies and suggest extensive hepatic involvement in the disease process. Our study found 16 patients (15.7%) with acute hepatitis with the types consisting of HBV (2 patients, 2%), HCV (6 patients, 5.9%), HAV (5 patients, 4.9%), and HEV (3 patients, 2.9%) consistent with the elevated levels of liver enzymes identified by Jagadish K. et al.[16] Notably, the demographic association with acute hepatitis, such as higher prevalence within rural populations (27.5% were infected), also aligned with results from the NICD guidelines, which indicate that enteric fever occurs most frequently within communities with inadequate water and sanitation facilities and unsafe sources of drinking water.[17] This association indicates the strong role of socio-economic factors.

Besides this, our results also yielded a significant correlation between parents' HBV/HCV history and acute hepatitis in children with a p-value of <0.001. This reflects either environmental or genetic risk factors which are yet to be investigated, as with the study by Iqbal SMJ et al., where socio-economic factors were found to significantly contribute towards the prevalence of typhoid fever.[18]

These findings mirror the complexity of the diseases and the influence of demographic and socioeconomic status and indicate the necessity for specially tailored public health interventions.

However, the study also contains some limitations. The results may not be applicable to the wider population because the study is a single center. The sample size is relatively low and may also limit the statistical power and the ability to make overall conclusions. Multicenter studies with larger cohorts are necessary in the future to validate the results and further explore the correlations between the values of the liver enzymes and the onset of acute liver failure in children.

CONCLUSION

In our study, acute hepatitis was found to be a primary health concern among children with Hepatitis A as the leading cause. The findings indicate the need for surveillance and early treatment with the critical role being played by elevated levels of enzymes in the liver and the development of acute liver failure. The findings demonstrate the need for public health interventions towards proper sanitation and accessibility of care for reducing the impacts of the diseases among children.

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*Author Contributions

The authors played significant roles in the preparation of this manuscript, as outlined below.

Dr. Salman Khan was responsible for formulating the study idea, drafting the article, and gathering data from the hospital.

Dr. Shahzad Najeeb participated in refining the article, contributing to the study's design, and analyzing and interpreting the data.

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