

# HOSPITAL PHYSICIAN®

## INFECTIOUS DISEASES BOARD REVIEW MANUAL

### STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Infectious Diseases Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in infectious diseases. Each manual reviews a topic essential to current practice in the subspecialty of infectious diseases.

### PUBLISHING STAFF

#### PRESIDENT, GROUP PUBLISHER

Bruce M. White

#### EDITORIAL DIRECTOR

Debra Dreger

#### SENIOR EDITOR

Bobbie Lewis

#### EDITOR

Tricia Faggioli

#### ASSISTANT EDITOR

Farrowh Charles

#### EXECUTIVE VICE PRESIDENT

Barbara T. White

#### EXECUTIVE DIRECTOR OF OPERATIONS

Jean M. Gaul

#### PRODUCTION DIRECTOR

Suzanne S. Banish

#### PRODUCTION ASSISTANT

Nadja V. Frist

#### ADVERTISING/PROJECT DIRECTOR

Patricia Payne Castle

#### SALES & MARKETING MANAGER

Deborah D. Chavis

#### NOTE FROM THE PUBLISHER:

This publication has been developed without involvement of or review by the American Board of Internal Medicine.

## Hepatitis C Virus Infection

### Contributors:

#### Varsha Moudgal, MD

*Assistant Professor of Medicine*

*Wayne State University*

*Detroit, MI*

*Infectious Diseases Faculty*

*St. Joseph Mercy Hospital*

*Ann Arbor, MI*

#### A. Rebecca Daniel, MD

*Department of Internal Medicine*

*St. Joseph Mercy Hospital*

*Ann Arbor, MI*

## Table of Contents

Introduction .....	3
Virology.....	3
Natural History.....	3
Transmission.....	4
Laboratory Testing.....	5
Clinical Manifestations.....	7
Treatment.....	8
References.....	11

Cover Illustration by Kathryn K. Johnson

Copyright 2008, Turner White Communications, Inc., Strafford Avenue, Suite 220, Wayne, PA 19087-3391, www.turner-white.com. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, electronic, photocopying, recording, or otherwise, without the prior written permission of Turner White Communications. The preparation and distribution of this publication are supported by sponsorship subject to written agreements that stipulate and ensure the editorial independence of Turner White Communications. Turner White Communications retains full control over the design and production of all published materials, including selection of topics and preparation of editorial content. The authors are solely responsible for substantive content. Statements expressed reflect the views of the authors and not necessarily the opinions or policies of Turner White Communications. Turner White Communications accepts no responsibility for statements made by authors and will not be liable for any errors of omission or inaccuracies. Information contained within this publication should not be used as a substitute for clinical judgment.

# Hepatitis C Virus Infection

Varsha Moudgal, MD, and A. Rebecca Daniel, MD

---

## INTRODUCTION

---

Hepatitis C virus (HCV) is a major cause of liver disease, cirrhosis, and hepatocellular carcinoma (HCC) in many countries around the globe. HCV was discovered in 1989 and was found to be the cause of most cases of non-A, non-B hepatitis. The half-life of HCV is believed to be about 3 hours, and it is estimated that up to  $10^{12}$  virions are produced daily in an infected individual.<sup>1</sup> This is roughly 100-fold greater than the rate reported for HIV. It has been estimated that 50% to 85% of patients infected with HCV go on to develop chronic infection.<sup>2</sup> The Centers for Disease Control and Prevention (CDC) estimates that 4.1 million (1.6%) Americans have been infected with HCV, of whom 3.2 million are chronically infected. The high rate of error in the RNA-dependant RNA replication has resulted in tremendous genetic diversity, complicating vaccine development. Over the last decade, significant advances have been made in the treatment of chronic HCV. Patients with HCV now have a greater than 40% probability of viral eradication with therapy. Currently, there are several new agents in development that will likely improve treatment outcomes. In this article, we will review HCV virology, natural history, transmission, clinical manifestations, diagnostic testing, and management.

---

## VIROLOGY

---

HCV is the most common chronic RNA virus affecting humans. It is a highly mutating single-stranded RNA virus belonging to the family Flaviviridae. The HCV genome is comprised of approximately 9600 nucleotides. Upon infection, the viral RNA enters the cell. The viral gene expression occurs outside the nucleus and encodes a polyprotein. This polyprotein is cleaved into separate protein components by cellular and viral proteases. The viral RNA genome is replicated by an RNA-dependant RNA polymerase, which is highly error prone. This replication process along with the high rate of virion turnover results in a rapid accumulation of mutations in the viral genome. Hence, multiple HCV variants or

“quasispecies” exist in each infected host. The host is unable to produce an adequate response to each mutant, and this results in the development of chronic disease in up to 85% of infected individuals. In addition to this heterogeneity in individuals, variations in the HCV genome fall into a series of specific patterns that have been classified into genotypes. Studies indicate that there are up to 6 major genotypes, several of which are further differentiated into subtypes. Depending on the genomic region involved, HCV sequences in different genotypes may have a less than 60% nucleotide sequence identity. Within each genotype, strains are further subclassified into subtypes that have 75% to 85% nucleotide sequence identity. Genotypes tend to favor a geographical distribution, with genotype 1 accounting for 70% to 75% of all HCV infections in the United States. In contrast, genotype 4 infections are prevalent in Africa and the Middle East (**Table 1**). HCV genotype has been clearly linked to interferon treatment response, with genotype 1 associated with the poorest response to therapy and genotypes 2 and 3 associated with the best response to treatment.<sup>2</sup>

With currently available therapeutic options, many viral infections such as chronic hepatitis B and HIV are impossible to eradicate: the hepatitis B virus integrates its DNA into host genome and the HIV virus establishes latency in memory CD4 cells. HCV lacks the ability to integrate its genetic material into chromosomal DNA and with its inherently unstable RNA genome, lacks the mechanism of virologic latency. Unlike these other chronic viral infections, HCV can be eradicated from patients if prolonged suppression of viral replication can be achieved.

---

## NATURAL HISTORY

---

Human and animal models of HCV infection have demonstrated that HCV RNA can be detected in plasma within days of exposure.<sup>3</sup> Viremia usually peaks at 8 to 12 weeks and then drops to lower levels. In approximately 15% of patients, plasma HCV RNA becomes undetectable within a few months and remains undetectable indefinitely. Viremia becomes persistent in up to 85% of patients. The chance of early resolution appears