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Pathology of Chronic Hepatitis C in Children: Liver Biopsy Findings in the Peds-C Trial

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Abstract

There is relatively little information in the literature on the histopathology of chronic hepatitis C in children. The Peds-C Trial, designed to test the efficacy and safety of peginterferon alfa-2a and ribavirin in children, provided an opportunity to examine liver biopsies from 121 treatment-naïve children, ages 2 to 16 (mean, 9.8 years) infected with the hepatitis C virus (HCV) and with no other identifiable cause for liver disease, signs of hepatic decompensation, or another significant nonhepatic disease. Liver biopsies were scored for inflammation, fibrosis, steatosis, and other histological features. Inflammation in the biopsy was minimal in 42%, mild in 17%, moderate in 38%, and severe in only 3%. Five had bridging fibrosis, and 2 had cirrhosis. Steatosis was absent in 56%, minimal in 34%, and mild in 10%. Inflammation scores correlated with fibrosis scores,

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serum alanine aminotransferase levels, and duration of infection, but not with age, body mass index z score, or HCV genotype. Fibrosis scores correlated with inflammation but not with age, HCV genotype, body mass index z score, or steatosis parameters. Steatosis correlated with serum alanine aminotransferase levels and body mass index z scores; overweight children had more fibrosis than the non-overweight. In conclusion, in this cohort of HCV-infected children, inflammation, fibrosis, and steatosis were milder than reported for treatment-naïve adults with chronic hepatitis C, but there were several with bridging fibrosis or cirrhosis. The positive correlation of inflammation with duration of infection and fibrosis and of obesity with fibrosis suggest that children with chronic hepatitis C will be at risk for progressive liver disease as they age and possibly acquire other comorbid risk factors.

Although chronic hepatitis C is one of the most common liver diseases, affecting approximately 4 million individuals in the United States, clinically significant liver disease due to the hepatitis C virus (HCV) is relatively uncommon in children. In the National Health and Nutrition Examination Survey III population-based survey, the estimated prevalence of antibody to HCV in children and adolescents up to 14 years of age was 0.2% to 0.4%. Thus, it is estimated that there are approximately 60,000 to 100,000 children, most of them asymptomatic, with chronic hepatitis C in the United States.¹ In adults, evaluation for possible therapy of hepatitis C is the most frequent indication for liver biopsy. Consequently, most pathologists are very familiar with its histological features, typically chronic hepatitis with variable degrees of hepatocellular injury, inflammation, and fibrosis, frequently steatosis and portal lymphoid aggregates, and occasionally bile duct damage.^{2,3} By contrast, relatively few children with chronic hepatitis C undergo liver biopsy, and there are only a few published series describing the range of histopathology in a significant number of patients.⁴⁻¹⁰ In general, these have found that children tend to have milder disease than adults, with less inflammation, steatosis, and fibrosis, but with some variation between series collected in different parts of the world.

The Peds-C Trial is an ongoing multicenter study evaluating the safety and efficacy of pegylated interferon with or without ribavirin for the treatment of chronic hepatitis C in children. One of the inclusion criteria is a liver biopsy performed within 36 months of entry into the trial. Biopsy specimens from 110 of the children entered into the trial, along with 11 others that were excluded for various reasons, constitute a large series of tissue samples from well-characterized patients and allowed us to study the histopathology of chronic hepatitis C in a cohort of American children.

Patients and Methods

Patients were recruited to the study from children referred to the 11 participating centers. They were eligible for the trial if they were between 5 and 18 years of age and had 2 positive blood tests for HCV RNA at least 6 months apart. They were excluded if there was clinical or laboratory evidence of decompensated liver disease, serological tests indicating active hepatitis A or B or human immunodeficiency virus, or laboratory tests suggesting another diagnosis, such as Wilson's disease, alpha-1-antitrypsin deficiency, or autoimmune hepatitis (antinuclear antibody >1:160, anti-smooth muscle actin > 1:80, or antiliver– kidney microsomal > 60 units). They were also excluded if there was a history of treatment with interferon or ribavirin or if there was evidence of a nonhepatic disease or chronic condition that might make it difficult to complete the study. All candidates for participation in the study underwent extensive screening including detailed history, physical, anthropometric, ophthalmological, and laboratory examinations.

A liver biopsy performed within 36 months of screening and interpreted at the local center as having no disease process other than hepatitis C was required for entry into the trial. After

screening, unstained sections of each biopsy specimen were forwarded to the central pathologist (Z.G.), or if these could not be obtained, stained sections from the participating center's pathology files were submitted. Sections stained with hematoxylin-eosin and Masson's trichrome were examined in all cases and scored for inflammation and fibrosis with the Knodell,¹¹ Ishak,¹² and Metavir¹³ systems. Steatosis was graded as in other studies as 0 (none), 1 (up to 5% of parenchyma replaced by fat), 2 (6%-33% replaced with fat), 3 (34%-66% replaced with fat), or 4 (>66% fat).¹⁴ Other histological features, including hepatitis-associated bile duct lesions, portal lymphoid aggregates, and perisinusoidal fibrosis, were noted when present.

Biopsy findings were correlated with clinical and laboratory findings at the time of screening for entry into the trial, because data at the time of biopsy were not uniformly available. The median delay between biopsy and screening was 5 months, with a range of 1 day to 37 months. Spearman correlation coefficients (ρ) were used for correlations between continuous functions and non-parametric histological data. The Cochran-Armitage trend test and Fisher's exact test were used for evaluation of contingency tables. All *P* values were 2-sided, with *P* < 0.05 considered statistically significant.

Results

Patient Characteristics and Biopsy Specimens

There were 126 biopsy specimens submitted from the 128 patients evaluated for entry into the study. Five liver biopsy samples had fewer than 3 portal tracts and were not adequate for interpretation. Of the remaining 121 patients with evaluable liver biopsy specimens, 110 fulfilled inclusion criteria and were entered into the trial, whereas 11 were excluded or withdrew before entry. Seven of these 11 were excluded because of a positive autoantibody test (antinuclear antibody, anti-smooth muscle actin, or liver-kidney microsome), 1 because of abnormal thyroid-stimulating hormone, 1 because of thrombocytopenia and esophageal varices, and 2 for reasons that were not specified. All 121 patients with evaluable liver biopsy specimens were included in the subsequent analyses. The material that was reviewed included 1 surgical wedge biopsy and 120 needle biopsies. All biopsies with at least 3 portal areas were evaluated with the understanding that small biopsy specimens tend to be underscored for inflammation and fibrosis.¹⁵ The needle biopsies had a mean length of 14 mm, with a mean of 14.8 and a median of 11 portal areas (complete or partial). There were 95 (79%) biopsy specimens that were at least 10 mm long, with a mean of 16.6 portal tracts.

The 121 patients whose biopsy specimens were reviewed were 56% male (Table 1). There were 92 (75%) who were white, 6 African-American, 4 Asian, 2 Native American, and 17 mixed or unknown race. At the time of biopsy, the patients ranged from 2 to 16 years of age, with a mean of 9.8 and a median of 10 years. Most (100/121) had HCV genotype 1; 7 had genotype 2, 13 genotype 3, and 1 was unknown. The source of infection was thought to be perinatal transmission in 94, transfusion in 9 (7%), intravenous drug use in 1, sexual contact in 1, and unknown in 16. At the time of screening, 42 patients (35%) had normal alanine aminotransferase (ALT) levels, and 77 had elevated ALT. Anthropomorphic evaluation at screening revealed a mean body mass index (BMI) of 20.3, with a range from 12.1 to 35.8. BMI-Z, which is expressed in standard deviations from age-adjusted ideal and which is considered more appropriate for comparing children of varying ages, had a mean of 0.7 with a range of -3.4 to 4.8 standard deviations. There were 29 children (24%) with a BMI-Z of 1.64 or greater, above the 95th percentile and considered overweight for their ages, whereas 3 children (2.5%) were significantly underweight (BMI-Z -1.64).

Liver Biopsy Findings

The biopsies showed pathological findings (Table 2) that ranged from nearly normal to severe chronic hepatitis and cirrhosis (Fig. 1). Discrete portal lymphoid aggregates typical of chronic hepatitis C in adults were present in 28 biopsy specimens (24%), whereas only 7 had hepatitis-associated bile duct lesions (Fig. 2). The degree of hepatocellular injury and inflammation was quite variable, but many cases were very mild. In 52 biopsy specimens (43%), the biopsy was nearly normal or had only minimal inflammation. In the remainder, the degree of injury was mild in 20 (17%), moderate in 45 (37%), and severe in only 4 (3%) (Fig. 3). Using the Knodell Histology Activity Index,¹¹ the sum of the inflammatory components had a mean of 5.1, whereas with the Ishak modification,¹² it was 4.7. The 11 children who were screened but excluded from the trial had a mean Knodell score of 5.3, Ishak score 4.9, which was not significantly different from that of the rest of the cohort.

Fibrosis in the liver biopsy specimens was generally quite mild or absent. Some degree of mild fibrous expansion of at least a few portal tracts was seen in 97 (80%). Significant fibrosis was present in 7 patients, 5 patients with bridging fibrosis and 2 with cirrhosis, 1 of whom was excluded from the trial. Delicate intraparenchymal perisinusoidal fibrosis, which was noted in a high percentage of children with hepatitis C in one series,⁵ was present in 32 biopsy specimens (26%). When present it was randomly distributed within the lobule, and it was invariably mild and focal and a minor component of the injury.

Hepatocellular fat accumulation, typically a mixture of small and large droplet fat, was present in 41% of the biopsy specimens in the study and in 62% of the 13 children infected with HCV genotype 3. However, severe steatosis was not seen, and in only 11 biopsy specimens (9%) did the fat replace more than 5% of the liver tissue (Fig. 4). No Mallory bodies were present in any case.

Clinical–Pathological Correlations

Spearman's correlation coefficients (ρ) were calculated to examine the relationships of inflammation, fibrosis, and steatosis with clinical parameters and with each other (Table 3). Duration of infection was known with certainty in only the 94 patients who had contracted the virus by perinatal transmission, in which case the duration was the same as the patient's age (mean, 120 months; standard deviation, 42 months). There was no significant correlation of histological features with patient age at the time of biopsy for the entire cohort, but in the subset of 94 with perinatal transmission, there was a weak correlation ($\rho = 0.20$) of presumed duration with inflammation that approached statistical significance ($P = 0.058$). There was a statistically significant but weak correlation of duration with steatosis ($\rho = 0.21$). The serum ALT level at the time of screening had similar weak but significant correlations with inflammation ($\rho = 0.25$) and steatosis ($\rho = 0.28$) for the entire cohort of 121 patients and a slightly stronger correlation with inflammation ($\rho = 0.31$) and steatosis ($\rho = 0.33$) when the analysis was limited to the 64 patients whose biopsies were within 6 months of screening. The Knodell and Ishak hepatic activity index scores for inflammation yielded almost identical correlation coefficients and P values, with differences only at the third decimal except for a slightly larger difference in the correlation of inflammation with fibrosis (Knodell = 0.57; Ishak = 0.56). With both scores, however, there was a highly significant correlation of inflammation with fibrosis, even though only 7 patients had bridging fibrosis or cirrhosis. Even though there was a correlation of inflammation score with ALT within the entire cohort, there were no significant differences in mean inflammation score (4.9 versus 5.2, $P = 0.62$) or the proportion of patients (37% versus 45%, $P = 0.45$) with minimal inflammation (hepatic activity index ≤ 3) or in fibrosis scores ($P = 0.84$) between the 43 patients with normal ALT and the 78 patients with elevated ALT at screening. Similarly, there were no significant differences between the 18 children with

autoantibodies and the rest of the subjects. The lack of correlation of age or duration of infection with fibrosis may have been due to the small number of patients with advanced fibrosis. The 2 children with cirrhosis were both 14 years old, whereas the 5 with bridging fibrosis were 11 to 16, so a larger series might uncover a correlation.

The degree of fat accumulation in the liver biopsy specimens correlated weakly with duration of infection and with serum ALT, as noted previously. There was significantly more steatosis in children with elevated ALT compared with those with normal ALT (Fisher's exact test, $P = 0.026$), and all 11 children with 2+ steatosis had elevated ALT. However, there was a stronger correlation of steatosis with body mass index, both standard BMI ($\rho = 0.39$) and BMI-Z ($\rho = 0.33$). The mean BMI-Z for those with no fat in the liver biopsy was 0.5, whereas those with even minimal (<5%) fat had a mean BMI-Z of 0.8, and those with >5% fat had a mean BMI-Z of 1.98 (Table 4). Both the presence and the degree of steatosis were greater in the 29 children who were overweight (BMI-Z = 1.64) compared with the other 92 children (Cochrane-Armitage trend test, $P < 0.001$). Overall, there was no statistically significant correlation of fibrosis scores with either BMI ($P = 0.18$) or BMI-Z ($P = 0.31$). However, comparing the fibrosis scores of the 29 children with BMI-Z = 1.64 to the other 92 children (Table 5), there was significantly greater fibrosis in the overweight children (Cochrane-Armitage trend test, $P = 0.008$). There was no significant difference in the degree of steatosis, BMI, or BMI-Z between the 32 children with focal perisinusoidal fibrosis and the 89 children who lacked this finding.

Comparison with Adult Chronic Hepatitis C

There was no adult control group for comparison, but the results of the current study can be compared with the baseline biopsies of treatment-naïve adults performed in several large published trials,¹⁴⁻¹⁹ which were scored by the same pathologist as the current study (Table 6). Sixty-five percent of the patients in those trials were male, with a mean age of 43 years and a median of 18 years' estimated duration of infection. There was significantly more inflammation in adults, with a mean Knodell inflammatory score of 7.4 [standard deviation (SD) 2.6] in three trials comprising 3559 subjects,¹⁶⁻¹⁸ compared with the mean of 5.2 (SD 2.7) in children. In the cohort of children, more than 40% had minimal Knodell scores of 1 to 3, whereas in adults only approximately 10% were that mild, accounting for much of the difference in mean scores. Fibrosis was clearly less severe on average in children than in 4493 adults in 4 trials,¹⁶⁻¹⁹ with only 4.2% having bridging fibrosis compared with 19.6% in adults and 1.7% with cirrhosis compared with 4.9% in adults. Detailed analysis of steatosis reported in a series of 1428 adults found significantly greater incidence and severity of fat in the livers of adults with chronic hepatitis C¹⁴ than was found in children in the current study. Even though there was less steatosis, the children had a similar correlation of steatosis with BMI-Z score, and HCV genotype 3 infection was associated with a higher incidence of steatosis than other genotypes.

Discussion

In the cohort of U.S. children described in the current report, inflammation, fibrosis, and steatosis were milder than what is seen in treatment-naïve adults with chronic hepatitis C and were minimal in over 40%. Inflammation in the liver biopsy specimens was found to correlate with serum ALT, the duration of infection, and the degree of fibrosis. Steatosis was found to correlate with serum ALT and with BMI, whereas being overweight was associated with increased fibrosis.

There is considerable variability in what has been reported to be the pathology of chronic hepatitis C in children. The largest published series with sufficient detail⁴⁻¹⁰ for comparison are listed in Table 7. There is some degree of overlap in the patients in several of these

reports. The 3 publications^{6,8,9} reporting 80, 112, and 66 patients from a consortium of centers in Italy and Spain include some of the same patients in more than 1 paper. The series of Badizadegan et al.⁵ includes 50 biopsy specimens from 40 patients, but the results are reported as percentages of specimens, so that 10 patients are reported twice. None of the 121 patients in the current study has been previously reported, and each is represented by only 1 biopsy.

None of the previous reports of liver histopathology in childhood hepatitis C⁴⁻¹⁰ commented on the size or quality of the biopsy specimens. A recent study found that small biopsy size can affect the accuracy of histological interpretation,¹⁵ and it has been noted that the failure to note the specimen size and to limit studies to large (> 2 cm or 11 complete portal areas) biopsy specimens raises questions about most of the literature on the pathology of chronic viral hepatitis.^{20,21} Nevertheless, it seems unreasonable to discard all of the liver biopsy information in the literature, and it is still possible to compare the current results with previous studies, assuming that the quality of specimens was similar if sometimes suboptimal.

The greatest difference among the various pediatric series is in the degree of fibrosis reported. Cirrhosis was uncommon but was noted in several reports. There were no children with cirrhosis in either Japanese series^{4,9} and only 1 in the Italian-Spanish series.^{6,8} One of the previous US series⁵ had 3 of 40 patients with cirrhosis. The US series of Mohan et al.¹⁰ had 1 patient who developed cirrhosis on a subsequent biopsy. The current series found cirrhosis in 2 of 121 patients. Thus, a total of 6 patients had already developed cirrhosis while still in childhood. Conversely, the prevalence of precirrhotic bridging fibrosis ranged from 4% in the larger Japanese series⁴ to 44% in the earlier US series.⁵ In the current series, only 4.2% had bridging fibrosis. The reason for the wide range is uncertain, but it might be explained by differences in selection criteria for patients chosen for liver biopsy. The other series included a large proportion of children who had acquired hepatitis C by blood transfusion, and many had been treated for leukemia and other malignancies, perhaps resulting in increased severity of fibrosis. All reports, however, contain some children with progressive liver fibrosis, so it seems likely that, as in adults, the degree of fibrosis increases with time. In the series of 112 patients reported by Guido et al.,⁸ the degree of fibrosis correlated with both age and duration of infection. In the 40 reported by Badizadegan et al.,⁵ fibrosis correlated with age. Although the current series did not demonstrate a significant correlation of fibrosis stage with age or duration, it still seems reasonable to infer that fibrosis increases with duration of infection.

All observers agree that necroinflammatory injury tends to be mild in children. In the current series, we confirmed this by comparison with large cohorts of adults whose liver biopsy specimens were evaluated in similar treatment trials by the same pathologist.¹⁶⁻¹⁹ Similarly, Kage et al.⁴ compared the biopsy specimens from children with a cohort of 120 adults and demonstrated that on average there was milder inflammation in children. A noteworthy finding in the current series was that 42% of children had minimal inflammation, in contrast to treatment-naïve adults in whom inflammation is minimal in only approximately 10%. This suggests that the inflammatory response may take time to develop and raises the possibility of an immune-tolerant phase of infection in young children, similar to what is observed in chronic hepatitis B.²² This is supported by the observations of Murray et al.,²³ who compared liver biopsy findings in 21 children (mean duration of infection, 12 years) with those in 52 adults with less than 20 years of infection (mean duration, 14 years) and found that even with a similar duration of infection, children had significantly less inflammation than adults.

One potential limitation of the current study is the variable intervals between the liver biopsies and data obtained at screening, especially regarding the correlation of histology with serum ALT values. Nevertheless, despite the variable and sometimes long time intervals, there was a significant correlation of inflammation with serum ALT at screening, similar to what was found by Guido et al.⁶ However, we also found that children with normal ALT were as likely to have significant inflammation as those with elevated ALT, and consequently a normal ALT does not exclude progressive liver disease. In the current series, like those of Kage et al.⁴ and Guido et al.,⁶ there was a significant correlation of inflammation with the degree of fibrosis, supporting the concept that it is inflammation that leads to fibrosis as part of the wound healing response. Whether this might be used to guide treatment decisions remains to be determined.

The various published series have reported different incidences of steatosis in children with chronic hepatitis C. The 2 Japanese series reported steatosis in 18% and 24%.^{5,7} The Italian-Spanish series reported 27%,⁹ and another Italian series, 25%.²⁴ The current series found 42% and the other two US series 50% and 10%.^{5,10} Thus, it appears that there may be geographic trends, with more steatosis in the United States. Both the current series and that of Guido et al.⁹ found a correlation of BMI with the degree of steatosis, as in adults. Neither study found a significant overall correlation of steatosis with fibrosis. However, in the current study there was a significant association of being overweight with greater degrees of fibrosis on biopsy, raising the possibility that in a larger population, a stronger correlation of steatosis and fibrosis might become apparent.

In summary, although the total number of liver biopsies in children with chronic hepatitis C infection remains small in comparison with adults, some trends are apparent. Children in general have less inflammation, fibrosis, and steatosis than adults, presumably because of the shorter duration of infection, but significant fibrosis and even cirrhosis can develop during childhood, suggesting that as these patients survive into adulthood, more will be at risk for end-stage liver disease.

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Abbreviations

ALT	alanine aminotransferase
BMI	body mass index

HCV hepatitis C virus

Fig. 1.
Cirrhosis in a 14-year-old boy with chronic hepatitis C acquired by vertical transmission.

Fig. 2.
Portal lymphoid aggregate adjacent to an injured bile duct (arrow), typical of chronic hepatitis C.

Fig. 3. Severe chronic hepatitis C with extensive interface hepatitis and widespread parenchymal inflammation.

Fig. 4. Chronic hepatitis C with steatosis. The fat replaces less than one third of the liver tissue. A portal area with chronic inflammation is at the bottom of the field.

Table 1
Clinical Characteristics of 121 Patients Screened for Peds-C Trial with Liver Biopsy Specimens Available for Review

Sex	
Male	68 (56.2%)
Female	53 (43.8%)
Race	
White	92 (76%)
Nonwhite	29 (24%)
Age at biopsy (years)	
Mean $\pm$ SD	9.8 $\pm$ 3.7
Range	2–16
HCV genotype	
1	100 (82%)
2	7 (6%)
3	13 (11%)
Unknown	1 (1%)
Mode of transmission	
Perinatal	94 (78%)
Transfusion	9 (7%)
Other/unknown	18 (15%)
ALT at screening	
Normal	43 (36%)
Elevated	78 (64%)
BMI	
Mean $\pm$ SD	20.3 $\pm$ 4.9
Range	12.1–35.8
BMI-Z	
Mean $\pm$ SD	0.7 $\pm$ 1.2
Range	–3.4–4.8
1.64	29 (24%)

Table 2
Histopathological Features of Liver Biopsies from 121 Children with Chronic Hepatitis C Infection

Feature	Number of Specimens
Degree of injury/inflammation (Knodell HAI score) *	
Minimal (1–3)	52 (43%)
Mild (4–6)	20 (17%)
Moderate (7–9)	45 (37%)
Marked (10–12)	4 (3%)
Fibrosis	
None	17 (14%)
Portal-periportal fibrosis	97 (80%)
Ishak stage 1	55
Ishak stage 2	42
Bridging fibrosis	5 (4%)
Ishak stage 3	5
Ishak stage 4	0
Cirrhosis	2 (2%)
Ishak stage 5	1
Ishak Stage 6	1
Perisinusoidal fibrosis	32 (26%)
Portal lymphoid aggregates	28 (23%)
Germinal centers	3 (2%)
Bile duct lesions	7 (6%)
Steatosis	
None	71 (59%)
Minimal (< 5% of tissue)	39 (32%)
Mild (6%–33%)	11 (9%)

* Total of Knodell Histology Activity Index scores for periportal injury, parenchymal injury, and portal inflammation.

Table 3
Correlation Coefficients (Spearman Rank) of Clinical Characteristics with Pathological Features

	Correlation Coefficient	<i>P</i>
Age (n = 121)		
HAI inflammation (0–18) *	–	NS
Ishak fibrosis score (0–6)	–	NS
Steatosis score (0–4)	–	NS
Duration of infection (n = 94) (Perinatal transmission)		
HAI inflammation (0–18)	0.20	0.058
Ishak fibrosis score (0–6)	–	NS
Steatosis score (0–4)	0.21	0.043
ALT (n = 64) **		
HAI inflammation (0–18)	0.31	0.014
Ishak fibrosis score (0–6)	–	NS
Steatosis score (0–4)	0.33	0.006
HAI inflammation (0–18)		
Ishak fibrosis score (0–6)	0.56	<0.001
Steatosis score (0–4)	0.19	0.038
BMI-Z		
HAI inflammation (0–18)	–	NS
Ishak fibrosis score (0–6)	–	NS
Steatosis score (0–4)	0.33	<0.001

NOTE. Values are given only for those that approached or exceeded statistical significance ($P < 0.05$)

* Knodell and Ishak scores for inflammation (HAI) had nearly identical correlations with other factors. Both systems have a theoretical range of 0 to 18

** Correlations with ALT are limited to 64 patients whose biopsies were within 6 months of screening.

Table 4
Steatosis in Liver Biopsies From 121 Children With Chronic Hepatitis C Infection

Steatosis	BMI-Z(mean)	BMI-Z < 1.64* (n = 92)	BMI-Z 1.64* (n = 29)
None	0.5	65%	38%
1+ (<5%)	0.8	32%	34%
2+ (6-33%)	1.98	3%	28%

NOTE. Children with BMI-Z 1.64 or greater are above the 95th percentile and considered overweight for age

* BMI-Z < 1.64 significantly different from BMI-Z 1.64 by Cochran-Armitage Trend Test ($P < 0.001$)

Table 5
Relationship of Overweight Status and Fibrosis in 121 Children with Chronic Hepatitis C Infection

Ishak Fibrosis Score (0–6)	BMI-Z < 1.64* (n = 92)	BMI-Z ≥ 1.64* (n = 29)
0	16%	7%
1	46%	45%
2	36%	31%
3	2%	11%
4	–	
5	–	3%
6	–	3%

NOTE. Children with BMI-Z 1.64 or greater are above the 95th percentile and considered overweight for age

* BMI-Z < 1.64 significantly different from BMI-Z ≥ 1.64 by Cochran-Armitage Trend Test ($P = 0.008$)

Table 6
Comparison of Liver Biopsy Findings in Treatment-Naïve Children and Adults with Chronic Hepatitis C

	Children (n = 121)	Adults
Inflammation (mean Knodell HAI $\pm$ SD)	5.2 $\pm$ 2.7	7.4 $\pm$ 2.6 (n = 3559) ¹⁵⁻¹⁷
Fibrosis		
Bridging (Ishak 3/4, Metavir 2/3)	4.2%	19.6% (n = 4493) ¹⁵⁻¹⁸
Cirrhosis (Ishak 5/6, Metavir 4)	1.7%	4.9%
Steatosis		
0	58%	35% (n = 1428) ¹⁴
<5%	33%	38%
6%–33%	9%	20%
>33%	0	7%
Genotype 3	62% (n = 13) [*]	83% (n = 210) [*]

^{*} Percentage of patients infected by HCV genotype 3 with any degree of hepatic steatosis.

Table 7
Liver Biopsy Findings in Reported Large Series of Children with Chronic Hepatitis C

Author	Year	Country	Patients	Inflammation	Fibrosis	Steatosis
Kage et al. ⁴	1997	Japan	109	Less than adults	4% bridging No cirrhosis	18%
Badizadegan et al. ⁵	1998	US	40	Generally mild	44% bridging 8% cirrhosis	50%
Guido et al. ^{6,8,9}	1998	Italy/Spain	80 [*]	Generally mild	16% bridging 1.2% cirrhosis	27%
	2003	Italy/Spain	112 [*]	–	26% bridging 0.9% cirrhosis	–
	2006	Italy/Spain	66 [*]	–	–	27%
Fujisawa et al. ⁷	2000	Japan	49	Generally mild	20% bridging No cirrhosis	24%
Mohan et al. ¹⁰	2007	US	42	Generally mild	12% bridging No cirrhosis	10%
Present series	2007	US	121	Less than adults	4.2% bridging 1.7% cirrhosis	42%

^{*} Some patients included in more than 1 report from this group.