Hepatitis C Viral Infection in Children

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The National Health and Nutrition Examination Survey reported that 0.2% of 6- to 11-year-olds (31,000 children) and 0.4% of 12- to 19-year-olds (101,000 children) in the United States are chronically infected with hepatitis C virus (HCV).^{1,2} Consequently, chronic hepatitis C (CHC) continues to be a large disease burden and public health problem in the United States, and it is an important concern for pediatricians and pediatric hepatologists. Most cases of CHC in children are the result of mother-to-child (i.e., vertical) transmission and are thought primarily to occur around the time of birth, although some cases may occur *in utero*. A large review has estimated the risk of transmission to the infant to be 1.7% per pregnancy if the mother is anti-HCV⁺ only, 4.3% per pregnancy if the mother is anti-HCV⁺ and HCV RNA⁺ on one occasion, and 7.1% per pregnancy if the mother is HCV RNA⁺ on two occasions or at the time of delivery.³ The American Academy of Pediatrics support the use of breastfeeding because it appears to be safe for the newborn as long as the nipples are not cracked or bleeding, there is no evidence of mastitis, and the mother is not having an acute flare of HCV.⁴

Natural History and Clinical Manifestations

Spontaneous resolution of HCV viremia occurs in approximately 10% to 30%, and the rate may be as high as 75%.^{5,6} In most instances, spontaneous clearance occurs before 24 months of age, although approximately 6% to 12% of older children will experience viral clearance, which can occur as late as 7 years.^{7,8} Individuals who do not spontaneously clear their infection and develop CHC typically appear well and have normal or slightly elevated serum aminotransferase levels with little or no inflammation and fibrosis on liver biopsy samples. Ultimately, the development of cirrhosis or liver failure from CHC likely occurs in 1% to 2% of children.⁹

Diagnosis and Screening

Because HCV immunoglobulin G antibodies can cross the placenta, it is not useful to test neonates for potential mother-to-infant transmission until the infant is 18 months of age; at this time, the initial test should be for anti-HCV immunoglobulin G (Fig. 1). If this test is positive, then HCV RNA levels should be measured. Screening for HCV should be considered for children born to mothers who have HCV or use intravenous drugs, children with human immunodeficiency virus, illicit drug users, patients with a history of incarceration or other high-risk behaviors, international adoptees or immigrants from high-prevalence areas (e.g., Africa and Asia), individuals with unexplained or prolonged serum transaminase elevations, and patients with needle stick injuries. HCV genotyping is also an important component for characterizing HCV infections in pediatric patients because genotype 1 is associated with a decreased response to therapy and a need for prolonged treatment. Although there are currently no reports yet linking interleukin-28B polymorphisms to responses to pegylated interferon (PEG-IFN) therapy in children, the CC genotype for the interleukin-28B polymorphism may be associated with higher rates of spontaneous clearance in infants born to HCV-infected mothers.¹⁰

Treatment

Although adults with genotype 1 CHC have a range of treatment options, including direct-acting antivirals (DAAs), these drugs have not been approved for use in children, nor have they been tested in the pediatric population. Instead, the mainstay of treatment for children is the Food and Drug Administration–approved combination of PEG-IFN and ribavirin (RBV).^{11–13} At the same time, the decision to treat children can still be challenging because

Abbreviations: CHC, chronic hepatitis C; DAA, direct-acting antiviral; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin.

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FIGURE 1. Screening and initial evaluation of infants and children for HCV. *The high-risk category includes the homeless, intravenous drug users, patients with a history of incarceration, patients with human immunodeficiency virus and other sexually transmitted diseases, international adoptees, patients with unexplained liver enzyme levels, and patients with other behaviors that practitioners consider to increase the risk of HCV transmission. **For individuals who have been screened because of elevated liver enzymes with a negative workup, additional HCV screening with HCV RNA polymerase chain reaction should be considered.

FIGURE 2. Treatment algorithm for children older than 3 years with CHC.

the disease progresses slowly in childhood, serious complications from CHC are rare during childhood, and side effects from treatment are common (Fig. 2 and Table 1). Although liver biopsy is not universally indicated for the management of CHC, it may provide additional information about the baseline severity of the disease, especially

for cases with genotype 1, whose response to therapy is diminished.

PEG-IFN Plus RBV. The Food and Drug Administration recently approved PEG-IFN α and RBV for the treatment of CHC in children, and this combination is cited in the

TABLE 1: Most Common Adverse Side Effects Reported in Children Undergoing PEG-IFN Treatment for HCV

Adverse Event	Affected Patients (%)
Constitutional	
Fever (flu-like)	77-91
Fatigue	17-30
Headache	47-62
Anorexia	13-29
Myalgia/arthralgia	10-36
Gastrointestinal	
Nausea	18-27
Vomiting	20-27
Decreased weight	19-76
Blood/lymphatic system	
Neutropenia	27-56
Anemia	11-46
Neuropsychiatric	
Depressed mood/depression	4
Irritability	31-37
Insomnia/trouble with sleeping	11
Cutaneous	
Injection site reaction	29-45
Rash	20
Alopecia	17

The data for this table were taken from Rumbo et al.,⁹ Ruiz-Extremera et al.,¹⁰ and Schwarz et al.¹¹

American Association for the Study of Liver Diseases guidelines as the first-line treatment for childhood CHC because of its superior efficacy. PEG-IFN is available in the United States as two subcutaneous formulations: PEG-IFN α 2a (Pegasys, Genentech/Roche), which is approved for children 5 to 18 years of age and is dosed at 180 μ g/1.73 m²/week, and PEG-IFN α 2b (Peg-Intron, Merck), which is approved for children 3 to 18 years of age and is dosed at 60 μ g/m²/week. The recommended length of therapy in children is 48 weeks for genotypes 1 and 4 and 24 weeks for genotypes 2 and 3. The pediatric dose for RBV is 15 mg/kg/day, and it should be given orally in two divided doses; it is available in a 40 mg/mL suspension and as 200-mg capsules.

Side Effects. Both PEG-IFN and RBV are associated with multiple, frequently observed, and potentially serious side effects in children; these effects have been well described in three studies¹¹⁻¹³ and are summarized in Table 1. Bone marrow suppression by interferon α has been well described and predominantly affects leukocytes, although increased rates of bacterial infections in this setting have not been reported. A dose adjustment may be necessary in some instances (Table 2). At the same time, hemolytic anemia may occur in up to 25% of children on RBV, and this also necessitates a dose reduction. Neuropsychiatric symptoms are sometimes observed, although not nearly as frequently as they are in adults. Ocular complications due to interferon α have been rarely reported in children and typically reverse upon discontinuation. Hypothyroidism occurs in 2% to 3% of children and necessitates ongoing monitoring of thyroid-stimulating hormone throughout the course of therapy.

TABLE 2: Most Common Indications for Dose Reductions of PEG-IFN or RBV in Children With HCV

PEG-IFN
Decrease in absolute neutrophil count
Decrease in platelet count
Increase in alanine aminotransferase
RBV
Decrease in hemoglobin

Monitoring and Anticipatory Guidance

Treatment-naïve patients are generally seen yearly by a pediatric hepatologist. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition has recently published clinical practice guidelines for HCV, and they state that yearly checks may involve serum measurements, including aminotransferase, total and direct bilirubin, albumin, and HCV RNA levels, complete blood counts, and coagulation studies.¹⁴ Liver biopsy should be considered if it will influence treatment decisions, and it may not be necessary in patients with genotype 2 or 3 (who have a high rate of viral clearance with PEG-IFN and RBV). Hepatocellular carcinoma has been reported in children with CHC, and yearly α -feto-protein testing and ultrasound examinations should be considered for patients with advanced disease.¹⁴ Although the routine screening of all household contacts is not indicated, it is recommended that siblings be screened for HCV infection in cases of documented vertical transmission. The issue of disclosing HCV infections to daycare centers, schools, peers, and casual dates is challenging because of the tremendous stigma and people's ignorance about the disease. Generally, there is no legal requirement to disclose a person's HCV status to sexual contacts or to child care and school personnel, although it is recommended by the Centers for Disease Control and many patient advocacy groups.

Conclusion

Our understanding of the epidemiology, natural history, and pathophysiology of HCV and the treatment options for HCV have greatly advanced in recent years, and this has led to improved management for children with CHC. Our suggested approach to the screening and management of children with HCV is summarized in Figs. 1 and 2, and additional information is available as part of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines. Trials are underway to evaluate the role of protease inhibitors in children with CHC, and we hope that they will add new tools to the pediatric hepatologist's armamentarium for eradicating the potentially serious consequences of this infection. ■

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