Rationale for Treatment of HCV during Childhood
After 1992 and universal testing of blood products, vertical transmission has become the leading source of infection for children. The rate of vertical transmission averages approximately 5%. Universal screening of pregnant women is not considered cost effective or useful; the AAP Committee on Infectious Disease recommends testing of pregnant women for HCV only if they have an identifiable risk factor. The majority of children with chronic HCV infection have probably not yet been identified. Most chronic infection is asymptomatic during childhood, but long-term infection can lead to cirrhosis and hepatocellular carcinoma later in life. The proportion of HCV-infected children who will suffer these serious consequences in unknown, but several pediatric studies have demonstrated that the degree of hepatic fibrosis generally correlates with age and duration of infection, although progression seems to be slower than observed in those infected later in life. In a study of 121 children aged 2-16 years, 38% had moderate and 3% severe inflammation, 5 patients had bridging fibrosis and 2 had cirrhosis (1). The degree of inflammation correlated with the duration of the infection and the severity of inflammation and fibrosis correlated with each other. Additionally, this analysis revealed that overweight children had more fibrosis than those who were not overweight. One conclusion was that “the positive correlation of inflammation with duration of infection and fibrosis and of obesity with fibrosis suggests that children with chronic hepatitis C will be at risk for progressive liver disease as they age and possibly acquire other comorbid risk factors.” In addition to the physical impact of CHC on children, there is also potential for psychological impact on both the children and their families. Children with CHC had worse cognitive functioning than a normative sample, but their behavioral and emotional functioning was comparable (2). Their caregivers, on the other hand, experienced higher stress and strain on the family system. For these reasons, the primary indications for treatment of pediatric patients with HCV infection are prevention of future complications and the psychosocial benefits of eradication in this young and vulnerable population. Given the impact of CHC on children and their families, and the risk of advancing liver disease as the children age, treatment of this infection during childhood has significant potential for advantage. By the same token, the treatment itself may have adverse consequences, similar to or different from those in adults, that must be considered.

Results of Combination Therapy
There are now several reports regarding the use of peginterferon monotherapy or in combination with ribavirin in children. In an open-labeled, uncontrolled pilot study, 62 children and adolescents 2 to 17 years of age (mean 10.6), were treated with peginterferon alfa-2b and ribavirin for 48 weeks (3). The overall SVR rate was 59%. In 2008, the US Food and Drug administration (FDA) approved combination therapy with peginterferon alfa-2b and ribavirin for use in children with HCV 3 years and older with compensated liver disease. This decision was supported by the results of a multicenter open-label trial (4). In this study, children with genotype 1 or 4, or genotype 3 with > 600,000 IU/ml HCV (Group 1) were treated for 48 weeks, and those with genotype 2, or genotype 3 with < 600,000 IU/ml (Group 2), for 24 weeks. In
contrast to the study design, in practice 8 of the 9 children with genotype 3 and high viral load received only 24 weeks of treatment. The SVR rate was 55%, in Group 1 and 96% in Group 2. A randomized trial of peginterferon alfa-2a with or without ribavirin in 112 children 5 to 17 years of age (genotype 1 in 82%) demonstrated the superiority of combination therapy, with SVR of 53% vs. 21% (5). The difference was noted for both genotype 1 (47% vs. 17%) and non-1 (80% vs. 36%) infections. Analysis of the pretreatment liver biopsies in this cohort had reaffirmed the generally mild histologic disease during childhood, but cases of marked fibrosis and even cirrhosis were observed (1). More recently, another open-label study of peginterferon alfa-2a with ribavirin in 107 children aged 6 to 17 years, using 24 weeks of therapy for genotype 2 or 3 infection and 48 weeks for all others, demonstrated 89% SVR in the former group and 57% in the latter (6). A recent meta-analysis and systematic review confirmed that these results were consistent across studies (7).

Given these considerations, it is reasonable to infer that peginterferon in combination with ribavirin is the treatment of choice for children with chronic hepatitis C who are considered to be candidates for therapy. Examination of a liver biopsy may not be a treatment prerequisite; it is rare to find advanced histology in young children, and the response rates of children with genotype 2 or 3 HCV are so high that baseline biopsies may provide little information regarding either likelihood of response or long-term prognosis. Exceptions are children whose parents want to know the stage of disease in considering treatment, and those with comorbid diseases in whom the results of a biopsy might influence the decision to treat. In genotype 1 infections, especially in older children, biopsy information might be useful, since the SVR rate is not as high, and those with mild histologic changes may choose to wait for the availability of newer, more effective therapies. IL28B genotype has not yet been demonstrated as a predictor of response in the pediatric population. One published guideline recommends treatment of HCV infected children 3 years and older with persistently elevated aminotransferases or those with progressive disease demonstrated histologically, but concedes that individual treatment decisions may depend on the child's age and individual disease characteristics (8). Decisions regarding timing are influenced by disease factors, such as degree of hepatic inflammation and fibrosis and the presence of comorbid diseases, as well as psychosocial factors such as school and athletic activities, family stability and availability for support, and participation in high risk behaviors such as intravenous drug use. Treatment might be advocated for children with perinatally acquired HCV who are older than 10 years, those with at least moderate hepatic fibrosis, and in those with a comorbid disease or other features that raise concern for rapid progression. Just as in adults, obesity and insulin resistance might need to be addressed prior to HCV treatment in children, since these factors are likely to decrease the likelihood of SVR (9).

In all of the trials, peginterferon and ribavirin were generally well tolerated. Side effects were generally those observed in adults. Dose reductions and early discontinuation were not uncommon, primarily for neutropenia (7). Anemia was well tolerated, and hematopoietic growth factors were not used. TSH abnormalities were frequent. In the peginterferon-alfa 2b trials, weight loss and growth inhibition were common (3,4). Although this was not prominent in one of the peginterferon-alfa 2a trials (6), in the PEDS-C study there was a significant impact of peginterferon on both weight and BMI z scores as well as decrease in growth velocity (10). Both of the more recent large trials are collecting long-term follow-up data to determine whether there is recovery of growth in the years after treatment.

Now that more effective therapies for genotype 1 HCV are available for adults, with even better treatments on the horizon, a treatment algorithm for children and adolescents with mild GT1 infection should probably include watchful waiting.
References