

HOSPITAL PHYSICIAN®

PEDIATRIC GASTROENTEROLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Pediatric Gastroenterology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in pediatric gastroenterology. Each manual reviews a topic essential to the current practice of pediatric gastroenterology.

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Hepatitis C Virus Infection

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Hepatitis C Virus Infection

Katherine Roache, BA, and Barbara A. Haber, MD

INTRODUCTION

Hepatitis C virus (HCV) infection affects an estimated 170 million individuals worldwide.¹ In the United States, it is estimated that at least 4 million adults and approximately 200,000 children are infected with HCV.² It is the most common cause of liver transplantation in the United States.

Our understanding of hepatitis C is still in its infancy. The virus was first described in 1989,^{3,4} and diagnostic techniques have improved over time, with the screening and diagnosis methods shifting from surrogate marker screening (eg, elevated alanine aminotransferase [ALT]) to antibody testing and finally now to polymerase chain reaction (PCR) testing and genotype identification. Because infection with HCV can progress silently to chronic liver damage, physicians should understand its natural history to know which patients to screen and which patients to treat. This article reviews diagnosis and treatment options for HCV infection and presents clinical vignettes to underscore key issues in clinical decision making around the disease.

THE HEPATITIS C VIRUS

Blood banks in the United States first began screening for the hepatitis B surface antigen (HBsAg) in 1972.^{5,6} However, screening for HBsAg as well as hepatitis A IgM did not completely limit new cases of post-transfusion hepatitis. Approximately 10% of transfusion recipients still contracted hepatitis, indicating that yet another virus must be causing hepatitis. Initially it was referred to as *non-A, non-B hepatitis* (NANBH). In 1989, many years of international research efforts culminated in the identification of a novel single-stranded, positive-sense, enveloped RNA virus obtained from blood samples of individuals with NANBH; this viral agent was named hepatitis C virus.^{3,4} Because HCV has a low concentration in blood and tissue samples, studying the virus has been challenging. However, the use of filtration techniques and highly concentrated virus-positive material has allowed particles 30 to 39 nm in diameter to be measured.⁷

The genome organization of HCV was determined to be unique enough to be given its own separate genus (Hepacivirus) by the International Committee of Taxonomy of Viruses in 1991, although there are many similarities between HCV and the flaviviruses and pestiviruses.^{8,9} Other members of the Flaviviridae family include the viral agents responsible for yellow fever and dengue. Much of our understanding of the HCV proteins can be attributed to sequence comparisons with proteins of known function in other members of the Flaviviridae family.

The hepatitis C viral genome consists of 9600 nucleotides that encode a polyprotein of approximately 3000 amino acids¹⁰ that forms structural and nonstructural peptides (**Figure**). Structural components form the nucleocapsid core and envelope proteins. The exact function of the nonstructural components is still under investigation. However, the leading hypothesis is that nonstructural components act to directly affect host cell machinery and may be involved in the transition from acute to chronic infection.^{11,12} Regions of the polyprotein that contain the envelope gene display hyper-variable regions. These regions induce rapid mutations and are the critical factor that allows the virus to evade the immune system.¹³ Untranslated regions (UTRs) of the viral genome that flank the polyprotein are essential to the viral translation and replication processes.^{11,14,15} Because these UTRs are highly conserved, they are the preferred target for molecular diagnostics.

Genome sequencing has also allowed HCV to be further classified into unique genotypes, and the identification of genotypes has allowed a better understanding of the global and local epidemiology of viral infection. There are 6 hepatitis C genotypes, which vary in distribution throughout the world. In the United States, genotypes 1, 2, and 3 are most common, with genotype 1 accounting for the majority of cases. In a study that determined the prevalence of HCV infection using serum samples from 21,241 persons who participated in the National Health and Nutrition Examination Survey III conducted from 1988 through 1994, 56.7% of infections were classified as genotype 1a, 17% as 1b, 3.5% as 2a, 11.4% as 2b, and 7.4% as 3a.¹⁶

The genotype is clinically significant. It does not