NASPGHAN Practice Guidelines: Diagnosis and Management of Hepatitis C Infection in Infants, Children, and Adolescents

*Cara L. Mack, †Regino P. Gonzalez-Peralta, ‡Nitika Gupta, §Daniel Leung, *Michael R. Narkewicz, ||Eve A. Roberts, ¶Philip Rosenthal, and #Kathleen B. Schwarz

ABSTRACT

Hepatitis C virus (HCV) is an RNA virus that affects >180 million individuals worldwide with a high propensity for chronic infection. Children with HCV infection differ from adults in several ways including some modes of transmission, rates of clearance, progression of fibrosis, and the duration of potential chronic infection when acquired at birth. Since the discovery of HCV in 1989, there have been significant advances in the understanding of the virology and natural history of chronic HCV infection in children. In addition, there are now several treatment options for children with chronic hepatitis C infection and many new therapies on the horizon. As a consequence, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition brought together experts in pediatric hepatology to review the available data in children and provide clinicians with approaches to the diagnosis, management, and prevention of HCV infection in children and adolescents. The guideline details the epidemiology and natural history of HCV infection in children, the diagnostic workup, monitoring and treatment of disease, and provides an update on future treatment options and areas of research.

Received March 5, 2012; accepted March 7, 2012.

From the *Section of Pediatric Gastroenterology, Hepatology & Nutrition, Digestive Health Institute, Pediatric Liver Center, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, the †Division of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Florida College of Medicine and Shands Hospital for Children, Gainesville, FL, the ‡Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Emory University School of Medicine and Transplant Services, Children's Healthcare of Atlanta, Atlanta, GA, the §Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, the ||Division of Gastroenterology, Hepatology, and Nutrition, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada, the ¶Division of Pediatric Gastroenterology, Hepatology, and Nutrition, University of California, San Francisco, CA, and the #Division of Pediatric Gastroenterology and Nutrition, Pediatric Liver Center, Johns Hopkins Children's Center, Baltimore, MD.

Address correspondence and reprint requests to Cara L. Mack, MD, Children's Hospital Colorado, Aurora, CO 80045 (e-mail: cara.mack@childrenscolorado.org).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the *journal's* Website (*www.jpgn.org*).

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0b013e318258328d

Key Words: chronic hepatitis, infectious hepatitis, interferon therapy, pediatric liver disease

(*JPGN* 2012;54: 838–855)

Hepatitis C virus (HCV) is an RNA virus that affects >180 million individuals worldwide with a high propensity for chronic infection (*www.who.int/immunization/topics/hepatitis*). The overall prevalence of hepatitis C antibody positivity is estimated to be about 1% to 1.5% in North America (1). Recent data from NHANES3 suggest that 0.17% of 6- to 11-year-olds are HCV antibody–positive (31,000) and 0.39% of 12- to 19-year olds are positive (101,000). Chronic HCV infection (chronic hepatitis C [CHC]) is estimated to affect 0.1% to2% of children depending on the population and risk factors in the children (1), affecting an estimated 23,000 to 46,000 children in the United States (2) and 6600 in Canada (3). The prevalence of CHC in individuals older than 6 years in the United States has slightly decreased from 1.8% in 1988–1994 to 1.3% in 2007–2008 (4). Interestingly, the prevalence of CHC in Mexico appears to be lower (overall population prevalence of 0.36%), but there are no pediatric-specific data available (5). Thus, HCV infection is an important problem for pediatric gastroenterologists and hepatologists.

Children with HCV infection differ from adults in several ways including some modes of transmission, rates of clearance, progression of fibrosis, and the duration of potential chronic infection when acquired at birth. Vertical transmission of HCV infection is the most common route of acquiring HCV in infants and children and there are approximately 7500 new cases in the United States per year from vertical transmission. There is a significant economic effect from pediatric HCV infection. Ten-year costs associated with pediatric HCV infection were recently estimated to be $199 to $336 million (2). There is also a significant effect on death with a 26-fold increased risk of liver-related death associated with CHC acquired in childhood (6). Since the discovery of HCV in 1989, there have been significant advances in the understanding of the virology and natural history of chronic HCV infection in children. In addition, several treatment options are now available for children with CHC and many new therapies on the horizon. As a consequence, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) brought together experts in pediatric hepatology to review the available data in children and provide clinicians with approaches to the diagnosis, management, and prevention of HCV infection in children and adolescents. In addition, this group sought to identify gaps in knowledge to inform a pediatric HCV research agenda.

These guidelines apply to children living in North America, but not necessarily to those living in other continents, particularly in

developing countries with limited resources for health care. The guidelines may need to be adapted to national health care systems because certain tests or treatment regimens may not be available and/or reimbursed by health insurance programs.

SELECTION OF TOPICS AND PATIENTS

In 2010, NASPGHAN developed a pediatric HCV guidelines working group. Areas of interest were identified, and small groups were assigned to each area. The areas of interest included epidemiology, diagnosis, monitoring, anticipatory guidance and disclosures, treatment, side effects of treatment and monitoring for adverse events, special populations, outcome of therapy, and future therapies. There are a number of significant differences between HCV infection in the pediatric and adult populations. Perhaps one of the most important differences is the issue of maternal–fetal transmission. Although the majority of HCV-infected women do not transmit the virus to the offspring, uncertainty and guilt always surround possible transmission. The issue of whether or not to breast-feed is another concern as is the issue of disclosure. What people with whom the HCV-infected child interacts should be told about the infection? What are the legal rights of the child and caregivers in regard to disclosure? The child with CHC is frequently stigmatized; how should this issue be addressed? Can the child with CHC play sports without disclosing the HCV status? Although children with CHC generally have a mild course of liver disease during childhood, there is still concern for cirrhosis, liver transplantation, and cancer in the future. There may be age-related differences in response to treatment, as well as in compliance and tolerance to therapy. Finally, there is the worrisome question of the effect of HCV infection on the developing brain.

Pediatric patients (age bracket: 0–18 years) with CHC or at risk for HCV infection were identified as the target population. For issues that primarily affect adults with small overlap in the adolescent population, such as the role of intravenous drug use (IVDU) and subsequent acute HCV, the committee deferred to the recently published adult guidelines of the American Association for the Study of Liver Diseases (AASLD) due to limited data in children (7). The primary target audiences for these NASPGHAN guidelines are primary care providers caring for children, pediatric gastroenterologists and hepatologists, and pediatric infectious disease specialists. The secondary target audiences for these guidelines include, but are not limited to, adult gastroenterologists and hepatologists, other pediatric and adult subspecialists with high chance for contact with patients affected by chronic viral hepatitis, nurses, and obstetricians.

LITERATURE SEARCH

A systematic literature search was performed using accessible databases of relevance: PubMed, MEDLINE, EMBASE, Cochrane Library, Biosis Previews, EBM Reviews, ISI Web of Science, and Scopus including publications from 1990 to January 2011 by the small groups for the selected topics. The search included publications of all of the types presenting or reviewing data on HCV infection in patients younger than 18 years.

GRADES OF EVIDENCE

Grades of evidence for each statement were based on the grading of the literature and were assigned using the AASLD Practice Guidelines method: Grading of Recommendation Assessment, Development, and Evaluation workgroup with minor modifications (8). The strength of recommendations in the Grading of Recommendation Assessment, Development, and Evaluation system was classified as outlined in Table 1. The Working Group also applied the grading system used by the International Maternal Pediatric Adolescent AIDS Clinical Trial group that allows a comparative ranking between adult and pediatric studies (Table 1).

EPIDEMIOLOGY

Definitions

Nomenclature in this practice guideline conforms broadly to standard usage; however, as with other pediatric liver diseases, some definitions require additional specification and are summarized in Table 2. The liver diseases caused by HCV infection are acute hepatitis C (AHC) and CHC. Although AHC is not the subject of this practice guideline, it is relevant to neonates and individuals at risk for acute infection. Symptomatic AHC has been defined as the onset of acute hepatitis (alanine aminotransferase [ALT] $\geq 10\times$ normal) in an individual without previously known liver disease or other reason for acute liver disease, associated with detectable HCV RNA in the first serum sample and the development of anti-HCV antibody (9). AHC is frequently asymptomatic and not perceived clinically. Neonatal hepatitis C infection is defined as detectable HCV RNA in an infant's blood in the first 1 to 6 months of life, typically in the context of maternal-to-infant transmission of HCV infection. Resolution of neonatal HCV infection frequently occurs (10). Neonatal HCV infection must be distinguished from perinatal transient viremia in which HCV RNA is detected in peripheral blood within 0 to 5 days of birth (10); with respect to this transient viremia, detection of HCV RNA in cord blood is irrelevant. The definition of chronic HCV infection applies to adults and children: evidence of active viral infection with detectable HCV RNA for at least 6 months. The designation of CHC implies ongoing liver injury, which can be mild. The outcome variable of greatest interest in the pediatric age-bracket is resolution of infection. The definition is independent of having detectable anti-HCV antibody, which is a sentinel antibody and bears no relation to disease status. Resolution of CHC may be spontaneous or treatment-induced. Spontaneous resolution of chronic HCV infection is when an individual who had CHC loses detectable serum HCV RNA without any treatment (2 negative HCV RNA tests at least 6 months apart) (11).

Pathobiology of HCV

HCV is an RNA virus within the Flaviviridae family, which includes yellow fever virus, West Nile virus, dengue virus, and others. It occupies its own genus (*Hepacivirus*) and there are 6 main types, clinically known as genotypes. The metabolic effects and susceptibility to antiviral drugs vary between genotypes (12). Approximately, 10^{10} to 10^{12} viral genomes are produced each day in a chronically infected person. The viral genome encodes only 9 proteins, including its own RNA polymerase. This RNA polymerase is greatly error prone with an error rate estimated at 2×10^{-3} base substitutions per genome site per year. Because of the high error rate of the HCV RNA polymerase, many variant viruses known as ''quasispecies'' are produced and confer a survival advantage to HCV. In present usage clinically, ''quasispecies'' refers to the collection of variant HCVs in an individual, but it can also refer to the individual variants themselves, similar to its original usage biochemically. Extremely young infants infected with HCV by vertical transmission show changes in the composition of the infant's HCV quasispecies including new variants that were never found in the maternal quasispecies (13). Young children with CHC due to vertical transmission show differences in the natural history of their liver disease, which reflect changes in the composition of their quasispecies compared with the maternal quasispecies, in part because of interaction with their own host

TABLE 1. Grading systems for recommendations

Grading of recommendations, assessment, development and evaluation (GRADE)	Criteria
Strength of recommendation	
Strong [1]	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak [2]	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost, or resource consumption
Quality of evidence	
High [A]	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate [B]	Further research may change confidence in the estimate of the clinical effect
Low [C]	Further research is extremely likely to effect confidence on the estimate of clinical effect
IMPAACT pediatrics grading system	**Quality of evidence for recommendation**
Strength of recommendation	
A: Strong recommendation for the statement	I: One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	I∗: One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes
	II∗: One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data
	III: Expert opinion

IMPAACT = International Maternal Pediatric Adolescent AIDS Clinical Trial.
† Studies that include children or adolescents but not studies limited to postpubertal adolescents.

immune responses (14). Changes in quasispecies composition, typically a loss of diversity, are associated with disease progression (15).

Host Contribution to Disease

Little information is available about how host responses characteristic of infants and children actually contribute to the pathobiology of HCV infection. Factors relating to enhanced disease severity identified in adults may be relevant to children and adolescents with CHC. For example, a genome-wide scan strategy was used to identify 2 genes, *DDX5* and *CPT1A*, which may be associated with increased susceptibility to liver fibrosis in adult patients with CHC (16). Other preliminary data suggest numerous candidate genes related to HCV clearance or persistence (17).

Infants may have certain defense mechanisms, possibly age-related, which explain the relative inefficiency of mother-to-infant HCV transmission. In one study, infants with human leukocyte antigen (HLA) DR13 appeared significantly less likely to develop CHC after mother-to-infant transmission (18). Subsequent reports have suggested that additional HLA loci may influence disease transmission (19,20). Another study showed that infants exposed to HCV develop $CD4^+$ lymphocytes with specific reactivity to HCV even in the absence of detectable anti-HCV; however, infants who had vertical infection showed either no response or response to only 1 viral peptide (21). Infants with the Rs12979860 CC genotype for the IL28B polymorphism may be more likely to spontaneously

TABLE 2. Definitions used in practice guideline

Terminology	Definition
Infection with hepatitis C	Documentation of HCV RNA presence in the blood
Acute hepatitis C	Development of acute infection with HCV in a patient known to be negative in the previous 6 mo and evidence for hepatitis
Chronic hepatitis C	Evidence of chronic HCV infection for >6 mo with ongoing liver injury
Spontaneous resolution	Individual with HCV infection loses detectable serum HCV RNA without any treatment as indicated by 2 sequential negative tests for HCV RNA at least 6 mo apart

HCV = hepatitis C virus.

resolve vertical HCV infection (22). The placenta has been shown to play a protective role against HCV infection in the neonate. Various components of the innate immune system such as natural killer and γ-δ T cells operate within the placenta to eradicate HCV (23).

Liver Histology and Extrahepatic Manifestations in Pediatric CHC

CHC in children is associated with a variety of histological patterns of disease, generally not as severe as in adults. Indeed in many children, liver biopsy discloses no obvious histological changes or mild inflammation and fibrosis. Nevertheless, significant fibrosis or cirrhosis may occur (24). Children rarely require liver transplantation for CHC. Between 1988 and 2009, 133 children were transplanted for chronic liver failure due to CHC in the United States. To date, hepatocellular carcinoma appears extremely uncommon in children with CHC. Only 2 cases have been reported in children (25), but others may exist. Two further cases presented in young adults who had acquired CHC in childhood (26). Recent observations in adults with CHC indicate that hepatocellular carcinoma complicating CHC may develop in the absence of cirrhosis (27,28), a finding of potential importance to pediatric patients. Regression of cirrhosis after treatment for CHC has been reported in adult studies.

Numerous extrahepatic disorders have been associated with CHC in adults. Glomerulonephritis, typically membranoproliferative, may occur in children with CHC. Unlike in the adult population, neither cryoglobulinemia nor lymphoma has yet been reported in children. HCV infection in the central nervous system has been identified as causing cognitive impairment in some adults with CHC (29). These observations raise the issue of learning impairment in children with CHC. Impaired quality of life, potentially severe enough to have a negative effect on learning, has been reported in children with CHC. These findings include developmental delay, learning disorders, and cognitive deficits less severe than those of attention deficit hyperactivity disorder but still reflecting decreased executive function (30,31).

Epidemiology of Pediatric CHC

HCV infection is estimated to affect 0.1% to 2% of children in the United States, with seroprevalence of HCV infection estimated at 0.2% among children and 0.4% among adolescents (32). Transmission of infection is by contaminated blood or body fluids. At one time HCV infection accounted for the majority of transfusion-associated hepatitis, but presently the risk of acquiring HCV infection by transfusion of blood or blood products is negligible (33). Presently, the primary mechanism of HCV infection in children is mother-to-infant transmission (vertical transmission). The prevalence of CHC among pregnant women, taken as being both anti–HCV- and HCV RNA–positive during pregnancy, is approximately 0.75% (0.49%–1.7%) (34–40). In one large review, the estimated risk of transmitting HCV infection from mother to child was 1.7% per pregnancy if the mother had detectable anti-HCV antibodies, 4.3% if the mother had detectable HCV RNA, and 7.1% if the mother tested positive for HCV RNA at least twice during pregnancy or around the time of delivery (41). Even with the addition of several recent studies, the estimate of risk for HCV transmission is similar, 5% to 7% per pregnancy for a mother with HCV infection without human immunodeficiency virus (HIV).

It is not known exactly when mother-to-infant HCV transmission takes place. Several factors that affect the risk of HCV transmission have been studied. Several reports indicate that undetectable maternal HCV RNA is associated with a small risk of transmission (42,43), presumably because HCV RNA load can vary during pregnancy. Concomitant HIV infection increases the risk of HCV transmission 2- to 3-fold (41). Recently, this effect appears somewhat less prominent, perhaps because greatly effective antiretroviral therapy decreases HCV load during pregnancy or because infants of HIV-positive mothers may be born somewhat prematurely (43). High maternal HCV viral load (>600,000 IU/mL) appears to favor mother-to-infant HCV transmission (44–46). Internal monitoring of the fetus (''fetal scalp vein monitoring'') (10), prolonged rupture of membranes (10,43), and fetal anoxia around the time of delivery, as indicated by decreased cord blood pH (46), may enhance the risk of infection. The role of amniocentesis on the risk of mother-to-infant HCV transmission cannot be evaluated based on available data (47,48).

Several factors previously thought to affect mother-to-infant HCV transmission have not been found to alter risk. Elective cesarean section is not required for HCV-monoinfected women because it confers no reduction in the rate of mother-to-infant HCV transmission (41,43,46,49,50). With vaginal delivery, large vaginal tears should be avoided. Breast-feeding does not promote HCV transmission from mother to infant (41,43). It is prudent to avoid breast-feeding if the nipples are bleeding, if mastitis is present, or if the mother is experiencing a flare of hepatitis with jaundice postpartum. Cost-effectiveness analysis based on available epidemiological data indicates that screening all of the asymptomatic mothers for CHC is not cost-effective (51); however, mothers at high risk for HCV should be screened for HCV.

IVDU with sharing of contaminated needles or apparatus is a major contributor to the spread of HCV infection. Sharing of nasal straws can also transmit HCV infection. Tattooing and body piercing are potential modes of HCV transmission and have been reported as a risk for transmission in adults (52). Data regarding the risk of HCV transmission in households where 1 member has CHC are confusing. In general, there appears to be an extremely small risk (<2%) and this risk may differ in different parts of the world (53–55). No data are available regarding the risk of HCV transmission in infant day-care centers. The present consensus is that the risk of HCV transmission by sexual intercourse in stable relationships is negligible (56). Importantly, low risk of HCV transmission does not constitute grounds for sexually active adolescents to ignore safe-sex practices.

Natural History of HCV Infection in Infants

HCV infection acquired in infancy can have several different patterns of outcome. Spontaneous resolution of infection is an important outcome, although it remains unclear whether children are more likely than adults to clear HCV infection. Some infants appear to acquire HCV infection from their chronically infected mother, but they lose all evidence of infection during early infancy (10,43,57–59). This pattern is best described as spontaneous resolution of neonatal AHC. It is not evident that it is merely transient viremia, especially if serum ALT is elevated. Little information is presently available about the long-term course of these children, who are generally regarded as having recovered from HCV-associated disease. Other infants develop CHC but achieve spontaneous resolution during the first few years of childhood, generally by 7 years or earlier. This pattern of early spontaneous resolution may occur irrespective of whether the child acquired CHC by mother-to-infant transmission or via blood transfusion (11,53,60,61). The long-term course for those who do not have spontaneous resolution of CHC from infancy has been reported as mild: children are clinically well with normal or

near-normal serum aminotransferases and little inflammation on liver biopsy (62).

Natural History of HCV Infection in Children and Adolescents

Infants infected by vertical transmission have a high rate of spontaneous resolution approaching 25% to 40%. Most have spontaneous resolution by 24 months of age, but some may have spontaneous resolution as late as 7 years after vertical infection. Approximately 6% to 12% of older children experience spontaneous resolution (53,63) with a few reports of strikingly higher proportions (11,64).

The majority of children with CHC are clinically well. In a large European study, only 14% were mildly symptomatic. All of the children in the present study had mild chronic hepatitis on liver biopsy (minimal inflammation in the majority) and only 1 child of 224 had cirrhosis (53). Importantly, the consensus is that CHC in children is usually a progressive disease with accumulating liver damage. Cirrhosis has been reported in 1% to 2% of children with CHC, and liver transplantation has been performed for end-stage liver disease in advanced disease (24).

The natural history of CHC in children and teenagers may be affected by certain biological factors. Genotype 3 may be more likely to clear spontaneously (61). Medical conditions associated with increased risk of more severe disease include obesity (65,66), survivors of childhood cancer (67), congenital anemias requiring chronic transfusions, and children coinfected with HIV or hepatitis B virus (HBV). Natural history is also affected by social factors, which need to be addressed in a comprehensive management strategy for pediatric CHC. Risky behaviors are associated with more severe disease and include IVDU (68) and alcohol use (69,70). Homeless adolescents are at risk, partly through their behaviors that increase the likelihood of AHC and partly because of inadequate access to medical care (71). Incarcerated teens, who have a disproportionately high incidence of CHC, are also at increased risk for poor outcome (72).

DIAGNOSIS

Whom to Test for HCV

Testing is indicated in individuals at risk for HCV infection as outlined in Table 3 (73). A special mention is merited for investigation of mother-to-infant transmission of HCV. Because anti-HCV immunoglobulin G (IgG) crosses the placenta, testing anti-HCV is not informative until the infant is 18 months old, at which time antibody testing should be performed (74). Patients older than 18 months with positive anti-HCV IgG should have subsequent testing for serum HCV RNA to determine active infection. If requested by the family, the serum HCV RNA can be tested before 18 months of age; however, infants should be at least 2 months old (75). If serum HCV RNA is positive in early infancy, it should be rechecked after 12 months of age to determine presence of CHC.

Diagnostic Tests

The list of tests to diagnose HCV has evolved from a relatively insensitive enzyme immunoassay (EIA) in the early 1990s to greatly sensitive and specific EIAs as well as nucleic acid detection by reverse transcription-polymerase chain reaction (RT-PCR) assays for both qualitative and quantitative determination of HCV RNA. The purpose of this section is to review the list of diagnostic tests presently available for the detection of HCV and, where appropriate, to comment on their applicability to the pediatric population. Genotyping will be discussed and an age-appropriate diagnostic work-up will be described.

Antibody-Based (IgG)

The available tests are immunoassays, which are easy to perform, automated, characterized by low variability, and relatively inexpensive. For these reasons, antibody-based tests are generally recommended for screening; however, they should not be used in infants younger than 18 months given the likelihood of reactivity

TABLE 3. Persons for whom screening for HCV infection is indicated*

Group	Screening
Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users	Antibody
Persons with conditions associated with a high prevalence of HCV infection including: Persons with HIV infection Persons who have ever been on hemodialysis Persons with unexplained abnormal aminotransferase levels	Antibody or RNA
Earlier recipients of transfusions or organ transplants before July 1992 including: Persons who were notified that they had received blood from a donor who later tested positive for HCV infection Persons who received a transfusion of blood or blood products Persons who received an organ transplant	Antibody or RNA
Children born to HCV-infected mothers	Antibody after 18 mo of age, RNA for younger ages
Health care, emergency medical, and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood	Antibody or RNA
Present sexual partners of HCV-infected persons	Antibody
Children with chronically elevated transaminases	Antibody
Children from a region with high prevalence of HCV infection	Antibody

Adapted from reference (73). HCV = hepatitis C virus; HIV = human immunodeficiency virus.
* All of the positive anti-HCV antibody tests should be followed up with a HCV RNA test to determine active infection.

due to maternal antibody (76). There are 3 types of immunoassays: EIA, microparticle EIA, and chemiluminescence immunoassay. The third-generation EIAs can be performed in plasma or serum and use recombinant antigens from core (c22) and nonstructural proteins 3 (c33), 4 (c100), and 5. The specificity and sensitivity of the third-generation EIAs in patients with chronic liver disease due to HCV infection are >98% and >97%, respectively (77). Supplementary Table 1 (*http://links.lww.com/MPG/A112*) lists the Food and Drug Administration (FDA)–approved antibody-based assays. The first 2 are recommended for screening and use a mixture of proteins as the solid-phase agent. The third can be used for supplemental testing for detection of antibodies to individual HCV proteins. Given the ready availability of nucleic acid testing for viral RNA, the recombinant immunoblot assay is used less often than in the past when nucleic acid testing was not commonly available. One disadvantage of the antibody-based tests is that they cannot distinguish acute from chronic infection. The third-generation EIAs that detect antibodies against core protein and nonstructural proteins 3, 4, and 5 generally become positive about 6 to 8 weeks after acquisition of infection (78). Therefore, anti-HCV IgG antibodies are usually negative during the acute phase, and HCV infection during this time frame can only be determined by serum HCV RNA.

Another antibody-based test of interest, the OraQuick HCV rapid antibody test, was approved by the FDA in June 2010. It uses whole blood samples obtained by venipuncture. The major advantage of this test is that it allows point-of-care testing in that it is portable and easy to use; it provides an answer within 40 minutes and can therefore be used for HCV screening for persons who are at risk for hepatitis, such as youths who live on the streets or are incarcerated (79,80). Further testing is necessary to confirm HCV infection if the test result is positive. Anti-HCV IgM is not useful for distinguishing between acute and chronic HCV infection and measuring HCV IgM is not recommended.

Qualitative and Quantitative HCV RNA

Supplementary Table 2 (*http://links.lww.com/MPG/A112*) summarizes the FDA-approved qualitative and quantitative tests for HCV RNA, usually performed by RT-PCR. In the past, qualitative tests were used for diagnosis because they were more sensitive than the quantitative tests. Recently improved to be greatly sensitive, quantitative tests are now recommended for diagnosis in patients with positive anti-HCV antibody tests (81).

If the antibody test and the HCV RNA test are positive, this result is interpreted as acute or chronic HCV depending on the clinical context. If the antibody test is positive and the HCV RNA test is negative, this result indicates resolution of HCV infection or AHC during a period of low-level viremia. If the antibody test is negative but the HCV RNA test is positive, there are 3 possible interpretations: this represents early AHC, chronic HCV infection in the setting of an immunocompromised state, or a false-positive HCV RNA test. If the HCV RNA is negative and if repeated in 6 months it remains negative, the individual does not have chronic HCV infection. HCV RNA tests can be detected in serum or plasma as early as 1 to 2 weeks after exposure to the virus and weeks before the antibody tests become positive or the liver enzymes become elevated (78).

HCV Genotypes

HCV genotyping is useful for prediction of the likelihood of response to antiviral agents and for determining the optimal duration of therapy. The genotype assay uses subgenomic regions such as core/C1 or NS5B. Two HCV genotyping assays are available in the United States: the Truegene HCV Genotyping assay (Siemens) done by direct sequencing and the Versant HCV Inno-LiPA HCV II assay (reverse hybridization with genotype-specific probes). Subgenotypes such as 1a, 1b are not relevant to interferon (IFN)-α therapy but may be relevant in the future to treatment with direct-acting antiviral agents. IL28B receptor testing may be considered for children with genotype 1 before embarking on therapy because IL28B receptor variants have been quite useful for predicting response to pegylated (PEG)-IFN-α and ribavirin in adults with genotype 1 (82). Diagnostic tests suitable for future research in high-risk pediatric patients include dried blood spot testing from fingerstick or heelstick samples, salivary assays, point-of-care testing on venipuncture samples, and RT-PCR of frozen or formalin-fixed liver biopsies (83).

MONITORING AND ANTICIPATORY GUIDANCE

Monitoring of Children Who are Treatment Naïve

Children with chronic HCV infection not receiving antiviral therapy should be evaluated annually to provide ongoing education and to assess for clinical and biochemical evidence of chronic liver disease. Laboratory investigations during periodic assessments may include serum aminotransferases, bilirubin (total and direct/conjugated), albumin, HCV RNA levels, complete blood count (with platelet count), and prothrombin time/international normalized ratio (if cirrhosis is present) (2A; BII). Liver biopsy should be generally considered only if the result will influence medical decision making. Liver biopsy may be specifically useful to investigate unexplained clinical hepatic decompensation in a previously stable patient and in children who are being considered for antiviral treatment to assess severity of liver disease. It is reasonable to forego pretreatment liver biopsy in children with HCV genotypes 2 or 3 who have a high (>80%) probability of achieving a virological cure with presently available treatments (see below) (2B; BII).

Screening for Hepatocellular Carcinoma

As noted above, there are only a few reported cases of children with chronic HCV infection developing hepatocellular carcinoma (HCC) (25,26). In those with significant liver disease (ie, cirrhosis), abdominal ultrasonography and serum α-fetoprotein should be considered annually or biannually for surveillance of HCC (2B; BII∗).

Monitoring of Children Younger Than 3 Years With HCV Infection

Vertical transmission presently accounts for the majority of pediatric HCV infections. Children born to HCV-infected mothers should be screened for CHC with anti-HCV antibody testing at 18 months of age, when maternally derived antibodies have cleared (1B; AIII); however, sensitive nucleic amplification assays to detect HCV RNA may be useful in selected cases where the potential of having transmitted an infection results in significant maternal anxiety, despite the low risk of transmission (41) (2B; BIII). In this particular setting, the early exclusion of HCV infection is reassuring and may be worth the added expense. Of note, infants with detectable HCV RNA in infancy should be periodically monitored because spontaneous viral clearance may occur during childhood, particularly in HCV genotype 3 infections (84).

TABLE 4. Anticipatory guidance and screening

Category	No contraindication	Avoid	Routine screening
Household contacts	Sharing food, drink, eating utensils, clothes, towels, laundry, toilet seats (1A; AIII)	Sharing toothbrush, shaving equipment, nail clippers, tweezers, glucometers, or other personal item that may be contaminated with blood	Not recommended (2B; BIII)
Nonhousehold contacts	Attending day care, school, camps, playgrounds, play dates, community pools; participating in contact and non-contact sports	N.A.	Not recommended (2B; BIII)
Casual contacts	Kissing, hugging, holding hands	N.A.	Not recommended (2B; BIII)
Sexual contacts	Monogamous sexual contact	Unprotected sexual activity with multiple partners (85)	Not recommended: monogamous relations; Recommended: polygamous relations (2B; BIII)
Other activities	N.A.	Tattooing (86), body piercing (87)	N.A.

N.A. = not applicable.

Anticipatory Guidance and Screening

Present evidence does not support routine screening of household contacts (2B; BIII). One exception is that in the setting of known vertical transmission, siblings should be screened for vertical transmission of HCV infection as well. Children, caregivers, and their families exposed to HCV-infected patients require effective education on avoidance of virus acquisition as outlined in Table 4 (1A; AIII) (85–87). Adult data have shown an increase in transmission with multiple sexual partners, although the risk of transmission is between 1% and 5% in monogamous relationships. Indirectly, spouses of HCV-positive index cases have a greater risk of becoming infected. Children with CHC are encouraged to lead normal lives. Nonetheless, special situations need appropriate handling as delineated in Table 5 (88–97).

Disclosures

Disclosing HCV infection to day-care personnel, school teachers and school personnel, sports coaches, authorities, peers,

TABLE 5. Special considerations for pediatric HCV infection

Special situation	Recommendations
Blood spills (including dried blood)	Thoroughly clean spill area using a dilution of 1 part household bleach to 10 parts water. Gloves should be worn when cleaning up blood spills (refer to *www.CDC.gov*)
Minor cuts or bruises	Observe universal precautions
Use of over-the-counter analgesia, anti-inflammatory and antipyretics	Occasional use is acceptable. NSAIDs should be avoided in those with varices. Short intermittent courses of corticosteroids such as for asthma are acceptable
Vaccinations	Should receive all of the age-appropriate immunizations, including hepatitis A and hepatitis B vaccines (1A; AI*)
Obesity	Obesity may further burden liver health and negatively influence response to HCV therapy (88,89)
Exercise	No restrictions to school and sports
Alcohol consumption	Avoid alcohol consumption because it strongly correlates with rapid progression of liver disease (90)
Illicit drug use (nasal cocaine, intravenous agents)	Avoid high-risk behaviors that will promote HCV reinfection (posttreatment) and transmission of other viruses
Pregnancy	Because there are presently no effective strategies to prevent perinatal HCV transmission, universal screening of pregnant women is not recommended (91)
Obstetrical-perinatal factors	Vertical transmission of HCV is similar between infants born by C-section or vaginally; however, prolonged rupture of membranes and the use of fetal scalp probes are associated with increased HCV transmission rates and should be avoided (1B; AII) (92–94)
Postnatal period	The rate of vertical transmission is similar between breast- and bottle-fed infants. Hence, breast-feeding is not generally contraindicated in mothers with HCV infection. Breast-feeding should be avoided if there is mastitis or bleeding (1B; AII) (95–97)

HCV = hepatitis C virus; NSAIDs = nonsteroidal anti-inflammatory drugs.

and casual dates can be a contentious and anxiety-provoking proposition. Although there likely are national and international geographic regulations with regards to this issue, there is generally no legal requirement to disclose HCV infection to casual or sexual contacts in the United States; however, the Centers for Diseases Control and Prevention and many patient advocate groups suggest revealing this information to sexual partners when appropriate (*www.hcvadvocate.org*; *www.cdc.gov/hepatitis/hcv*). This recommendation poses further ethical concerns and questions regarding the appropriate timing to disclosure this information and how it should be done. This decision should be individualized and should be arrived at only after thoroughly weighing all of the advantages and disadvantages of transmitting this information, largely based on the cognitive development of the individuals involved. Further information can be obtained from the HCV Advocate website (*http://hcvadvocate.org*).

TREATMENT OF HEPATITIS C

There are several schools of thought regarding the need for treatment of children with CHC. Because CHC generally has a slow progression to fibrosis and severe disease is rare in children, follow-up without treatment until adulthood may be a valid option for many children. Treatment during childhood does not achieve increased rates of response compared with adults, and adverse events are frequent and in some cases, may be severe. Conversely, treatment may be justified because it allows definitive resolution in a subgroup of patients. Adolescence and young adulthood are associated with busy school and work demands, which may result in a lack of compliance with medical regimens and visits. All of those factors may lead to postponed treatment. Conversely, treatment of young children may be accomplished more easily given motivated caregivers and schedules, which can be more easily adjusted to therapeutic regimens than is the case for adolescents.

Children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (ie fibrosis on liver histology) should be considered for treatment. Although in adults the presence of bridging fibrosis on liver biopsy is an important predictor of future progression to cirrhosis (98), this observation has not been confirmed in children (64,99,100). One can also argue that children with CHC and only mild disease (low/normal aminotransferases, minimal inflammation, or fibrosis on biopsy) could be considered for treatment given the real possibility of viral eradication and the lack of predictors of progression. The goals of treatment in the individual patients are eradicating virus infection, preventing end-stage liver disease and HCC, and removing stigma associated with HCV infection. An overall goal is to decrease the global burden of disease. Presently available treatments for pediatric CHC are IFN-α or PEG-IFN-α and ribavirin. The AASLD recommends the FDA-approved combination of PEG-IFN-α with ribavirin as first-line treatment for CHC in adults and children ages 3 to 17 years (81) (1A; AI). Based on multiple smaller open-labeled, uncontrolled single-center and large blinded, multicenter pediatric studies (101–109) outlined in Table 6, combination treatment with PEG-IFN-α has demonstrated superiority in achieving sustained virological response (SVR) over IFN-α alone. PEG-IFN-α also requires only once weekly dosing rather than 3 times per week dosing as is necessary for standard IFN-α. Factors predictive of a higher virological response to treatment include HCV genotypes 2 and 3 (typically >80% SVR) and a lower viral load in those with genotype I (<600,000 IU/mL or $<2 \times 10^6$ copies/mL) (101,102,105).

IFN-α is a cytokine that has important functions in the innate antiviral immune response (110). Circulating IFN-α attaches to cell-surface receptors that signal through the system of Janus-activated kinase and signal transducers and activators of transcription, leading to the induction of multiple IFN-stimulated genes. These genes include double-stranded RNAses, inhibitors of viral protein translation, and proteins that destabilize viral messenger HCV RNA. The expression of these genes under activation of IFN-α also results in activation of natural killer cells, maturation of dendritic cells, proliferation of memory T cells, and prevention of T-cell apoptosis (111). This cytokine can be pegylated by the covalent attachment of large molecule polyethylene glycol to recombinant IFN-α. Once pegylated, recombinant IFN-α carries a longer half-life, better pharmacokinetic profile, and better rate of virological response than IFN alone (112,113).

The addition of ribavirin to IFN-α treatment dramatically improved SVR (up to 30%–40%) and the end-of-treatment response (ETR) in adults and children (102). Combination treatment also results in a significant decrease in the relapse rate of HCV infection as compared with PEG-IFN-α monotherapy (114,115). These advantages have also been confirmed in pediatric trials (102,106). Ribavirin is an oral nucleoside analogue with broad activity against viral pathogens and has immunomodulatory effects (116). Although the mechanism of action is not entirely clear, ribavirin has been shown to have some minimal direct activity against HCV replication (117) and its use may lead to rapid and lethal mutation of virions or depletion of intracellular GTP, which is necessary for viral RNA synthesis (118). Ribavirin is presently available as 200-mg capsules (Rebetol, Ribasphere, ribavirin) or an oral suspension formulated at 40 mg/mL (Rebetol).

Presently 2 US licensed PEG-IFNs are approved by the FDA for children with CHC. PEG-IFN-α-2b (PEGINTRON; Merck &

TABLE 6. Selected PEG-IFN/ribavirin treatment trials in children with chronic HCV infection

Author, year	No. studied	Treatment regimen	Sustained virological response* no./total (%)		
			All types	HCV type 1	HCV type 2/3
Christensson et al, 2000 (106)	11	IFN-2b-ribavirin	7/11 (64)	2/5 (40)	5/5 (100)
Lackner et al, 2000 (107)	12	IFN-2a-ribavirin	6/12 (50)	6/12 (50)	N/A
Wirth et al, 2002 (103)	41	IFN-2b-ribavirin	25/41 (61)	18/34 (53)	7/7 (100)
González-Peralta et al, 2005 (101)	118	IFN-2b-ribavirin	54/118 (46)	33/82 (36)	21/25 (84)
Wirth et al, 2005 (104)	62	PEG-IFN-2b-ribavirin	36/61 (59)	22/46 (48)	13/13 (100)
Wirth et al, 2010 (105)	107	PEG-IFN-2b-ribavirin	70/107 (65)	38/72 (53)	28/30 (93)
Schwarz et al, 2011 (102)	55	PEG-IFN-2a-ribavirin	29/55 (53)	21/45 (47)	8/10 (80)

HCV = hepatitis C virus; PEG-IFN = pegylated interferon.
* Undetectable serum HCV RNA 24 weeks after treatment cessation.

Co, Inc, Whitehouse Station, NJ) contains a ''linear'' 12-kDa PEG moiety. The optimal dose of PEG-IFN-α-2b is 60 $\mu g \cdot m^{-2} \cdot week^{-1}$ given subcutaneously. Formulations include premeasured vials (50, 80, 120, or 150 μg/0.5 mL, Peg-Intron Kit) that require reconstitution with a diluent or ready-to-use injection pens (80, 120, or 150 μg/0.5 mL Peg-Intron Redipen) with dials that allow for dosing adjustments (Schering Corporation; Merck & Co.). PEG-IFN-α-2a (Pegasys; Genentech/Roche, San Francisco, CA) contains a larger, ''branched'' 40-kDa PEG moiety. PEG-IFN-α-2a is given at a dose of 180 μg/1.73 m^2 weekly subcutaneously and is available either as prefilled syringes or as vials (180 μg/mL and 180 μg/0.5 mL). PEG-IFN-α-2a does not require reconstitution with diluents. Dosing of these PEG-IFNs is different and may be differentially efficacious (119–122), although one has not conclusively and consistently demonstrated superiority. Both should be given in combination with ribavirin at a dose of 15 $mg \cdot kg^{-1} \cdot day^{-1}$ PO divided twice daily. The recommended length of therapy is 48 weeks of treatment for genotypes 1 or 4 and 24-week duration of treatment for genotypes 2 or 3 in children (1A; A1∗). If HCV RNA does not become undetectable by 24 weeks, there is also no evidence that prolonged treatment improves clinical outcome (ie, cirrhosis, HCC, SVR) (123).

SIDE EFFECTS OF MEDICATIONS AND MONITORING FOR ADVERSE EVENTS

IFN-α and ribavirin are powerful medications that are associated with multiple potential side effects and adverse events that affect quality of life (124,125). A thorough understanding of side effects is essential to intervene in a timely fashion and to avoid severe adverse events. Caretakers need to educate the patient and family on the necessary monitoring for side effects. Two large multicentered trials reported on adverse events due to PEG-IFN-α and ribavirin in pediatric HCV: a North American study that used PEG-IFN-α-2a in 114 patients (102) and a European/North American study that used PEG-IFN-α-2b in 107 patients (105). Furthermore, a recent study from Egypt analyzed the safety of PEG IFN-α-2a and ribavirin in the first 12 weeks of therapy in 30 pediatric patients with HCV (126). The incidence of side effects associated with PEG-IFN-α and ribavirin therapy for pediatric CHC is shown in Table 7, and recommendations on monitoring for side effects are outlined in Table 8. Constitutional symptoms are almost universal in children undergoing therapy. These symptoms include fever, fatigue, myalgias, arthralgias, headaches, and nausea. With the exception of nausea, these constitutional complaints are predominantly side effects of IFN-α. The constitutional symptoms are usually most severe within 24 hours of the IFN injection, and many symptoms will wane or resolve after the first few months of therapy (104,124).

The pediatric population is uniquely susceptible to deficits in growth in both weight and height while receiving PEG-IFN-α and ribavirin. Both PEG-IFN-α and ribavirin can be associated with anorexia, nausea, and subsequent weight loss. In the preliminary study by Abdel-Aziz et al (126), 63% of patients showed significant reduction in body weight at weeks 4 and 12, with only 17% of patients regaining their original weight by week 12. The European study analyzed growth parameters and found that weight loss was common, with most patients experiencing compensatory weight gain after completion of treatment (105). A ribavirin dose adjustment was recommended for weight loss of ≥10% and

TABLE 7. Percentage of patients with adverse events during PEG-IFN/treatment

Adverse event	Schwarz et al, North America, PEG-IFN-α-2a, RBV, n = 55 (102)	Wirth et al, Europe/United States, PEG-IFN-α-2b, RBV, n = 107 (105)	Abdel-Aziz et al,* Egypt, PEG-IFN-α-2a, RBV, n = 30 (126)
Constitutional			
Fever, ''flu-like''	91	80	77
Fatigue	27	30	17
Headache	62	62	47
Anorexia	13	29	27
Myalgia/arthralgia	36	17	10
Gastrointestinal			
Nausea	—†	18	27
Vomiting	—†	27	20
Decreased weight	—	19	76
Blood/lymphatic system			
Neutropenia	27	33	56
Anemia	—	11	46
Neuropsychiatric			
Depressed mood/depression	4	4	—
Irritability‡	31	37	—
Insomnia/trouble sleeping	11	3	—
Cutaneous			
Injection site reaction	45	29	—
Rash	20	—	—
Alopecia	—	17	—

PEG-IFN = pegylated interferon; RBV = ribavirin.
* For the present study only, the side effect profile was based on first 12 weeks of therapy.
† Gastrointestinal symptoms (nausea, emesis, diarrhea or abdominal pain): 56% in this study.
‡ Includes irritability, anxiety, nervousness, agitation, restlessness, mood alteration, affective lability, mood alteration.

TABLE 8. Recommendations for monitoring during therapy

Laboratory test to be monitored	Obtain test on following wk of therapy
CBC with differential, absolute neutrophil count	0, 1, 2, 4, 8, 12 and every 4–8 wk thereafter
Hepatic panel, glucose	0, 1, 2, 4, 8, 12 and every 4–8 wk thereafter
TSH/total T4	0, 12, 24, 36, 48
Urine HCG (for female patients 13 y or older)	0, 24
Prothrombin time	0; only repeat if clinically indicated
Urinalysis	0; only repeat if clinically indicated
HCV RNA	0, 24, 48, 72

CBC = complete blood cell; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; TSH = thyroid-stimulating hormone.

a PEG-IFN-α adjustment for a BMI decrease of ≥10%. With regard to growth in height, inhibition of growth velocity was observed in 70% of patients. Growth velocity increased after treatment completion, and at 24-week follow-up, the mean height percentile of 44.3% was slightly below the baseline height percentile of 50.9%. Long-term follow-up of growth parameters is necessary to determine whether the growth inhibition is temporary or long-lasting.

Bone marrow suppression induced by IFN-α constitutes the next most common toxicity after constitutional symptoms, occurring in approximately one third of treatment recipients (102,105). The bone marrow toxicity is associated with depressed levels of total white cell and absolute neutrophil counts, and, to a lesser extent, platelets and red cells. The neutropenia usually reaches a sustained nadir by 8 weeks of therapy and returns to baseline within weeks after cessation of therapy (102,126). In the 2 larger studies of IFN/ribavirin treatment for pediatric HCV, neutropenia was not associated with increased rates of bacterial infections. Dose reductions due to neutropenia occurred in 38% of patients in the North American study and 12% in the European study. Drug cessation due to neutropenia did not occur in either study.

IFN-α–induced reductions in platelet counts are usually asymptomatic and manifest within the first 8 weeks of therapy. Platelet levels then stabilize at this lower level for the duration of therapy (124). The mechanisms leading to the thrombocytopenia include suppression of megakaryopoiesis, platelet sequestration in capillaries (127), and immune-mediated thrombocytopenia (128,129). In the North American study, there was no significant thrombocytopenia, and in the European study 1 patient discontinued therapy at week 42 due to thrombocytopenia (platelet count 45,000 cells/mm^3).

Ribavirin is the main contributor to the onset of hemolytic anemia that most commonly manifests in the first month of treatment, reaching a nadir by week 4 (124,126). The mechanism of ribavirin-induced anemia is thought to involve ribavirin metabolites that impair antioxidant defenses and promote red cell oxidative damage (130). Dose reductions due to ribavirin-induced anemia occurred in 25% of patients who received PEG-IFN-α-2a (102) and 7% of patients who received PEG-IFN-α-2b (103). Recommendations for dose reductions due to bone marrow suppression are outlined for both forms of PEG-IFN in Supplementary Table 3 (*http://links.lww.com/MPG/A112*). Dose reduction was not associated with significant decreases in SVRs (102,105).

Dose adjustments may be insufficient to ameliorate marrow suppression, and interventions to treat severe or symptomatic anemia or neutropenia may be necessary (131). Available agents include Epogen (epoetin alfa, Amgen Inc, Thousand Oaks, CA) for anemia, granulocyte colony stimulating factor (GCSF) for neutropenia, and blood products. Epogen is a synthetic glycoprotein that acts similarly to endogenous erythropoietin (EPO) (132). It is a hormone produced by the kidneys that stimulates bone marrow erythropoiesis and in turn increases red cell counts, hemoglobin, and hematocrit levels (133). It has been found to be safe in the settings of cancer chemotherapy, HIV infection, and chronic renal failure (134–136). In the adult world, >85% of patients on PEG-IFN/ribavirin for HCV become anemic as endogenous EPO production is decreased (137,138); 20% to 25% of patients require dose reduction due to anemia and its symptoms (139). Interestingly, anemia is also linked to improved SVR and Epogen does not alter this phenomenon while ameliorating clinically significant anemia (135,138). This adjuvant therapy has been documented to enhance compliance to treatment regimens, improve rates of SVR, and improve quality of life (140–142); however, there is presently no approved EPO dosing for children in the context of therapy for CHC.

GCSF is a cytokine that is naturally produced by monocytes, activated T cells, fibroblasts, and endothelial cells. GCSF stimulates myeloid progenitor cells in bone marrow to induce cell proliferation, differentiation, and selected end-cell functional activation. It is approved for use in the setting of chemotherapy, induction/consolidation for AML, bone marrow transplantation, and severe chronic neutropenia (142). As neutropenia is the most common cause of PEG-IFN-α dose reduction (up to 25%) in adult CHC treatment, GCSF is effective in normalizing the absolute neutrophil count, is well tolerated, and improves SVR (143,144). As with Epogen, there is presently no approved GCSF dosing for children in the context of therapy for CHC. With respect to thrombocytopenia, bleeding has not been observed in patients with low platelet counts (<50,000) and dose modifications are rarely necessary. Clinical implications or advantages of platelet transfusion are both unclear (131). In the North American trial (102), hematopoietic growth factors were not allowed by the FDA and bone marrow suppression was easily managed by drug dose reduction, suggesting that such factors may not generally be necessary in treating children with CHC.

IFN-associated neuropsychiatric complications can be the most challenging to manage during treatment for CHC. IFN-α therapy has been associated with the initiation or worsening of underlying depression, anxiety, and suicidal ideation (145). It is essential to perform a baseline neuropsychiatric evaluation and specifically to survey for signs of depression before initiation of therapy. The onset of neuropsychiatric symptoms may not occur until 3 to 6 months into therapy (124). In the pediatric trials of CHC treatment, psychiatric or adverse events were reported in approximately one third of patients. In the North American study, irritability was reported in 31% and depression in 4% of patients. One patient required discontinuation of therapy due to a suicidal gesture (102). The European analysis included reports of nervousness, agitation, aggression, mood alteration, anxiety, depression, and affective lability (105). These events did not require dose adjustments or treatment cessation. Insomnia was reported by both groups and occurred in 3% to 11% of patients. It is recommended that whenever there is a concern for major depression or other psychiatric illnesses, the child should be referred to a psychiatrist for consideration of initiating antidepressant therapy or discontinuing IFN-α therapy. Discontinuation of therapy is strongly recommended in the setting of suicidal ideations or attempted suicide.

Thyroid abnormalities are the most common endocrinological adverse effect induced by IFN-α, occurring in 1% to 6% of adults treated with IFN-α (124). Thyroid abnormalities can occur at any time during therapy. Possible mechanisms of this thyroid dysfunction include direct inhibition of thyroid synthetic functions and secretion or development of antithyroid peroxidase or antithyroglobulin autoantibodies (146). The incidence of hypothyroidism in the pediatric CHC treatment trials was 2% to 3%, with the majority of these patients requiring thyroxine supplementation (102,105). Interestingly, the European study reported that 23% of patients had at least 1 abnormal thyroid-stimulating hormone (TSH) value during therapy. It is recommended that TSH and total T4 levels be measured every 3 months during therapy. The diagnosis of clinical hypothyroidism should be confirmed and subsequently managed by an endocrinologist. Similar to the autoimmune-mediated mechanism of thyroid injury, antibodies to the adrenal cortex or pancreatic islet cells can result in IFN-induced adrenal insufficiency or diabetes, respectively. New-onset type 1 diabetes mellitus was described in 1 patient receiving PEG-IFN-α and ribavirin (102).

A wide variety of occular complications can occur while receiving IFN-α therapy, such as retinopathy, optic neuritis, or neuropathy. In a large ophthalmological follow-up study of adults receiving IFN-α therapy, the retinopathy did not require cessation of therapy in the majority and the retinopathy resolved in all of the affected patients after completion of therapy (147). The North American pediatric trial performed surveillance eye exams and identified lesions in 3 patients (ischemic retinopathy with cotton wool spots, uveitis, transient monocular blindness) (148). Two of these patients were taken off of therapy with resolution of lesions in all. It is recommended that visual disturbances or complaints while receiving therapy warrant expeditious evaluation by an ophthalmologist.

Numerous cutaneous drug reactions can occur, including IFN-induced injection site reactions, dry skin, pruritus, and alopecia. Furthermore, ribavirin can induce a rash characterized by a diffuse inflammatory, erythematous, and maculopapular lesion that resolves after stopping ribavirin (149). The dry skin may mimic eczematous or psoriatic lesions (150). In the North American pediatric trial, a rash was documented in 20% of patients. The alopecia is more common in females (124) and was identified in 17% of patients in the pediatric European study. Finally, another potential complication of CHC treatment is that ribavirin (and to a lesser extent, IFN-α) is greatly teratogenic (151). Therefore, a urine human chorionic gonadotropin test is recommended for all of the females 13 years or older at baseline and should be repeated at 24 weeks of therapy. Ribavirin can cause teratogenesis when either partner is taking it. In sexually active teenagers, the use of and strict adherence to contraception is mandatory.

In summary, conscientious and thorough monitoring for potential adverse events is essential to optimize care of pediatric patients being treated for CHC. Overall, cessation of therapy due to adverse events is rare and side effects can be managed with appropriate referral care and treatment when necessary.

SPECIAL POPULATIONS AND OUTCOMES

Individualization of therapy warrants serious consideration under several circumstances. There is a paucity of both data and adequately powered clinical trials in these unique pediatric groups that may warrant therapy for HCV infection.

Young Age

Children who are younger than 3 years should generally not be treated, and treatment is not approved in this age group. In young children, HCV infection may still spontaneously resolve and adverse effects of IFN-α in extremely young children are not well elucidated, although spastic diplegia has been reported in infants treated with IFN-α for hemangiomas (152). There are no published studies or reports of treatment in children who are younger than 3 years. The decision to treat should consider several aspects including age, severity of disease, efficacy of the chosen therapy, its adverse effects, compliance to treatment, and willingness to be treated.

History of Substance Abuse

In general, patients are excluded from therapy if they have severe comorbid medical conditions that could compromise the tolerability of the drugs or interfere with compliance to the regimen. Adolescents and young adults with a history of substance abuse may fall into this category. There are no studies of CHC treatment in adolescents with a history of substance abuse; however, in a meta-analysis of 16 prospective studies from an adult cohort of 953 illicit drug users, it was found that they had comparable effectiveness and tolerability of therapy as to those in the general population (153). The estimated overall SVR and dropout rates in illicit drug users were 52% (95% CI 44%–60%) and 26% (95% CI 18%–35%), respectively. The rate of psychiatric severe adverse events that led to treatment discontinuation was 2% (95% CI 1%–3%). These prevalence rates were not significantly different from those reported in registration trials of treatment of chronic HCV that excluded illicit drug users from the study population (SVR 50% [95% CI 39%–61%]; dropout rate 26% [95% CI 12%–41%]; and psychiatric serious adverse events 2% [95% CI 0%–6%]). By subgroup analysis, active ongoing drug use negatively affected the rate of treatment success (39% [95% CI 30%–49%] vs 55% [95% CI 45%–64%]; $P = 0.02$) (153). Thus, adolescents with a history of substance abuse may be candidates for therapy on an individualized basis.

Psychiatric Illness

Treatment for CHC is well known to have multiple neuropsychiatric side effects including depression, confusion, mania, psychosis, hallucinations, and suicidal ideation. There is also risk that a patient's known psychiatric disorder will flare or become unmanageable once therapy is initiated. Psychoeducation groups have shown promise for preparing patients with chronic medical illness to anticipate and endure intensive medical treatment that has substantial psychiatric side effects (154). The goal is to aid patients to overcome barriers to treatment, particularly psychosocial problems, because available CHC treatments have become increasingly effective. Clearance by an appropriately trained psychiatrist for therapy is advisable before commencing treatment. Ongoing psychiatric evaluation and therapy are appropriate during CHC treatment, allowing for either prompt intervention or discontinuation of treatment should severe neuropsychiatric side effects develop.

Juvenile Detention Center Resident

Incarcerated adolescents or residents of detention centers who have CHC are another special population. Often such individuals have lifestyles and behaviors that place them at risk for HCV infection. Again, there are no trials in the medical literature addressing this special population. Arguments in favor of treatment for CHC in these individuals include prominently that the patients are a captive audience and much more likely to be

compliant with medications, laboratory studies, and visits; however, these individuals are often not incarcerated for the entire length of time required for HCV treatment, and when released may not have the finances or resources to continue therapy.

Co-infection: HIV

Limited evidence is available presently regarding the timing, efficacy, and safety of PEG-IFN-α and ribavirin in children and adolescents coinfected with HIV and HCV. We know that HIV has a negative effect on the natural history of HCV infection. Coinfected HCV/HIV patients have higher rates of viral persistence, increased viral load, and a more rapid progression to end-stage liver disease. Thus, for many clinicians, this increased progression rate supports earlier and aggressive therapy for HIV/HCV coinfected children. Restoration and maintenance of immune function by the use of greatly active antiretroviral therapy reduce the negative effect of HIV on HCV infection, but the SVR to PEG-IFN-α and ribavirin therapy is 15% to 50% lower than in HCV-monoinfected individuals (155). Although there have been substantial reductions in morbidity and mortality in HIV-infected patients using greatly active antiretroviral therapy, liver-related deaths have become the leading cause of mortality. Given this lower treatment response rate, regardless of genotype, coinfected HCV/HIV patients including children should receive at least 48 weeks of treatment (156,157). No guidelines presently exist for the optimal regimen for HCV/HIV coinfected children. (158) Limited experience in the clinical management of this group and the lack of evidence to guide policy are barriers to achieving optimal care and treatment for this special population. If therapy for CHC is initiated, extremely close monitoring for adverse events is necessary.

Co-infection: HBV

HBV also has a negative effect on the natural history of HCV infection, as shown by adult retrospective and cross-sectional data. In a study in which the long-term outcome of infection acquired in childhood was assessed in patients coinfected with HBV and HCV after a median follow-up of 23 years, there was a low rate of progression to liver fibrosis, no liver failure, and a low development of HCC (159). If a decision is made to treat an HBV/HCV coinfected child, combination of PEG-IFN-α and ribavirin for a full course, independent of genotype, is recommended based upon adult data.

Patients With Hematological Disorders Who Have Undergone Multiple Blood Transfusions

The majority of children in this special population will have hemolytic conditions such as sickle cell anemia and thalassemia. The risk of acquiring HCV infection is dependent upon the number of units of blood exposure; however, these risks have declined with the introduction of universal HCV screening of blood products that began in the 1990s. The risk of hemolysis due to ribavirin makes combination therapy a complicated issue. Multiple transfusions are associated with hepatic iron overload, which complicates therapy for CHC and may accelerate the progression of cirrhosis and risk for HCC. Treatment may be effective but the issues of hemolysis with ribavirin, use of injections, and iron overload all need to be considered in the decision to treat (160).

Transplantation (Renal or Liver)

CHC remains the leading indication for liver transplantation in adults in the United States. After liver transplant, graft reinfection is almost universal and development of chronic HCV, cirrhosis, and death occurs in about one third of adult liver transplant recipients (161). Although rare in children, pediatric liver transplant recipients for end-stage liver disease due to CHC demonstrated patient and allograft survival rates of 72% and 55%, respectively, at 5 years. Following retransplantation, these rates decreased to 55% and 34%, respectively. Recipients were listed for retransplantation in 31%, and were retransplanted in 19% for HCV recurrence. A mean of 1.2 liver transplants was performed per patient for CHC. The median time between liver transplants for CHC was 290 days. The risk of HCV recurrence in pediatric OLT recipients is high and is associated with a high rate of retransplantation (162).

Pediatric recipients of kidney transplants with CHC are another unique population. Again, the prevalence is rare. Data in adults suggest that kidney transplant recipients with CHC have similar graft and patient survival outcomes as do recipients who do not have CHC (163). In general, antiviral therapy after renal transplant is not considered a safe option (164). Postrenal transplant use of IFN-α has limited efficacy and high cost. It increases the risk of irreversible renal graft rejection in 15% to 64% of cases (165,166) by promoting the cytotoxic action of T lymphocytes and monocytes, cytokine, and HLA antigen production (167). If a decision is made to treat a pediatric kidney or liver transplant recipient who has CHC, extremely close monitoring is mandatory for adverse events due to intolerance of the drugs used and an increased risk for graft rejection when IFN is administered.

Renal Disease (Dialysis)

HCV-infected hemodialysis patients have lower survival rates compared with HCV-positive patients without renal failure because they often present with comorbid diseases and co-infections. Treatment of HCV-positive hemodialysis patients is complex and difficult. Both nephrologists and hepatologists must closely monitor these patients. Patients with CHC on hemodialysis may receive standard or a reduced dose of IFN-α with or without the addition of low-dose ribavirin. IFN-α therapy is modestly effective for the treatment of CHC in patients with end-stage renal disease (168). Approximately one third of patients can achieve a SVR after conventional or PEG-IFN-α monotherapy. Treatment before renal transplantation is recommended because of the risk of increased graft rejection posttransplant.

Considerations for Patients Cirrhotic at Presentation

A meta-analysis of 45 studies concluded that anti-HCV treatment in cirrhotic adult patients was less effective than in noncirrhotic patients (169). Viral eradication reduced the risk of liver complications and improved survival in noncirrhotic patients. Based on both effectiveness and tolerability, therapy has a significantly beneficial effect in patients with compensated cirrhosis, whereas decompensated patients must weigh the risks versus the benefits of treatment. If treatment is to be undertaken in such patients, a low accelerating dose protocol may aid in successfully treating these patients (170). Using this approach, an ETR of 46% and SVR of 24% in patients with advanced disease were achieved. Specifically, the ETR was 30% and SVR 13% in genotype 1, but 82% and 50%, respectively, in nongenotype 1.

OUTCOME OF THERAPY

There are several possible outcomes of HCV therapy. To compare different treatment regimens, it is imperative that standard definitions of outcomes are used (Table 9). Each outcome has been

TABLE 9. Treatment definitions

Rapid virological response	Undetectable serum HCV RNA (<50 IU/mL) after 4 wk of treatment
Early virological response	Undetectable or at least a 2 log decrease in serum HCV RNA from baseline level after 12 wk of treatment
End-of-treatment response	Undetectable serum HCV RNA (<50 IU/mL) at the conclusion of treatment
Sustained virological response	Undetectable serum HCV RNA (<50 IU/mL) 24 wk after the end of treatment
Partial response	Decrease in serum HCV RNA level but still detectable HCV RNA level at 24 wk of treatment
Nonresponse	Detectable serum HCV RNA at 24 wk of treatment without any significant decrease in serum HCV RNA level
Relapse	Detection of serum HCV RNA after an end-of-treatment response had been achieved

HCV = hepatitis C virus.

found to have specific prognostic significance. The interplay between viral dynamics and the host immune response determines viral persistence and the success of treatment. Rapid virological response (RVR) is now considered the strongest predictor of SVR in patients with HCV undergoing antiviral treatment. Patients with an RVR may achieve an SVR using a shorter duration of antiviral treatment. The goal of treatment is to obtain an SVR once therapy is discontinued. Genotype, age, viral load, fibrosis score, and compliance with therapy all affect the likelihood of achieving an SVR. Two large multicenter studies have investigated the use of combination PEG-IFN-α and ribavirin for the treatment of CHC in children. In a multicenter (European and American) open label study, Wirth et al (105) evaluated the efficacy and safety of PEG-IFN-α-2b and ribavirin in 107 naïve-to-treatment children (3–17 years of age) with CHC and compensated liver disease. Subjects with genotype 2 or 3 with a low viral load (<600,000 IU/mL) were treated for 24 weeks, whereas children infected with genotype 1 or 4 and genotype 3 with a high viral load (>600,000 IU/mL) received 48 weeks of therapy. The primary endpoint was a SVR 24 weeks following therapy. Secondary endpoints were RVR and EVR. Results demonstrated a high SVR of 90% in genotype 2 and 3, and 53% for children with genotype 1. As anticipated, in genotype 1, RVR and EVR predicted SVR, and subjects with a low viral load had a greater SVR than subjects with a high viral load. Twelve percent of relapses were in children with genotype 1. At the end of treatment, 77% of subjects with elevated ALT at baseline displayed ALT normalization that was associated in 79% of cases with SVR. The other large trial evaluated the use of PEG-IFN-α-2a with and without ribavirin for chronic HCV. The PEDS-C trial was a randomized controlled trial of PEG-IFN-α and ribavirin or placebo in children 5 to 17 years old with CHC (n = 114) (102). SVR was achieved in 53% of children treated with PEG-IFN-α and ribavirin combination therapy compared with 21% of children who received PEG-IFN-α and placebo therapy. Children with HCV genotype 1 had a 47% response rate with PEG-IFN-α/ribavirin and 17% on monotherapy.

FUTURE THERAPIES AND AREAS OF RESEARCH FOCUS

Despite significant advances in the therapies available for treating HCV infection in adults, little to no data are available on the use of these emerging therapies for CHC in children. The goal of this section is to provide an outline for the therapies that have been recently approved or are in phase III trials for adults and in which there are no data in children. There are multiple targets for these newer therapies, outlined in Table 10 (171–173). Recently 2 NS3/4a protease inhibitors were approved by the FDA for use in adults with CHC. These medications are combined with PEG-IFN-α and ribavirin and specifically target genotype 1 virus. In treatment naïve individuals, sustained viral response rates of up to 80% have been demonstrated (174,175). These medications are the first direct-acting antivirals against HCV and show tremendous promise in the treatment of the most recalcitrant virus. They merit investigation in children and adolescents; however, protease inhibitors have not been studied in children and there are no published pharmacokinetic data or pediatric safety data. Thus, protease inhibitors should only be used in children in the context of a clinical trial (2B; CIII). Further advances in direct-acting antivirals offer the potential for treatment protocols for CHC exclusive of IFN-α and will merit investigation in children given the growth and developmental issues of IFN-α in children.

At least 2 polymorphisms in the IL28B receptor have been shown to have a predictive value in adults in regards to the response to PEG-IFN-α and ribavirin (176). To date, there are no published studies of IL28B receptor polymorphisms and response to treatment in children. The predictive value of IL28B receptor polymorphisms should be studied in children infected with HCV

TABLE 10. Therapeutic targets for HCV

Mechanism	Categories
Block cellular entry of the virus	Neutralizing antibody, SR-B1 inhibitor
Inhibit or interfere with protein synthesis	NS3/4a: protease inhibitor
Inhibit or interfere with genome replication	NS5B polymerase nucleos(t)ide and nonnucleoside analogs, NS5A inhibitors, NS4B, miR-122, cyclophilins, HMG CoA, siRNAs
Inhibit or interfere with assembly and secretion	Glucosidases, LDL pathway blockers
Other mechanisms	Immunomodulators, antifibrotic agents, new interferons

HCV = hepatitis C virus; LDL = low-density lipoprotein; siRNA = silencing RNA.

who are undergoing IFN-α–based treatment (2B; CIII). Interestingly, this polymorphism does not appear to influence the response to triple therapy with PEG-IFN-α, ribavirin, and protease inhibitors (174,175). Thus, it may not prove to be of use with the development of newer therapies.

An important area for the prevention of HCV infection in children would be the prevention of perinatal transmission. With the development of new therapies that target HCV, it is possible that some of the therapies may prove useful in the prevention of perinatal transmission, much like the dramatic effect of azidothymidine therapy and the perinatal transmission of HIV; however, the low rate of perinatal transmission will mandate that the therapies have an excellent safety profile. An extremely large study will be required to detect a significant reduction in the rate of perinatal transmission.

The working group has recommended the following areas of focus for research in pediatric HCV-related disease:

1. Research focusing on the interruption of vertical transmission could effectively eliminate the majority of the pediatric cases.
2. Development of an HCV vaccine would have the potential to significantly reduce adolescent transmission. Based on the previous experience with hepatitis B vaccination, this will need to target universal vaccination to be effective.
3. There is a significant need for the development of long-term epidemiological data focused on the long-term outcome of perinatal acquisition of HCV infection.
4. With the development of direct-acting antivirals, early inclusion of children in studies of pharmacokinetics and safety is needed to allow children to have early access to effective therapies.
5. Because adolescents with high-risk behaviors are at increased risk of acquiring HCV infection, investigations of the utility of point-of-care testing in this population are needed to determine whether counseling, access to treatment, and interventions for prevention can be effective. Furthermore, there is a need for research on the most effective education and interventions targeted at the entire adolescent population to reduce risk of HCV transmission.
6. Chronic HCV infection may lead to isolation and stigmatization of children and their families. There has not been any research in the effects of disclosure or nondisclosure and their role in the potential stigmatization of children and their families.
7. One of the unique aspects of HCV infection in children relates to growth and cognitive development. Many of the present therapies may have an effect on both of these issues. Studies of CHC outcome and treatment effect must include assessments of growth and cognitive issues of CHC in children to assist in decision making on the timing of therapy.

REFERENCES

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144:705–14.
2. Jhaveri R, Grant W, Kauf TL, et al. The burden of hepatitis C virus infection in children: estimated direct medical costs over a 10-year period. *J Pediatr* 2006;148:353–8.
3. Zou S, Tepper M, El Saadany S. Prediction of hepatitis C burden in Canada. *Can J Gastroenterol* 2000;14:575–80.
4. McQuillian GM, Kruszon-Moran D, Denniston MM, et al. Viral hepatitis. *NCHS Data Brief* 2010;27:1–8.
5. Chiquete E, Panduro A. Low prevalence of anti-hepatitis C virus antibodies in Mexico: a systematic review. *Intervirology* 2007;50:1–8.
6. Omland LH, Krarup H, Jepsen P, et al., DANVIR Cohort Study-Mortality in patients with chronic and cleared hepatitis C viral infection: a nationwide cohort study. *J Hepatol* 2010;53:36–42.
7. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the AASLD. *Hepatology* 2011;54:1433–44.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Brit Med J* 2008;336:924–6.
9. Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaenous and treatment-induced viral clearance. *Gastroenterology* 2003;125:80–8.
10. Mast EE, Hwang LY, Seto DS, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005;192:1880–9.
11. Yeung LT, To T, King SM, et al. Spontaneous clearance of childhood hepatitis C virus infection. *J Viral Hepatol* 2007;14:797–805.
12. Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. *Gastroenterology* 2006;131:478–84.
13. Murakami J, Okamoto M, Miyata H, et al. Evolution in the hypervariable region of hepatitis C virus in infants after vertical transmission. *Pediatr Res* 2000;48:450–6.
14. Farci P, Quinti I, Farci S, et al. Evolution of hepatitis C viral quasispecies and hepatic injury in perinatally infected children followed prospectively. *Proc Natl Acad Sci USA* 2006;103:8475–80.
15. Sullivan DG, Bruden D, Deubner H, et al. Hepatitis C virus dynamics during natural infection are associated with long-term histological outcome of chronic hepatitis C disease. *J Infect Dis* 2007;196:239–48.
16. Huang H, Shiffman ML, Cheung RC, et al. Identification of two gene variants associated with risk of advanced fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2006;130:1679–87.
17. Mosbruger TL, Dugga P, Goedert JJ, et al. Large-scale candidate gene analysis of spontaneous clearance of hepatitis C virus. *J Infect Dis* 2010;201:1371–80.
18. Bosi I, Ancora G, Mantovani W, et al. HLA DR13 and HCV vertical infection. *Pediatr Res* 2002;51:746–9.
19. Martinetti M, Pacati I, Cuccia M, et al. Hierarchy of baby-linked immunogenetic risk factors in the vertical transmission of hepatitis C virus. *Int J Immunopathol Pharmacol* 2006;19:369–78.
20. Bevilacqua E, Fabris A, Floreano P, et al. Genetic factors in mother-to-child transmission of HCV infection. *Virology* 2009;390:64–70.
21. Della Bella S, Riva A, Tanzi E, et al. Hepatitis C virus-specific reactivity of CD4+-lymphocytes in children born from HCV-infected women. *J Hepatol* 2005;43:394–402.
22. Ruiz-Extremera A, Munoz-Gamez JA, Salmeron-Ruiz MA, et al. Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. *Hepatology* 2011;53:1830–8.
23. Waasdorp Hurtado C, Golden-Mason L, Brocato M, et al. Innate immune function in placenta and cord blood of hepatitis C-seropositive mother-infant dyads. *PLoS One* 2010;5:e12232.
24. Rumbo C, Fawaz RL, Emre SH, et al. Hepatitis C in children: a quaternary referral center perspective. *J Pediatr Gastroenterol Nutr* 2006;43:209–16.
25. Gonzalez-Peralta RP, Langham MR Jr, Andres JM, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2009;48:630–5.
26. Strickland DK, Jenkins JJ, Hudson MM. Hepatitis C infection and hepatocellular carcinoma after treatment of childhood cancer. *J Pediatr Hematol Oncol* 2001;23:527–9.
27. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology* 2009;136:138–48.
28. Madhoun MF, Fazili J, Bright BC, et al. Hepatitis C prevalence in patients with hepatocellular carcinoma without cirrhosis. *Am J Med Sci* 2010;339:169–73.
29. Forton DM, Thomas HC, Murphy CA, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology* 2002;35:433–9.
30. Rodriguez JR, Balistreri W, Haber B, et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol Nutr* 2009;48:341–7.

31. Nydegger A, Srivastava A, Wake M, et al. Health-related quality of life in children with hepatitis C acquired in the first year of life. *J Gastroenterol Hepatol* 2008;23:226–30.
32. Hepatitis C virus infection. American Academy of Pediatrics. Committee on Infectious Diseases. *Pediatrics* 1998;101(3 Pt 1):481–5.
33. Luban NL, Colvin CA, Mohan P, et al. The epidemiology of transfusion-associated hepatitis C in a children's hospital. *Transfusion* 2007;47:615–20.
34. Moriya T, Sasaki F, Mizui M, et al. Transmission of hepatitis C virus from mothers to infants: its frequency and risk factors revisited. *Biomed Pharmacother* 1995;49:59–64.
35. Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. Lombardy Study Group on Vertical HCV Transmission. *Lancet* 1995;345:289–91.
36. Okamoto M, Nagata I, Murakami J, et al. Prospective reevaluation of risk factors in mother-to-child transmission of hepatitis C virus: high virus load, vaginal delivery, and negative anti-NS4 antibody. *J Infect Dis* 2000;182:1511–4.
37. Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *Brit Med J* 1998; 317:437–41.
38. Conte D, Fraquelli M, Prati D, Minola E, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 2000;31:751–5.
39. Claret G, Noguera A, Esteva C, et al. Fortuny C.Mother-to-child transmission of hepatitis C virus infection in Barcelona, Spain: a prospective study. *Eur J Pediatr* 2007;166:1297–9.
40. Mast EE. Mother-to-infant hepatitis C virus transmission and breastfeeding. *Adv Exp Med Biol* 2004;554:211–6.
41. Yeung LT, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001;34:223–9.
42. Granovsky MO, Minkoff HL, Tess BH, et al. Hepatitis C virus infection in the mothers and infants cohort study. *Pediatrics* 1998; 102:355–9.
43. European Paediatric Hepatitis C Virus Network. A significant sex—but not elective cesarean section—effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis* 2005;192:1872–9.
44. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. The Vertical Transmission of Hepatitis C Virus Collaborative Study Group. *N Engl J Med* 1994;330:744–50.
45. Tajiri H, Miyoshi Y, Funada S, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. *Pediatr Infect Dis J* 2001; 20:10–4.
46. Steininger C, Kundi M, Jatzko G, et al. Increased risk of mother-to-infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. *J Infect Dis* 2003;187:345–51.
47. Minola E, Maccabruni A, Pacati I, et al. Amniocentesis as a possible risk factor for mother-to-infant transmission of hepatitis C virus. *Hepatol* 2001;33:1341–2.
48. Ducarme G, Ceccaldi PF, Bernuau J, et al. [Amniocentesis and viral risk (hepatitis B, C virus and HIV)]. *J Gynecol Obstet Biol Reprod (Paris)* 2009;38:469–73.
49. Ferrero S, Lungaro P, Bruzzone BM, et al. Prospective study of mother-to-infant transmission of hepatitis C virus: a 10-year survey (1990–2000). *Acta Obstet Gynecol Scand* 2003;82:229–34.
50. Shiraki K, Ohto H, Inaba N, et al. Guidelines for care of pregnant women carrying hepatitis C virus and their infants. *Pediatr Int* 2008; 50:138–40.
51. Plunkett BA, Grobman WA. Routine hepatitis C virus screening in pregnancy: a cost-effectiveness analysis. *Am J Obstet Gynecol* 2005;192:1153–61.
52. Haley RW, Fischer RP. Commercial tattooing as a potentially important source of hepatitis C infection: Clinical epidemiology of 626 consecutive patients unaware of their hepatitis C serologic status. *Medicine (Baltimore)* 2001;80:134–51.
53. Jara P, Resti M, Hierro L, et al. Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. *Clin Infect Dis* 2003;36:275–80.
54. Ackerman Z, Ackerman E, Paltiel O. Intrafamilial transmission of hepatitis C virus: a systematic review. *J Viral Hepat* 2000;7:93–103.
55. Mohamed MK, Magder LS, Abdel-Hamid M, et al. Transmission of hepatitis C virus between parents and children. *Am J Trop Med Hyg* 2006;75:16–20.
56. Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? *Hepatology* 2010;52:1497–505.
57. Ketzinel-Gilad M, Colodner SL, Hadary R, et al. Transient transmission of hepatitis C virus from mothers to newborns. *Eur J Clin Microbiol Infect Dis* 2000;19:267–74.
58. Ceci O, Margiotta M, Marello F, et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. *J Pediatr Gastroenterol Nutr* 2001;33:570–5.
59. Shebl FM, El-Kamary SS, Saleh DA, et al. Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. *J Med Virol* 2009;81:1024–31.
60. Rerksuppaphol S, Hardikar W, Dore GJ. Long-term outcome of vertically acquired and post-transfusion hepatitis C infection in children. *J Gastroenterol Hepatol* 2004;19:1357–62.
61. Bortolotti F, Verucchi G, Camma C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* 2008;134:1900–7.
62. Casiraghi MA, De Paschale M, Romano L, et al. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. *Hepatology* 2004;39:90–6.
63. Iorio R, Giannattasio A, Sepe A, et al. Chronic hepatitis C in childhood: an 18-year experience. *Clin Infect Dis* 2005;41:1431–7.
64. Vogt M, Lang T, Frosner G, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. *N Engl J Med* 1999; 341:866–70.
65. Delgado-Borrego A, Healey D, Negre B, et al. Influence of body mass index on outcome of pediatric chronic hepatitis C virus infection. *J Pediatr Gastroenterol Nutr* 2010;51:191–7.
66. Delgado-Borrego A, Jordan SH, Negre B, et al. Reduction of insulin resistance with effective clearance of hepatitis C infection: results from the HALT-C trial. *Clin Gastroenterol Hepatol* 2010;8:458–62.
67. Cesaro S, Bortolotti F, Petris MG, et al. An updated follow-up of chronic hepatitis C after three decades of observation in pediatric patients cured of malignancy. *Pediatr Blood Cancer* 2010;55:108–12.
68. Page K, Hahn JA, Evans J, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *J Infect Dis* 2009;200:1216–26.
69. Serra MA, Escudero A, Rodriguez F, et al. Effect of hepatitis C virus infection and abstinence from alcohol on survival in patients with alcoholic cirrhosis. *J Clin Gastroenterol* 2003;36:170–4.
70. Wise M, Finelli L, Sorvillo F. Prognostic factors associated with hepatitis C disease: a case-control study utilizing U.S. multiple-cause-of-death data. *Public Health Rep* 2010;125:414–22.
71. Beech BM, Myers L, Beech DJ. Hepatitis B and C infections among homeless adolescents. *Fam Commun Health* 2002;25:28–36.
72. Murray KF, Richardson LP, Morishima C, et al. Prevalence of hepatitis C virus infection and risk factors in an incarcerated juvenile population: a pilot study. *Pediatrics* 2003;111:153–7.
73. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease, Control and Prevention. *MMWR Recomm Rep* 1998;47 (RR-19):1–39.
74. England K, Pembrey L, Tovo PA, et al. Excluding hepatitis C virus (HCV) infection by serology in young infants of HCV-infected mothers. *Acta Paediatr* 2005;94:444–50.
75. Polywka S, Pembrey L, Tovo PA, et al. Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. *J Med Virol* 2006;78:305–10.
76. American Academy of Pediatrics. *2006 Report of the Committee on Infectious Diseases, 27th ed. Hepatitis C*. Elk Grove Village, IL: American Academy of Pediatrics; 2006: 355–359.
77. de Leuw P, Sarrazin C, Zeuzem S. How to use virological tools for the optimal management of chronic hepatitis C. *Liver Int* 2011;31 suppl 1:3–12.

78. Mukherjee S, Lin J, Bronze MS. Hepatitis C virus (HCV) assays are used to evaluate for HCV infection. *Medscape* 2011; 1996209.
79. Lee SR, Yearwood GD, Guillon GB, et al. Evaluation of a rapid, point-of-care test device for the diagnosis of hepatitis C infection. *J Clin Virol* 2010;48:15–7.
80. Lee SR, Kardos KW, Schiff E, et al. Evaluation of a new, rapid test for detecting HCV infection, suitable for use with blood or oral fluid. *J Virol Methods* 2011;172:27–31.
81. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335–74.
82. Halfon P, Bourliere M, Ouzan D, et al. A single IL28B genotype SNP rs12979860 determination predicts treatment response in patients with chronic hepatitis C Genotype 1 virus. *J Gastroenterol Hepatol* 2011; 23:931–5.
83. Gruppioni E, Vasuri F, Fiorentino M, et al. Real-time quantitative assay for routine testing of HCV RNA in formalin-fixed, paraffin-embedded liver samples. *Diag Mol Pathol* 2009;18:232–323.
84. Guido M, Rugge M, Jara P, et al. Chronic hepatitis C in children: the pathological and clinical spectrum. *Gastroenterology* 1998;115: 1525–9.
85. Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? *Hepatology* 2010;52:1497–505.
86. Larzo MR, Poe SG. Adverse consequences of tattoos and body piercings. *Pediatr Ann* 2006;35:187–92.
87. Daniel AR, Shehab T. Transmission of hepatitis C through swapping body jewelry. *Pediatrics* 2005;116:1264–5.
88. Baizhanova Z, Ignatova TM, Nekrasova TP. [Metabolic syndrome and insulin resistance in patients with chronic hepatitis C]. *Terapevticheskii arkhiv* 2010;82:51–6.
89. Hwang SJ, Lee SD. Hepatic steatosis and hepatitis C: Still unhappy bedfellows? *J Gastroenterol Hepatol* 2011;26(suppl 1):96–101.
90. Peters MG, Terrault NA. Alcohol use and hepatitis C. *Hepatology* 2002;36 (5 suppl 1):S220–5.
91. Rose VL. AAP releases hepatitis C screening recommendations. *Amer Fam Phys* 1998;58:1218.
92. Pembrey L, Newell ML, Tovo PA. European paediatric hepatitis C virus network. Antenatal hepatitis C virus screening and management of infected women and their children: policies in Europe. *Eur J Pediatr* 1999;158:842–6.
93. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *Brit J Obstet Gynaecol* 2001;108:371–7.
94. European Paediatric Hepatitis C Virus Network. A significant sex—but not elective cesarean section—effect on mother-to-child transmission of hepatitis C virus infection. *J Inf Dis* 2005; 192:1872–9.
95. Lin HH, Kao JH, Hsu HY, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J Pediatr* 1995; 126:589–91.
96. Resti M, Bortolotti F, Azzari C, et al. Transmission of hepatitis C virus from infected mother to offspring during subsequent pregnancies. *J Pediatr Gastroenterol Nutr* 2000;30:491–3.
97. Mok J, Pembrey L, Tovo PA, et al. When does mother to child transmission of hepatitis C virus occur? *Arch Dis Child: Fetal Neonat Ed* 2005;90:F156–60.
98. NIH Consensus Statement on Management of Hepatitis C: 2002. NIH Consens State Sci Statements 2002; 19:1–46.
99. Camarero C, Ramos N, Moreno A, et al. Hepatitis C virus infection acquired in childhood. *Eur J Pediatr* 2008;167:219–24.
100. Goodman ZD, Makhlouf HR, Liu L, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *Hepatology* 2008;47:836–43.
101. Gonzalez-Peralta RP, Kelly DA, Haber B, et al., International Pediatric Hepatitis C Therapy GroupInterferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C in children: efficacy, safety, and pharmacokinetics. *Hepatology* 2005;42:1010–8.
102. Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. *Gastroenterology* 2011;140:450–8.
103. Wirth S, Lang T, Gehring S, et al. Recombinant alfa-interferon plus ribavirin therapy in children and adolescents with chronic hepatitis C. *Hepatology* 2002;36:1280–4.
104. Wirth S, Pieper-Boustani H, Lang T, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. *Hepatology* 2005;41:1013–8.
105. Wirth S, Ribes-Koninckx C, Calzado MA, et al. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. *J Hepatol* 2010;52:501–7.
106. Christensson B, Wiebe T, Akesson A, et al. Interferon-alpha and ribavirin treatment of hepatitis C in children with malignancy in remission. *Clin Infect Dis* 2000;30:585–6.
107. Lackner H, Moser A, Deutsch J, et al. Interferon-alpha and ribavirin in treating children and young adults with chronic hepatitis C after malignancy. *Pediatrics* 2000;106:E53.
108. Schwarz KB, Mohan P, Narkewicz MR, et al. Safety, efficacy and pharmacokinetics of peginterferon alpha2a (40 kd) in children with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2006;43:499–505.
109. Tsunoda T, Inui A, Etani Y, et al., Working Group for the Study of Pegylated Monotherapy for Children with Chronic Hepatitis C in the Japan Society of Pediatric HepatologyEfficacy of pegylated interferon-alpha2a monotherapy in Japanese children with chronic hepatitis C. *Hepatol Res* 2011;41:399–404.
110. Bekisz J, Schmeisser H, Hernandez J, et al. Human interferons alpha, beta and omega. *Growth Factors* 2004;22:243–51.
111. Feld J, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature* 2005;436:967–72.
112. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;343:1666–72.
113. Lindsay KL, Trepo C, Heintges T, et al., Hepatitis Interventional Therapy GroupA randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001;34:395–403.
114. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998;339:1485–92.
115. Poynard T, Marcellin P, Lee SS, et al. Randomized trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998;352:1426–32.
116. Lau JY, Tam RC, Liang TJ, et al. Mechanism of action of ribavirin in the combination treatment of chronic HCV infection. *Hepatology* 2002;35:1002–9.
117. Maag D, Castro C, Hong Z, et al. Hepatitis C virus RNA-dependent RNA polymerase (NS5B) as a mediator of the antiviral activity of ribavirin. *J Biol Chem* 2001;276:46094–8.
118. Crotty S, Maag D, Arnold JJ, et al. The broad-spectrum antiviral ribonucleoside ribavirin is an RNA virus mutagen. *Nat Med* 2000;6:1375–9.
119. Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. *Gastroenterology* 2010;138:116–22.
120. McHutchison JG, Lawitz EJ, Shiffman ML, et al., IDEAL Study TeamPeginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580–93.
121. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. *Gastroenterology* 2010;138:108–15.
122. Sporea I, Danila M, Sirli R, et al. Comparative study concerning the efficacy of Peg-IFN alpha-2a versus Peg-IFN alpha-2b on the early virological response (EVR) in patients with chronic viral C hepatitis. *J Gastrointestin Liver Dis* 2006;15:125–30.
123. Di Bisceglie AM, Shiffman ML, Everson GT, et al., HALT-C Trial InvestigatorsProlonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008;359:2429–41.
124. Sung H, Chang M, Saab S. Management of Hepatitis C antiviral therapy adverse events. *Curr Hepatitis Rep* 2011;10:33–40.
125. Foster GR. Quality of life considerations for patients with chronic hepatitis C. *J Viral Hepat* 2009;16:605–11.
126. Abdel-Aziz DH, Sabry NA, El-Sayed MH, et al. Efficacy and safety of pegylated interferon in children and adolescents infected with chronic hepatitis C: A preliminary study. *J Pharm Prac* 2011;24:203–10.

127. Yamane A, Nakamura T, Suzuki H, et al. Interferon-alpha-2b-induced thrombocytopenia is caused by inhibition of platelet production but not proliferation and endomitosis in human megakaryocytes. *Blood* 2008;112:542–50.
128. Pockros PJ, Duchini A, McMillan R, et al. Immune thrombocytopenic purpura in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 2002;97:2040–5.
129. Dourakis SP, Deutsch M, Hadziyannis SJ. Immune thrombocytopenia and alpha-interferon therapy. *J Hepatol* 1996;25:972–5.
130. DeFranceschi L, Fattovich G, Turrini F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; 31:997–1004.
131. Collantes RS, Younossi ZM. The use of growth factors to manage the hematologic side effects of PEG-interferon alfa and ribavirin. *J Clin Gastroenterol* 2005;39:S9–13.
132. Egrie JC, Dwyer E, Browne JK, et al. Darbepoetin alfa has a longer circulating half-life and greater in vivo potency than recombinant human erythropoietin. *Exp Hematol* 2003;31:290–9.
133. Adamson J. Erythropoietin, iron metabolism, and red blood cell production. *Semin Hematol* 1996;33:5–7.
134. Allon M, Kleinman K, Walczyk M, et al. Pharmacokinetics and pharmacodynamics of darbepoetin alfa and epoetin in patients undergoing dialysis. *Clin Pharmacol Ther* 2002;72:546–55.
135. Dieterich DT, Wasserman R, Bräu N, et al. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *Am J Gastroenterol* 2003;98:2491–9.
136. Sulkowski MS, Dieterich DT, Bini EJ, et al., for the HIV/HCV Coinfection Study GroupEpoetin alfa once weekly improves anemia in HIV/hepatitis C virus-coinfected patients treated with interferon/ribavirin: a randomized controlled trial. *J Acquir Immune Defic Syndr* 2005;39:504–6.
137. Van Vlerken LG, Van Soest H, Janssen MP, et al. Suboptimal endogenous erythropoietin response in chronic hepatitis C patients during ribavirin and PEG interferon treatment. *Eur J Gastroenterol Hepatol* 2010;22:1308–15.
138. Sievert W, Dore GJ, McCaughan GW, et al., CHARIOT Study GroupVirological response is associated with decline in hemoglobin concentration during pegylated interferon and ribavirin therapy in hepatitis C virus genotype 1. *Hepatology* 2011;53: 1109–17.
139. Afdhal NH, Dieterich DT, Pockros PJ, et al., Proactive Study GroupEpoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004;126:1302–11.
140. Pockros PJ, Shiffman ML, Schiff ER, et al., PROACTIVE Study GroupEpoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatol* 2004;40: 1450–8.
141. Shiffman ML, Salvatore J, Hubbard S, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. *Hepatology* 2007;46:371–9.
142. Cash WJ, Patterson K, Callender ME, et al. Adjuvant therapy used in conjunction with combination therapy for chronic hepatitis C improves sustained virus response rates in genotype 1 patients. *J Viral Hepat* 2010;17:269–73.
143. Ong JP, Younossi ZM. Managing the hematologic side effects of antiviral therapy for chronic hepatitis C: anemia, neutropenia, and thrombocytopenia. *Cleve Clin J Med* 2004;71:S17–21.
144. Sulkowski MS. Management of the hematologic complications of hepatitis C therapy. *Clin Liver Dis* 2005;9:601–16.
145. Al-Huthail YR. Neuropsychiatric side-effects of interferon alfa therapy for hepatitis C and their management: a review. *Saudi J Gastroenterol* 2006;12:59–67.
146. Hsieh MC, Yu ML, Chuang WL, et al. Virologic factors related to interferon-alpha-induced thyroid dysfunction in patients with chronic hepatitis C. *Eur J Endocrinol* 2000;142:431–7.
147. Mehta N, Murthy UK, Kaul V, et al. Outcome of retinopathy in chronic hepatitis C patients treated with peginterferon and ribavirin. *Dig Dis Sci* 2010;55:452–7.
148. Narkewicz MR, Rosenthal P, Schwarz KB, et al., PEDS-C Study GroupOphthalmologic complications in children with chronic hepatitis C treated with pegylated interferon. *J Pediatr Gastroenterol Nutr* 2010;51:183–6.
149. Veluru C, Atluri D, Chadalavada R, et al. Skin rash during chronic hepatitis C therapy. *Gastroenterol Hepatol* 2010;6:323–5.
150. Mistry N, Shapero J, Crawford RI. A review of adverse cutaneous drug reactions resulting from the use of interferon and ribavirin. *Can J Gastroenterol* 2009;23:677–83.
151. Ward RP, Kugelmas M. Using pegylated interferon and ribavirin to treat patients with chronic hepatitis C. *Am Fam Phys* 2005;72:655–62.
152. Barlow CF, Priebe CJ, Mulliken JB, et al. Spastic diplegia as a complication of interferon α-2a treatment of hemangiomas of infancy. *J Pediatr* 1998;132:527–30.
153. Zanini B, Covolo L, Donato F, et al. Effectiveness and tolerability of combination treatment of chronic hepatitis C in illicit drug users: meta-analysis of prospective studies. *Clin Ther* 2010;32:2139–59.
154. Hong BA, North CS, Pollio DE, et al. The use of psychoeducation for a patient with hepatitis C and psychiatric illness in preparation for antiviral therapy: a case report and discussion. *J Clin Psychol Med Settings* 2011;18:99–107.
155. Tural C, Galeras JA, Planas R, et al. Differences in virological response to pegylated interferon and ribavirin between hepatitis C virus (HCV)-monoinfected and HCV-HIV-coinfected patients. *Antivir Ther* 2008; 13:1047–55.
156. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep* 2009;58:1–166.
157. Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS* 2007;21:1073–89.
158. England K, Thorne C, Pembrey L, et al. Policies and practices for the clinical management of HIV/HCV coinfected children in Europe: an epidemiological survey. *Eur J Pediatr* 2009;168:915–7.
159. Zampino R, Marrone A, Merola A, et al. Long-term outcome of hepatitis B and hepatitis C virus co-infection and single HBV infection acquired in youth. *J Med Virol* 2009;81:2012–20.
160. Harmatz P, Jonas MM, Kwiatkowski JL, et al. Safety and efficacy of pegylated interferon alpha-2a and ribavirin for the treatment of hepatitis C in patients with thalassemia. *Haematologica* 2008; 93:1247–51.
161. Ferrell LD, Wright TL, Roberts J, et al. Hepatitis C viral infection in liver transplant recipients. *Hepatology* 1992;16:865–76.
162. Barshes NR, Udell IW, Lee TC, et al. The natural history of hepatitis C virus in pediatric liver transplant recipients. *Liver Transplant* 2006; 12:1119–23.
163. Arango J, Arbelaez M, Henao J, et al. Kidney graft survival in patients with hepatitis C: a single center experience. *Clin Transplant* 2008; 22:16–9.
164. Pereira BJ, Natov SN, Bouthot BA, et al. Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. *Kidney Int* 1998;53:1374–81.
165. Schmitz V, Kiessing A, Bahra M, et al. Peginterferon alfa-2b plus ribavirin for the treatment of hepatitis C recurrence following combined liver and kidney transplantation. *Ann Transplant* 2007;12:22–7.
166. Baid S, Cosimi AB, Tolkoff-Rubin N, et al. Renal disease associated with hepatitis C infection after kidney and liver transplantation. *Transplantation* 2000;70:255–61.
167. Baid S, Tolkoff-Rubin N, Saidman S, et al. Acute humoral rejection in hepatitis C-infected renal transplant recipients receiving antiviral therapy. *Am J Transplant* 2003;3:74–8.
168. Liu CH, Kao JH. Treatment of hepatitis C virus infection in patients with end-stage renal disease. *J Gastroenterol Hepatol* 2011;26:228–39.
169. Vezali E, Aghemo A, Colombo M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis. *Clin Ther* 2010;32:2117–38.

170. Everson GT, Trotter J, Forman L, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *Hepatology* 2005;42:255–62.

171. Soriano V, Vispo E, Poveda E, et al. Directly acting antivirals against hepatitis C virus. *J Antimicrob Chemother* 2011;66:1673–86.

172. Vermehren J, Sarrazin C. New HCV therapies on the horizon. *Clin Microbiol Infect* 2011;17:122–34.

173. Lemon SM, McKeating JA, Pietschmann T, et al. Development of novel therapies for hepatitis C. *Antiviral Res* 2010;86:79–92.

174. Jacobson IM, McHutchison JG, Dusheiko G, et al., ADVANCE Study TeamTelaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405–16.

175. Poordad F, McCone J Jr, Bacon BR, et al., SPRINT-2 Investigators-Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011;364:1195–206.

176. Clark PJ, Thompson AJ, McHutchison JG. IL28B genomic-based treatment paradigms for patients with chronic hepatitis C infection: the future of personalized HCV therapies. *Am J Gastroenterol* 2011;106:38–45.