WHO/CDS/CSR/LYO/2003.? Hepatitis C

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Hepatitis C

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Hepatitis C - an introduction

Hepatitis is a general term meaning inflammation of the liver and can be caused by several mechanisms, including infectious agents. Viral hepatitis can be caused by a variety of different **viruses* such as hepatitis A, B, C, D and E. Since the development of **jaundice* is a characteristic feature of liver disease and not just viral hepatitis, a correct diagnosis can only be made by testing patients' **sera* for the presence of specific anti-*viral **antibodies*.

The first demonstration that most cases of transfusion-associated hepatitis were caused by neither hepatitis A *virus (HAV) nor hepatitis B *virus (HBV), the only two known human hepatitis *viruses at the time, came in 1975. This new form of disease was called non-A non-B hepatitis and the presumed etiologic agent, non-A non-B hepatitis *virus.[39, 74]

In 1989 the *virus responsible for most transfusion-associated non-A non-B hepatitis was identified and cloned, and named hepatitis C *virus (HCV).[19, 39, 74]

Hepatitis C is also called type C hepatitis, Parenterally transmitted non-A non-B hepatitis (PT-NANB), Non-B transfusion-associated hepatitis, Posttransfusion non-A non-B hepatitis, HC.

* refer to glossary

What causes the disease?

Hepatitis C is caused by infection with the hepatitis C **virus* (HCV), an enveloped, single stranded, positive sense RNA **virus*.[39, 52, 74]

The *virus infects liver cells and can cause severe inflammation of the liver with long-term complications.[96]

The onset of disease is usually insidious, with anorexia, vague abdominal discomfort, nausea and vomiting, fever and fatigue, progressing to *jaundice in about 25% of patients, less frequently than hepatitis B.[5, 41, 55, 94, 96]

Of those exposed to HCV, about 40% recover fully, but the remainder, whether they have symptoms or not, become chronic *carriers. Of these, 20% develop *cirrhosis. Of those with *cirrhosis, up to 20% develop liver cancer.[5, 96]

How is HCV spread?

Hepatitis C *virus is usually spread by sharing infected needles with a *carrier, from receiving infected blood, and from accidental exposure to infected blood. Some people acquire the infection through nonparenteral means that have not been fully defined, but include sexual transmission in persons with high risk behaviours, although transmission of HCV Is less common than that of HBV and HIV.[11, 41, 96]

HCV is not spread by breast feeding, sneezing, coughing, hugging, sharing eating utensils or drinking glasses, other normal social contact, food or water.[56]

Mother-to-baby transmission is now well documented, but uncommon.[39] Needs a high viraemia (>1 log$^{\uparrow}$) as found in HIV co-infection[5]

A person who has hepatitis C can still get other types of hepatitis, such as hepatitis A or hepatitis B.[56]

Who is susceptible to infection?

Susceptibility is general.
Humans and chimpanzees are the only known species susceptible to infection, with both species developing similar disease.[101]

Where is HCV a problem globally?

HCV infections are common worldwide. It is estimated that about 3% of the world's population have HCV. There are about 4 million *carriers in Europe alone.[96]

When is hepatitis C contagious?

HCV positive persons are those who:
- have anti-HCV antibodies in their blood,

and/or - have HCV RNA or HCV core antigen detected in their blood

All HCV positive persons are considered potentially infectious. Imprudent contact with their blood can lead to HCV infections.

HCV positive persons should :
- not donate blood, body organs, tissue, or semen
- not share toothbrushes or razors
- keep cuts and skin lesions covered

The presence of anti-HCV *antibodies cannot be confirmed until 12-27 weeks after exposure creating a window period of seronegativity and potential infectivity.[95]

HCV RNA, as detected by *polymerase chain reaction (PCR) or HCV core antigen detection, becomes positive within days of inoculation, PCR has become the method of choice for early diagnosis, core antigen detection is currently under evaluation.[28, 51, 92]

There are no available vaccines for HCV. Why?

Currently there is no *vaccination against hepatitis C. One reason being that the *virus comes in many forms and constantly mutates leading to “swarms” of closely related viral genomic sequences (referred to as quasi-species).[7, 73, 96]

The hepatitis C virus

Although its means of transmission are well documented, the hepatitis C *virus itself still remains an enigma.

The hepatitis C *virus is an enveloped RNA *virus with a diameter of about 50 nm, classified as a separate genus (Hepacivirus) within the Flaviviridae family. The *genomic organization and sequence of HCV resembles that of the pestiviruses and flaviviruses.[39, 52, 74, 97]

The reservoir of HCV is man, but the *virus has been transmitted experimentally to chimpanzees.[39, 41, 52, 74, 97]

The *genome of HCV is highly mutable. Because HCV is an RNA *virus and lacks efficient proofreading ability as it replicates, *virions infecting humans undergo evolution with time, giving rise to the notion that HCV persists as a collection of *virus quasispecies. By constant mutation, HCV may be able to escape host immunologic detection and elimination.[41, 52, 74, 97]

HCV undergoes rapid mutation in a hypervariable region of the *genome coding for the envelope *proteins and escapes immune surveillance by the host. As a consequence, most HCV-infected people develop chronic infection.

HCV also knocks out the host's Innate Immunity.[30]

Mutations are not randomly distributed along the *genome, but are most pronounced within a hypervariable region located near the N-terminus of E2. This region maps at a surface loop of the E2 *protein containing a B-cell *epitope that undergoes *antigenic evolution over time.[52, 74, 97]

HCV is highly heterogeneous. Eleven HCV *genotypes with several distinct subtypes have been identified throughout the world. These diversities have distinct consequences: although different strains have not been shown to differ dramatically in their virulence or pathogenicity, different *genotypes vary in their responsiveness to *interferon/ribavirin combination therapy. Moreover, such heterogeneity hinders the development of *vaccines, since *vaccine *antigens from multiple *serotypes will probably be necessary for global protection.[39, 41, 52, 68, 74, 97]

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Electron Microscopy (EM) picture of the hepatitis C virion

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The hepatitis C virus life cycle

Very little is known about the replication cycle of HCV, because there is no in vitro cell culture system that is permissive for *virus replication.[74] However, progress has been made.[5, 39, 52]

HCV probably follows the replication strategy of other positive-strand RNA *viruses. The *virus enters the cell and is uncoated in the cytoplasm. The *viral *genome is transcribed to form a complementary negative-sense RNA molecule, which, in turn, serves as a template for the synthesis of progeny positive-strand RNA molecules. The newly translated polyprotein is cleared by a host-cell signalase as well as virus-specific non-structural proteins, NS-2 and NS-3. The *enzyme capable of performing both steps of RNA synthesis is the *virally encoded RNA-dependent RNA *polymerase NS5b.[23] The NS-3 of HCV also has helicase (unwindase) activity.

HCV replicates by a negative-strand RNA intermediate and has no *reverse transcriptase activity.[41, 97]

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HCV genotypes

HCV is classified into eleven major *genotypes (designated 1-11), many subtypes (designated a, b, c, etc.), and about 100 different strains (numbered 1,2,3, etc.) based on the *genomic sequence heterogeneity.[89]

The variability is distributed throughout the *genome. However, the non-coding regions at either end of the *genome (5'-UTR and 3'-UTR; UTR-untranslated region) are more conserved and suitable for *virus detection by PCR.[89]

The genes coding for the envelope E1 and E2 glyco*proteins are the most variable. Amino acid changes may alter the *antigenic properties of the *proteins, thus allowing the *virus to escape neutralizing *antibodies.[89]

*Genotypes 1-3 have a worldwide distribution. Types 1a and 1b are the most common, accounting for about 60% of global infections. They predominate in Northern Europe and North America, and in Southern and Eastern Europe and Japan, respectively. Type 2 is less frequently represented than type 1. Type 3 is *endemic in south-east Asia and is variably distributed in different countries. *Genotype 4 is principally found in the Middle East, Egypt, and central Africa. Type 5 is almost exclusively found in South Africa, and *genotypes 6-11 are distributed in Asia.[39, 58, 94, 103]

The influence of *viral *genotype in the pathogenesis of liver disease is still controversial. Environmental, genetic, and immunological factors may contribute to the differences in disease progression, so characteristic of HCV infection, observed among patients.[58]

The determination of the infecting *genotype is however important for the prediction of response to anti*viral treatment: *genotype 1 is generally associated with a poor response to *interferon alone, whereas *genotypes 2 and 3 are associated with more favourable responses.[58] The current gold standard of therapy - pegylated interferon-α in combination with ribavirin – significantly improves response for all genotypes. [65]

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Morphology and physicochemical properties

HCV particles have a buoyant density of 1.24 g/cm^3 in CsCl, and a sedimentation coefficient of 200 S in sucrose gradients.[74]

The density of HCV in sucrose gradients has been measured between 1.08 and 1.11 g/ml. A lighter fraction of 1.04 to 1.06 g/ml appears to be due to the association of HCV with serum beta-lipoprotein. A denser fraction of about 1.17 g/ml in sucrose appears to correspond with noninfectious immune complexes of *virus and *antibody. The nucleocapsid of the virus was found to have a density in sucrose of 1.25 g/cm^3.[39, 74]

Genome and proteins

HCV contains a single-stranded, positive-sense RNA molecule of 9.6 kb with one long open reading frame coding for a large poly*protein of about 3000 *amino acids which undergoes co- and post*translational cleavage by host and *viral proteases to yield individual *viral *proteins.[23, 39, 41, 52, 74, 97]

The HCV *genome has been cloned in 1989.[19]

A highly conserved, 5'-un*translated region of about 340 *nucleotides precedes the *translation initiation *codon. There is also a 3'-un*translated region of variable length (consisting of a short, poorly conserved sequence (28-42 nucleotides), a poly(u)/polypyrimidine tract and a highly conserved 98-base element).[39, 41, 52]

The N-terminal quarter of the *genome encodes the core and structural *proteins. These consist of a non-glycosylated nucleic acid-binding nucleocapsid *protein (C) of about 190 *amino acids (about 21 kD) and one or possibly two membrane-associated glyco*proteins (E1 and E2/NS1) of about 190, respectively 370 *amino acids respectively (33 and 70 kD when glycosylated).[41, 52, 74, 97]

The glycosylated E1 and E2 molecules are anchored inside the *lumen of the *endoplasmic reticulum (ER). The C *protein remains on the cytosol side.[39]

The rest of the *genome encodes the nonstructural *proteins NS2-NS5.

The NS2 (250 *amino acids), NS3 (500 *amino acids), and NS4a *proteins interact to mediate the processing of the presumed NS region of the poly*protein. NS3 (500 *amino acids) is both a proteolytic cleavage *enzyme and a helicase, to facilitate unwinding of the *viral *genome for replication. NS5b is the RNA-dependent RNA *polymerase needed for *viral replication.[39, 41, 52, 74, 97]

NS *proteins have been localized to the membrane of the ER, suggesting that it is the site of poly*protein maturation and *viral particle assembly.[39, 97]

Little is known about the three dimensional structure of the HCV *proteins.[74]

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HCV coding organization

From: Houghton M. Hepatitis C viruses. In: Fields BN, Knipe DM, Howley PM, eds. Fields Virology, 3rd ed. Philadelphia, Lippincott - Raven, 1996:1035-1058, with permission.

Genetic organization of HCV genome. Cleavage site coordinates in the putative structural regions of isolates HCV-J, HCV-1, HCV-H, and HCV-1b are shown along with those in the putative nonstructural regions on HCV-H and HCV-1.[39]

Stability

HCV is inactivated by:[74]
- exposure to lipid solvents or detergents
- heating at 60°C for 10 h or 100°C for 2 min in aqueous solution
- formaldehyde (1:2000) at 37°C for 72 h
- ß-propriolactone
- UV irradiation

HCV is relatively unstable to:
- storage at room temperature
- repeated freezing and thawing

The disease

Hepatitis C is a major global public health problem. HCV infection is one of the main causes of *cirrhosis and HCC. HCV-related end stage liver disease is the leading reason for liver transplantation in the USA.

Acute HCV infection

The incubation period for acute hepatitis C averages 6 to 10 weeks.[41]

Most persons (~80%) who develop acute hepatitis C have no symptoms.[56]

The onset of disease is usually insidious, with anorexia, vague abdominal discomfort, nausea and vomiting, fever and fatigue, progressing to *jaundice in about 25% of patients, less frequently than hepatitis B.[5, 41, 55, 94]

Rapid, fulminant liver failure associated with HCV infection is a rare event.[39]

Probably as many as 70%-90% of infected people fail to clear the *virus during the acute phase of the disease and become chronic *carriers.[5, 52, 103]

Severity ranges from inapparent cases in approximately 75% of infections to rare fulminating, fatal cases.[41] Chronic liver disease with fluctuating or persistently elevated liver *enzymes is common, occurring after >60% of HCV infections in adults.[41, 52]

Of those with chronic liver disease, 5%-20% may develop *cirrhosis.

About 5% of infected persons may die from the consequences of long term infection (liver cancer or *cirrhosis).[94]

The course of acute hepatitis C is variable, although elevations in *serum *ALT levels, often in a fluctuating pattern, are its most characteristic feature. Normalization of *ALT levels might occur and suggests full recovery, but this is frequently followed by *ALT elevations that indicate progression to chronic disease.[39, 94]

After acute infection, 15%-25% of persons resolve their infection without sequelae.[94] Spontaneous elimination of the *virus is rare.

Chronic HCV infection

Chronic hepatitis can be defined as a continuing disease without improvement for at least six months.

Chronic hepatitis is not a single disease, but rather a complex clinico-pathological syndrome with multiple causes, varying stages of necro-inflammatory and sclerosing liver damage, different prognoses and responses to treatment.[3]

Most persons (60%-80%) who have chronic hepatitis C have no symptoms.[56]

Chronic HCV infection develops in 75%-85% of persons, with persistent or fluctuating *ALT elevations indicating active liver disease developing in 60%-70% of chronically infected persons. No clinical or *epidemiologic features among patients with acute infection have been found to be predictive of either persistent infection or chronic liver disease.[94]

An important clinical feature of infection with HCV is the high rate of chronic hepatitis and slowly progressive lifelong infection, which may lead to *cirrhosis and liver failure in about 10%-20% of persons with chronic hepatitis C.[41, 94, 101]

HCV-associated *cirrhosis leads to liver failure and death in about 20%-25% of cirrhotic cases. HCV-associated *cirrhosis now represents a leading indication for liver transplantation.[39]

Chronic HCV infection appears to be associated with the development of hepatocellular *carcinoma (HCC) in 1%-5% of persons with chronic hepatitis C.[5, 39, 41, 94, 101]

Development of HCC is rare in patients with chronic hepatitis C who do not have *cirrhosis.[5]

Chronic infection is often not symptomatic, until evidence of liver failure becomes clinically apparent. The rate of progression to *cirrhosis is usually slow, with 20 or more years elapsing between infection and the development of serious complications.[5, 41, 52]

The period of communicability spans from one or more weeks before onset of the first symptoms and may persist in most persons indefinitely.

Based on infectivity studies in chimpanzees, the **titre* of HCV in the blood appears to be relatively low. Peaks in *virus concentration appear to correlate with peaks in *ALT activity.

Susceptibility is general. The degree of immunity following infection is not known. Repeated infections with HCV have been demonstrated in an experimental chimpanzee model.[74]

HCV infection does not cause fulminant hepatic failure, but, occurring in the setting of another chronic liver disease such as chronic HBV infection, may precipitate liver failure.[41]

Persons who have chronic liver disease are at increased risk for fulminant hepatitis A.[94]

Most of the serious liver disease associated with HCV is a consequence of the chronic, persistent nature of the infection.[39]

Even in the asymptomatic *carrier, a decrease in quality of life has been reported.

*Histopathology grade and stage of liver damage is not reflected by *serum *ALT/*AST levels or serological status.[25]

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HCV and hepatocellular carcinoma (HCC)

An important late complication of hepatitis C is primary HCC, usually occurring in patients with *cirrhosis.[5, 39, 41, 52, 97]

The mechanisms by which HCV may lead to HCC are still unsolved. Unlike HBV, HCV does not integrate into the host *genome, and HCV does not seem to encode a transforming *protein. HCV itself may therefore not be directly oncogenic. The feature that links HCV with cancer may rather be the repeated cycles of *hepatocyte destruction and regeneration over many years. These repetitive-destruction-regenerative cycles may cause neoplastic changes, which then progress to *carcinoma.[21, 39, 41, 52, 97, 101]

Specific diagnosis requires liver biopsy.[52] The clinical usefulness of liver biopsy is to establish the diagnosis, to identify or exclude other lesions, to obtain a grading of necro-inflammatory activity, to stage the progression of the disease (clinical follow-up), and to assess the effects of treatment.[25]

The yearly *incidence of HCC in people with *cirrhosis is 3-5%.

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Extrahepatic manifestations of HCV infection

Damage to the bile ducts, lymphoid aggregates or *follicles, and *microvesicular steatosis are some characteristic findings associated with HCV infection.[41, 52]

Manifestations of HCV infection are primarily nonhepatic, and include *membranoproliferative glomerulonephritis and *necrotizing vasculitis of the skin.[39, 41, 52, 53, 97]

No unique histopathologic findings that allow specific histopathologic diagnosis are associated with HCV infection.[41]

Hepatitis C may be associated with autoimmune diseases such as *Sjögren's syndrome and *sialadenitis, *idiopathic pulmonary fibrosis, *polyarteritis nodosa, *porphyria cutanea tarda, and a variant of autoimmune hepatitis associated with the presence of anti-kidney and liver microsomal auto*antibodies.[39, 41, 52, 53]

Anti*viral treatment should be considered for hepatitis C patients manifesting extrahepatic complications.[53]

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Course of acute infection progressing to chronicity

Fig 87-1 [41]

From: Hsu HH and Greenberg HB. Hepatitis C. In: Hoeprich PD, Jordan MC, and Ronald AR, eds. Infectious Diseases. A treatise of infectious processes, 5th ed. JB Lippincott Co, Philadelphia, 1994:820-825,[41] with permission.

Typical course of acute HCV infection progressing to chronicity. HCV RNA, as detected by *polymerase chain reaction (PCR), becomes positive within days of inoculation. Clinical disease develops after an incubation period ranging from 6-10 weeks. Symptoms, when present, are generally mild. *Antibodies to HCV (anti-HCV) develop a mean of 12 weeks after infection and persist. The *serum alanine aminotransferase (*ALT) level remains elevated but can fluctuate widely. Treatment with *interferon in this patient led to a complete response during therapy with normalization of *ALT and loss of HCV RNA, but the patient relapsed upon discontinuation of treatment.[41]

The clinical latent period between acquisition of HCV infection and the development of end-stage cirrhosis and HCC may be longer than 20 years.

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Schemes of potential clinical sequelae of HCV infection

Fig. 4 [39]

From: Houghton M. Hepatitis C viruses. In: Fields BN, Knipe DM, and Howley PM, eds. Fields Virology, 3rd ed. Philadelphia, Lippincott - Raven, 1996:1035-1058,[39] with permission.

Summary of potential clinical sequelae of HCV infection.[39]

Fig. 1 [55]

***From:** Marcellin P. Hepatitis C: the clinical spectrum of the disease. Journal of Hepatology, 1999, 31(Suppl.1):9-16,[55] with permission ().*

Spectrum of HCV infection.[55]

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Atypical forms of chronic hepatitis C

Normal aminotransferases

Patients with chronic hepatitis C may have no elevations in *serum aminotransferases, although some of these may show signs of hepatitis by liver biopsy. Since no symptoms are often shown, these patients are detected when they donate blood.

Treatment of patients with chronic hepatitis C with normal aminotransferase levels is not generally recommended, but this issus is the subject of ongoing clinical research.

Atypical serologic patterns

Some patients with chronic hepatitis C test negative for anti-HCV. Detection of HCV RNA by PCR can establish the diagnosis. If the diagnosis is still elusive, and other diseases like autoimmune hepatitis, drug-induced liver injury, sclerosing cholangitis, Wilson's disease, and a-1-antitrypsin deficiency are excluded, a course of corticosteroids before the use of anti-viral therapy should be tried. If there is no response to corticosteroids, *interferon therapy may be considered under careful monitoring in a tertiary specialist referral centre.[31]

Decompensated liver disease

Only patients with early or mildly decompensated *cirrhosis should be treated. The treatment of decompensated *cirrhosis should be evaluated by a specialist. The best possibility for a sustained improvement in health for advanced cases is liver transplantation.[5, 31]

Immunosuppressed patients

Only limited experience of therapy of chronic hepatitis C in immunosuppressed patients is available. Although preliminary reports suggest that *interferon-a/ribavirin can suppress *viral replication and improve *serum aminotransferase levels in immunosuppressed patients, the safety and relative benefit of * interferon-a/ribavirin therapy in this setting is still unclear, and should be considered experimental and carried out in the context of prospective clinical trials .[31]

Cryoglobulinemia

*interferon therapy for patients with essential mixed cryoglobulinemia and associated hepatitis C improves symptoms, but once *interferon is discontinued, symptoms recur. A long-term maintenance *interferon therapy may be warrented, the efficacy of which is currently under investigation.[31]

Children

There are no licensed treatments or guidelines for the treatment of infants or children infected with HCV.[77, 94]

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Diagnosis

Diagnosis of hepatitis is made by biochemical assessment of liver function. Initial laboratory evaluation should include: total and direct **bilirubin*, **ALT*, **AST*, alkaline phosphatase, prothrombin time, total **protein*, albumin, globulin, complete blood count, and coagulation studies.

Hepatitis C diagnosis depends on demonstration of anti-HCV detected by an *EIA. Anti-HCV is generally not detectable in patients with initial signs or symptoms of hepatitis C. Anti-HCV develop in acute infection generally between 2 and 8 weeks after evidence of liver injury. Some persons may not test positive for 6-9 months after onset of illness. Hepatitis C *viremia may be detected by *RT-PCR within days after infection.[39, 41, 52, 55]

Tests are not yet available to distinguish acute from chronic HCV infection: Positive anti-HCV *IgM levels are found in 50-93% of patients with acute hepatitis C and in 50-70% of patients with chronic hepatitis C. Therefore, anti-HCV *IgM cannot be used as a reliable marker of acute HCV infection.[41, 69]

Most *sera containing anti-HCV *antibodies are also HCV PCR-positive, indicating that these *antibodies are markers of ongoing infection and do not correlate with resolution or clearance of infection. The ability of *serum *antibodies to recognize all HCV quasispecies is restricted, and neutralizing anti-HCV *antibodies have not yet been identified.[41, 52, 97]

Target amplification techniques using either polymerase chain reaction (PCR) or transcription-mediated amplification (TMA) have been developed as qualitative tests for detecting HCV RNA, whereas both target amplification (PCR) and signal amplification techniques (branched DNA) may be used to measure HCV RNA levels.[65] Because of assay variability, rigorous quality assurance and control should be introduced in clinical laboratories performing these assays, and proficiency testing should be recommended.[94] For these purposes, the First International Standard for Nucleic Acid Amplification Technology (NAT) Assays for HCV RNA have been established.[78]

An *EIA test for HCV core-antigen detection has been established and appears to be suitable for large-scale screening of blood donations, whilst its use in clinical monitoring remains to be determined.[51, 62, 67]

The chronic hepatitis associated with HCV infection acts as a cofactor in increasing the severity of hepatic injury in patients with other chronic liver diseases.[41, 52]

Children should not be tested for anti-HCV before 12 months of age as anti-HCV from the mother may last until this age.[94] Diagnosis relies on determination of *ALT levels and presence of HCV RNA in baby blood after the second month of life. [77]

An early diagnosis in the course of the disease can:
- increase the chances of successful treatment
- increase impact of essential lifestyle changes
- limit cross-infection

***EIA result**	***Suggested action***
anti-HCV positive	HCV infection in a patient with a positive EIA test should be confirmed by a qualitative HCV RNA assay. However confirmation may be unnecessary in a patient who has evidence of liver disease and obvious risk factors for HCV. The immunoblot assay is still useful as a supplemental assay for persons screened in nonclinical settings and in persons with a positive EIA who test negative for HCV RNA.
anti-HCV negative	A negative EIA test is sufficient to exclude a diagnosis of chronic HCV infection in immune-competent patients, if the test is performed

	within 4-6 weeks of infection. Rarely, patients on haemodialysis and patients with immune deficiencies may have false-negative EIAs. In these patients, an assay for HCV RNA is necessary for diagnosis of chronic infection.

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HCV serologic markers in hepatitis patients

From: Marcellin P. Hepatitis C: the clinical spectrum of the disease. Journal of Hepatology, 1999, 31(Suppl.1):9-16,[55] with permission.

Time course of HCV markers for acute hepatitis C.[55]

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Time course of HCV markers for chronic hepatitis C.[55]

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Diagnostic tests for hepatitis C

Test/Type	Purpose	Comments
Anti-HCV (antibody) - EIA (enzyme immunoassay) - recombinant immunoblot assay (e.g. RIBA™)	Verify if necessary positive EIA with HCV RNA detection Indicates past or present infection, but does not differentiate between acute, chronic or past infection.	Sensitivity >95%. Detects anti-HCV in 80% of patients within 5-6 weeks of onset of hepatitis. Late seroconversion can occur. High false-positive rate for EIA in low prevalence populations and in those with auto-immune disorders.
HCV RNA (virus) *Qualitative tests* • PCR - Amplicor HCV™ • Transcription-mediated amplification" (TMA) - Versant HCV	Detect presence or absence of virus. Detects virus 1-3 weeks after exposure. Detection of HCV RNA during course of infection may be intermittent. A single negative PCR is not conclusive.	False positive and false negative results can occur from improper handling, storage, and contamination of test samples.
Quantitative tests • PCR - Amplicor HCV Monitor™ • branched DNA signal amplification - Quantiplex™ HCV RNA (bDNA) - Versant HCV RNA Quantitative Assay • other tests - SuperQuant, LCx, real-time PCR…	Determines *titre* of HCV. Used to monitor patients on antiviral therapy.	Less sensitive than qualitative PCR. Should preferably not be used to confirm or exclude the diagnosis of HCV or to monitor treatment end point.
HCV core antigen EIA • Trak-C	Detects presence or absence of virus. Detects virus 1-3 weeks after exposure. Under evaluation for the monitoring of patients on antiviral therapy	Not licensed. Appears to be suitable for large-scale screening of blood donations, its use in clinical monitoring remains to determined
Genotype	Groups isolates of HCV into 6 genotypes based on genetic differences. With new therapies, length of treatment varies based on genotype.	Genotype 1 and possibly 4 is/are associated with a lower response to antiviral therapy.

Serological tests give an insight into the patient's immune response to HCV infection.[56, 94]

Since 1990, serological tests such as *enzyme-linked immunoassays (*EIAs /*ELISAs) are used to screen blood donations and to diagnose HCV infection in symptomatic patients.[5, 39, 93]

Recombinant immunoblot assays (*RIBA™ strips, Chiron Diagnostics, Emeryville, CA) may be used for confirmation of HCV infection in anti-HCV positive, HCV RNA negative sample.[5, 39, 65, 93]

The *EIA test is done first. If positive, it should be confirmed e.g. by the same assay but on a second, different sample and if necessary by HCV RNA. If the EIA test is negative or borderline positive, the patient is unlikely to be infected with HCV.[39, 93]

The high sensitivity of diagnostic assays should be verified in different parts of the world. Account should be taken of the possibility that different *genotypes may change their distribution, due to the large population movements in the modern age.

*HCV RNA assays provide a direct measure of *viral load:*

PCR-based assays, the branched-DNA (bDNA) assays and other are used to determine qualitatively or quantitively HCV RNA. They are used in blood screening, to follow disease progression and to monitor therapeutic response, e.g. to *interferon-a/ribavirin, in HCV-infected people.[65, 93]

*Genotyping and quantitative HCV RNA tests are recommended prior to the treatment of patients.[5]

Qualitative HCV RNA testing, which is not performed routinely, should be restricted to the following situations:[69]
- etiological diagnosis of seronegative acute hepatitis of unknown cause
- etiological diagnosis of seronegative chronic hepatitis of unknown cause
- patients with weakly positive *EIA results, particularly in immuno-suppressed patients
- chronic hepatitis C with repeatedly normal *ALT levels
- diagnosis of HCV infection in babies born to HCV-infected mothers
- monitoring of anti-viral therapy
- diagnosis performed within the “window period” (1-3 weeks after infection)

Virological tests do not provide information on severity or prognosis of HCV-related disease.[69]

From: *Pawlotsky J-M. Diagnostic tests for hepatitis C. Journal of Hepatology, 1999, 31(Suppl.1):71-79,[69] with permission.*

Principles of target amplification techniques for the detection of hepatitis C virus (HCV) RNA. HCV particles are lyzed and the released RNA is reverse transcribed (RT) into a double-stranded (ds) complementary DNA (cDNA). Double-stranded cDNAs are then processed into a cyclic enzymatic reaction, leading to the production of a large number of copies: polymerase chain reaction (PCR) produces ds-DNA molecules, whereas transcription-mediated amplification (TMA) produces single-stranded (ss) molecules.[69]

From: *Pawlotsky J-M. Diagnostic tests for hepatitis C. Journal of Hepatology, 1999, 31(Suppl.1):71-79,[69] with permission.*

Principles of branched DNA-based single amplification for the detection and quantification of hepatitis C virus (HCV) RNA. HCV particles are lyzed and the released RNA is hybridized onto the wells of a microtiter plate. Hybridized RNAs are then labeled by means of branched DNA (bDNA) molecules, which achieve signal amplification.[69]

Click here for: HCV serologic markers in hepatitis patients (LINK TO PAGE 27)
Click here for: Three generations of ELISA tests (LINK TO PAGE 31)

Three generations of "ELISA" tests

Detection of *antibody to a single *epitope by *ELISA (EIA) was the first test developed in 1990.[48] It had poor sensitivity and was not helpful early after infection since the *antibody appears four to six months after infection. Second and third generation *ELISA and *RIBA™ tests have increased sensitivity and narrowed the window period between infection and *viral detection:

Second-generation *EIAs detect *antibodies to structural (core) and nonstructural (NS3 and NS4) *proteins.[69]

Third-generation *EIAs detect the same *antibodies with better sensitivity, plus *antibodies directed to NS5.[69]

With the current third-generation assays, the window period between HCV infection and the detection of anti-HCV *antibodies is, on average, of 7-8 weeks. As a consequence, the residual risk of HCV transmission by anti-HCV-negative blood products in 1999 in France has been estimated to 4.9/million donations.[69, 95]

Existing assays do not differentiate between:
- false positive *EIA results
- patients having recovered from acute infection
- patients with chronic HCV infection and HCV RNA levels below the detection limit

Generally, the performance of currently available screening assays requires only one test for the diagnosis of HCV infection in clinical virology laboratories.[69]

Click here for: HCV serologic markers in hepatitis patients (LINK TO PAGE 27)
Click here for: Diagnostic tests for hepatitis C (LINK TO PAGE 28)

Host immune response

The first marker of HCV infection is *serum HCV RNA detectable by PCR as early as 1 week after infection and increasing to 10^6 – 10^8 *genomes/ml.[55]

Different *antibodies appear in *serum at different intervals from the time of initial inoculation. Anti-core *antibodies directed to the nucleocapsid *protein are generally the first to appear and can be detected by the time *ALT is peaking.[3]

Infected individuals generally develop *antibodies reactive with the core (C) *protein as well as several nonstructural *protein *antigens of HCV within days to weeks after onset of clinical symptoms. However, protective *antibodies have not been identified yet.[39, 52, 74]

The serology of HCV infection does not follow the classical pattern of *IgM response observed in other *viral infections because it may be absent, late or persistent after HCV infection and does not correlate with the histologic activity.[3]

If *antibodies reactive with the hypervariable region of E2 possess *virus neutralizing activity, the *virus escapes this neutralizing activity by selecting out new *amino acids within this hypervariable domain.[39, 52]

The immunological correlates of hepatitis C virus (HCV)-specific immunity are not well understood.[64, 74]

CD8+ cytotoxic T *lymphocytes have been found in the liver of chronically infected patients, suggesting that they are not always capable of eliminating the infection.[18, 52, 63, 88, 91]

HCV specific CD4+ T cells have been identified in the peripheral blood of chronically infected patients.[39]

Reinfection is common after rechallenge of previously infected chimpanzees, although manifestations of HCV infection are generally reduced in secondary infections. Reinfections with both homologous and heterologous HCV strains indicate that poor immunity is not only related to *antigenic variation among different strains of HCV.[52, 74] Chimpanzees differ though from humans in that they make a weak (if any) *humoral immune response to the structural *proteins.[39]

Another host response to HCV is the induction of *interferon.[39]

However, HCV persists despite the induction of a broad *humoral and cell-mediated immune response. One mechanism of HCV persistence occurs via the generation of immune-escape mutants.[39]

Immunosuppressed organ recipients infected with HCV often do not seroconvert to the nonstructural *proteins, but they do to envelope glyco*proteins and the nucleocapsid *proteins.[39]

HCV readily causes a persistent infection, although some individuals spontaneously control infection. 'Successful' immune responses appear to be multi-specific and sustained-including a major role for CD4(+)T cells. Some antiviral CD8(+)T cells show reduced capacity to secrete antiviral cytokines either temporarily ('stunning') or in the long term ('stunting'). The co-ordination of multiple immune effector functions may be required to gain control of HCV.[29, 47]

Prevalence

HCV is parenterally transmitted and has been found in every part of the world where it has been sought.[74, 101]

Prior to donor screening for anti-HCV (1992), HCV was the most common cause of post-transfusion hepatitis worldwide, accounting for about 90% of this disease in the USA.[52]

Studies carried out in the 1970s suggested that about 7% of transfusion recipients developed NANB hepatitis, and that up to 1% of blood units might contain the responsible *virus.[52] The introduction of anti-HCV screening has reduced the transmission by up to almost 100%.[52, 84, 95]

Currently in the USA, HCV accounts for about 20% of acute *viral hepatitis cases, of which less than 5% are associated with blood transfusion. The *prevalence of anti-HCV is highest in injecting drug users and haemophilia patients (up to 98%)[33, 54, 65, 76, 85, 105], highly variable in haemodialysis patients (<10%-90%)[12, 15, 42, 59, 66, 81, 83], low in heterosexuals with multiple sexual partners, homosexual men, healthcare workers and family contacts of HCV infected persons (1%-5%), and lowest in volunteer blood donors (0.3%-0.5%). In the general population it varies (0.2%-18%).[52, 102]

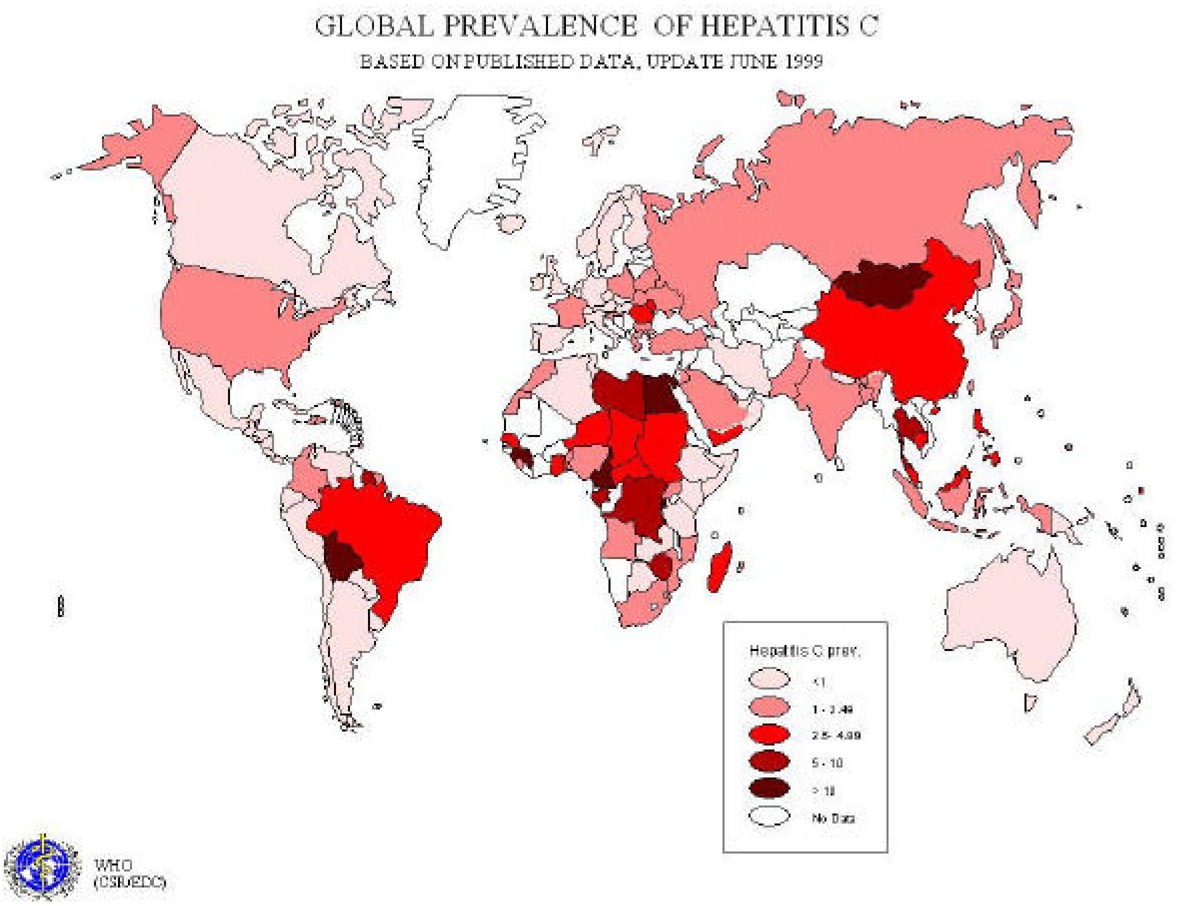
Areas of higher *prevalence include countries in the Far East, Mediterranean countries and certain areas in Africa and eastern Europe.[39, 41, 52, 104]

HCV infection has no recognized seasonal distribution.[74]

WHO estimates that about **3%** of the world's population has been infected with HCV and that some 170 million are chronic *carriers at risk of developing liver *cirrhosis and/or liver cancer. These chronic *carriers represent a reservoir sufficiently large for HCV to persist.

Click here for: Global prevalence of hepatitis C (LINK TO PAGE 34)

Global prevalence of hepatitis C[100]



Pathogenesis

HCV infects *hepatocytes. It is still unclear whether the liver damage associated with HCV infection is the result of a direct *cytopathic effect or is caused by a host immune-mediated cytolytic response. Both processes are probably involved in causing hepatic damage.[39, 41, 52, 74, 97, 103]

Chronic hepatitis C is characterized by portal inflammation, typically periportal hepatocellular necrosis, and fibrosis.[74, 97]

Mean intervals between the onset of acute PTH and detection of CAH (10 years), *cirrhosis (20 years) and HCC (30 years) are reported in separate Japanese and American studies.[39, 97]

Factors that may affect the natural history of HCV infection:
Various cofactors such as presence of HBV and alcohol intake appear to promote disease progression. Chronic HBV / HCV co-infection (HBsAg and anti-HCV positive) is uncommon globally, although it may be emerging in China. Co-infected patients have a higher risk of hepatocellular carcinoma than those who are only infected with one virus. However, it is unclear whether this high risk reflects a combined effect of the two viruses in the absence of interaction or some synergistic effect. The serological profile of anti-HBc alone / anti HCV positive is common. Some evidence suggests that presence of anti-HBc alone might increase the risk of hepatocellular carcinoma among patients with chronic HCV infection [14, 24, 39] Intake of more than 50 g alcohol / day accelerates progression to cirrhosis with a threefold risk increase.[35, 99] Consistently normal ALT levels are associated with slower fibrosis progression. Limited evidence suggests that steatohepatitis may affect fibrosis progression. Steatohepatitis, rather than obesity, seems to be the important co-factor. However, one intervention study from Brisbane, Australia, suggests that reducing weight reduces fibrosis progression.[8, 37, 40, 70]

The influence of HIV infection depends upon CD4 count with a confounding effect of immune reconstitution following successful HAART. The relative risk for the development of cirrhosis among HIV and HCV co-infected patients is around two.[26, 80]

Preliminary evidence suggests that smoking may influence the development of HCC.

Factors that probably do not affect the natural history of HCV infection:
Most studies suggest that in general, viral load or genotypes do not influence disease severity or progression.

The size of the *viral inoculum received may determine the course of disease: posttransfusion cases may proceed more aggressively than infections associated with injecting drug use (IDU).[39]

Disease expression is related to *viral expression: low levels of circulating HCV RNA are generally found in asymptomatic patients with normal *ALT levels.[39]

Experiments carried out with chimpanzees have shown that the administration of powerful immunosuppressants before and after *virus inoculation prevents the development of acute hepatitis despite *viremia in the animal and *viral expression in the liver. Removal of the immunosuppressant triggered an immune response which resulted in the onset of acute hepatitis followed by *virus elimination.[39]

Transmission

Transmission occurs by percutaneous exposure to contaminated blood and *plasma derivatives. Contaminated needles and syringes are most important vehicles of spread, especially among injecting drug users.[5, 41, 52, 101]

Because the *virus possesses a lipid-containing envelope, exposure of *virus to bile and secretion from the liver through the biliary tract to the gut would result in rapid loss of *virus infectivity.[52]

Transmission by household contact and sexual activity appears to be low.[5, 41, 52, 98, 101]

Uncommon but occasional is the transmission at birth from mother to child. About 5 out of every 100 infants born to HCV infected women become infected at the time of birth. Unfortunately, no treatment can prevent this from happening.[5, 94, 106] Perinatal transmission explains only a small proportion of chronic HCV infections. This contrasts with HBV infection, in which most adult chronic *carriers acquired infection in the newborn period.[41, 52, 101]

The risk of mother to infant transmission of HCV increases dramatically if the mother is co-infected with HIV possibly due to an increase in HCV **titre* as a result of immunosuppression.[5, 39, 52, 101, 106]

The risk of mother-baby transmission correlates with the **titre* of maternal HCV *viremia.[5]

For women found to be HCV positive, there are no recommendations against pregnancy or breast-feeding, nor is a special method recommended to deliver the baby.[103] However, invasive fetal monitoring (eg. using scalp electrodes) should be avoided.[5] HCV-positive mothers should consider abstaining from breast-feeding if their nipples are cracked or bleeding.[94]

The presence of HCV RNA in *serum indicates the presence of active infection and a potential for transmission of the infection and/or the development of chronic liver disease.[101]

There is no such thing as safe blood since there is still the risk of having *antibody-negative and PCR-negative blood units that can transmit disease. The advice is to use blood products only in the most necessary cases.[3, 86, 95]

Click here for: Risk factors associated with hepatitis C in the USA (LINK TO PAGE 37)

Risk factors associated with hepatitis C in the USA

From: http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_c/slide_21.htm, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Recent studies have demonstrated that injecting-drug use currently accounts for 60% of HCV transmission in the United States.[10] Although the role of sexual activity in transmission of HCV remains unclear, less than or equal to 20% of persons with HCV infection report sexual exposures (i.e., exposure to an infected sexual partner or to multiple partners) in the absence of percutaneous risk factors. Other known exposures (occupational, hemodialysis, household, perinatal) together account for approximately 10% of infections. Thus, a potential risk factor can be identified for approximately 90% of persons with HCV infection. In the remaining 10%, no recognized source of infection can be identified, although most persons in this category are associated with low socioeconomic level. Although low socioeconomic level has been associated with several infectious diseases and might be a surrogate for high-risk exposures, its nonspecific nature makes targeting prevention measures difficult.[10]

Risk groups

In over 40% of cases the risk factor(s) cannot be identified.[52, 74]

The major risk factor for HCV infection is parenteral exposure, primarily through blood products and needle sharing among injecting drug users.[5]

Screening for HCV (introduced in 1990) among blood donors has reduced the risk of acquiring HCV from blood products by half to two thirds to a rate of 3 to 6 cases per 1000 recipients.[41, 74]

In the past, recipients of blood products were at high risk (for HCV infection). Over the last 25 years, testing blood donations for HCV has became a universal requirement. Testing procedures have made major progress in sensitivity in the last 15-20 years. However 48% of countries reported that they were not testing 100% of blood donations for HCV (WHO Global Database on Blood Safety, unpublished data). In the many countries where pretransfusion screening of blood donations for HCV is systematically performed, the residual risk of HCV transmission is minimal. Moreover, plasma derived medicinal products (including antihaemophilic factors) are undergoing additional viral inactivation and removal procedures resulting in greatly reduced or eliminated transmission of HCV by these products.

However, the risk is still present in many developing countries. Contaminated and inadequately sterilized syringes and needles have resulted in outbreaks of hepatitis C among patients in clinics and physicians' offices. Occasionally, outbreaks have been traced to tattoo parlors and acupuncturists.
Rarely, transmission to patients from HCV positive health care workers or to health care workers from HCV positive patients have been documented. It is clear from the various studies that the risk of occupational risk of HCV transmission does exist and rigorously applied universal infection precautions are the mainstay against nosocomial HCV infection.[57, 87]

A low frequency of HCV infection (0.004 to 0.0004% per unit transfused) continues to accompany blood transfusion due to the presence of infectious donors who are not detected by currently available *antibody screening tests.[95, 103] Before any screening test was available, the risk of contracting the *virus was 1 in 200 units transfused.[56]

Groups at risk of contracting an HCV infection :
• recipients of previously unscreened blood, blood products and organs
(blood transfusion or solid organ transplant before 1992, coagulation factor concentrates before 1987)
• patients and employees in hemodialysis centers (nosocomial infections)
• hemophiliacs
• injecting drug users sharing contaminated needles and/or injection materials
• people exposed to unsterile medical or dental equipment
• occupational exposure to blood
• people administrating or receiving acupuncture and/or tattooing with unsterile medical devices
• health care workers
• sexual, household and perinatal transmission are possible.[39]
• infants born to infected mothers
A number of cases, 10% to 40%, have no identifiable risk factor.[10]

Surveillance and control

Hepatitis C disease surveillance and control procedures should include:[3, 103]

- screening of blood and blood products with reliable kits of acceptable sensitivity and specificity to reduce the chances that the blood supply system may contain pathogens like HCV.

- vigorous implementation of universal precautions to prevent the spread of HCV.

Endemicity

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive. Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable socioeconomic conditions and hygienic standards for invasive medical, dental, or paramedical procedures. The strong homogeneity of HCV subtypes found in Egypt (mostly 4a) suggests an epidemic spread of HCV. Since a history of injection treatment has been implicated as a risk factor for HCV, a prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis. The large reservoir of chronic HCV infection established in the course of these campaigns remains likely to be responsible for the high prevalence of HCV morbidity and may be largely responsible for the continued endemic transmission of HCV in Egypt today.[49]

In Italy the prevalence of anti-HCV is greater than 5% in some communities. In one region where the prevalence of anti-HCV was 12.6% overall, the rate among persons younger than 30 years of age was only 1.3% compared with 33.1% in those above 60. The demographic characteristics of this community were typical of many small towns in southern Italy. The use of glass syringes for medical treatment, a common practice before 1970 in Italy, or a history of dental therapy were found to be associated with anti-HCV positivity. A similar risk from immunizations in the 1950s using non-disposable syringes was reported from Japan.[49]

Incidence/Epidemiology

HCV Infection occurs throughout the world, and up until the introduction of anti-HCV screening tests for blood donors, introduced in 1990/1991 in Europe and the United States, it has represented the major cause of transfusion-associated hepatitis.[39, 95]

The *incidence of HCV on a global scale is not well known, because acute infection is generally asymptomatic.[100]

As many as 2 to 4 million persons may be chronically infected in the United States, 5 to 10 million in Europe, and about 12 million in India, and most do not know they are infected. About 150 000 new cases occur annually in the US and in Western Europe, and about 350 000 in Japan. Of these, about 25% are symptomatic, but 60 to 80% may progress to chronic liver disease, and 20% of these develop *cirrhosis. About 5%-7% of patients may ultimately die of the consequences of the infection.[3, 39, 41, 52, 74, 93, 96]

Most European countries report a *prevalence of HCV in the general population of between 0.5 and 2%.[96, 104]

WHO estimates that about **3%** of the world's population has been infected with HCV and that there are more than 170 million chronic *carriers who are at risk of developing liver *cirrhosis and/or liver cancer.[5, 100, 101]

Very high rates of HCV *antibody reactivity (>70%) have been reported in injecting drug users and in haemophiliacs. Intermediate *prevalences of 20 to 30% have been observed in patients receiving haemodialysis.[96]

The *incidence is declining since transmission by blood products has been reduced to almost zero and universal precautions in medical settings are followed.[5]

Trends

Transfusion-associated cases occurred prior to donor screening. Now they are very rare where blood is screened with 2nd and 3rd generation EIAs, about 0.004% to 0.0004% per unit transfused.[84, 94, 95]

Most new infections are the consequence of high risk drug behavior (60%) or unsafe injection practices.[5, 45, 94]

New HCV infections have decreased by over 80% since 1990 in the USA.[56]

Costs

In 1998, the estimated annual costs of acute and chronic hepatitis C (medical and work loss) was above US$ 1 billion in the USA.[46, 56]

Prophylaxis

The development of effective pre- and postexposure *prophylaxis is complicated because of the genetic diversity of HCV.

No effective post-exposure *prophylaxis (*immune globulin, anti*viral agents) is available for hepatitis C.[56] Passive immune *prophylaxis against HCV using *immune globulin containing detectable levels of anti-HCV has not been convincingly documented and active immune *prophylaxis is a goal for the future.[94, 103] A preliminary study showed that administration of anti-HCV *immune globulin to chimpanzees shortly after challenge delayed the onset of acute hepatitis.[39]

Mechanisms of the effect of *interferon in treating patients with acute hepatitis C are still poorly understood. High SVR rates (83 to 100 percent) have been reported by small uncontrolled trials with interferon monotherapy. Accordingly, treatment of persons with acute hepatitis C is warranted, but the timing of therapy and the type of regimen to use remains to be determined from future trials. The preliminary evidence suggests that treatment with interferon in the early phase of infection[43] or 2-4 months after infection leads to virus elimination in about 80% of cases.[9, 34, 60, 72] The use of pegylated interferons does increase the sustained virological response (SVR) rate.

Vaccines

There is no *vaccine against HCV.

There are major challenges to the future development of a hepatitis C *vaccine. Primary infection of chimpanzees does not protect against subsequent challenge by either the identical *viral strain or a heterologous strain. Protective or neutralizing *antibodies have not been found.[41, 52]

An additional major obstacle to *vaccine development is the extensive genetic variation between different strains and *genotypes, and even the significant *antigenic variation among *virus quasispecies within individual patients.[7, 41, 52, 97]

The absence of a clearly defined protective immune response after natural infection complicates the prospects of ultimately developing a *vaccine against HCV infection.[52, 101]

Although an ideal *vaccine should give immunity to infection, in the case of HCV, where acute HCV infection is a limited health problem and infection can only be assessed by PCR, a more realistic goal might be to find a *vaccine that protects from chronic infection.[7]

Preliminary results with chimpanzees show that a *vaccine made of recombinant envelope *proteins can prevent chronic infection in the majority of *vaccinees.[7]

In the absence of a *vaccine, all precautions to prevent infection by other means must be taken.[101]

Prevention

There are no *vaccine or *immune globulin (IG) products available to prevent HCV infection.[52]

Blood banks should discard donor units with elevated liver *enzyme levels (ALT and/or AST) even after the test for anti-HCV has been established.[52]

The value of *prophylactic IG is not clear.[41, 74]

Post-exposure *prophylaxis with IG is not effective in preventing infection.

A small fraction of potentially infectious donors who escape detection because they lack detectable *antibodies still exists. For the prevention of posttransfusion hepatitis it is therefore important that blood transfusions should be given only when absolutely necessary.[41]

Needle-exchange programs for injecting drug users may help to limit the spread of HCV infection as well as of HIV and HBV.[5, 41]

For couples in a stable relationship, the risk posed to sexual partners of HCV-infected patients is not sufficiently high to support recommendations against specific sexual practices.[41]

HCV *carriers should be strongly discouraged from drinking alcohol because there is evidence that HCV acts as a cofactor in developing more severe liver injury in alcoholics.[24, 39, 41, 94, 97]

As there is no *vaccine against hepatitis C available, the only means of protection are the implementation universal precautions and safe injection practices. Screening and treatment of blood products is the only way to prevent transfusion-associated cases.[95, 96]

*Comprehensive strategy to prevent and control hepatitis C *virus (HCV) infection and HCV-related disease*[94, 103]*:*

- Primary prevention activities include
  - screening and testing of blood, *plasma, organ, tissue, and semen donors
  - *virus inactivation of *plasma-derived products
  - adequate sterilization of reusable material such as surgical or dental instruments
  - risk-reduction counseling and services
  - implementation and maintenance of infection-control practices
  - needle and syringe exchange programs

- Secondary prevention activities include
  - identification, counseling, and testing of persons at risk
  - medical management of infected persons

- Professional and public education

- Surveillance and research to monitor disease trends and the effectiveness of prevention activities and to develop improved prevention methods.

Prevention of spread of infection should be the main goal at the current time until cost effective therapies become available.[3]

Treatment

The rationales for treatment of chronic hepatitis are to reduce inflammation, to prevent progression to fibrosis, *cirrhosis, and HCC through the eradication of the *virus in chronically infected patients, and to decrease infectivity and control the spread of the disease.[103]

Combination therapy results in better treatment responses than monotherapy; the highest response rates have been achieved with pegylated interferon in combination with ribavirin. Genotype determinations influence treatment decisions. Currently the best indicator of effective treatment is a sustained viral response, defined by the absence of detectable HCV RNA in the serum as shown by a qualitative HCV RNA assay with lower limit of detection of 50 IU/mL or less at 24 weeks after the end of treatment.[3, 5, 94]

*Interferon has been shown to normalize liver tests, improve hepatic inflammation and reduce *viral replication in chronic hepatitis C and is considered the standard therapy for chronic hepatitis C. Currently, it is recommended for patients with compensated chronic hepatitis C (anti-HCV positivity, HCV RNA detection, abnormal *ALT levels over at least 6 months, fibrosis shown by liver biopsy).[3, 5, 94, 103]

*Interferon-a is given subcutaneously at doses of 3 million units 3 times a week for 24 months. Patients with a reduced *ALT activity or HCV RNA level within the first month of treatment are more likely to have a sustained response than patients in whom these changes do not occur. About 50% of patients respond to *interferon-a by normalizing *ALT at the end of therapy, but half of these relapse within the 6 months of follow-up after IFN withdrawal. The long-term biochemical response falls then to 20-25%. Only a minority of these have a persistent disappearance of HCV RNA from *serum. [3, 31, 39, 41, 94, 101]

The duration of therapy depends on the *genotype and level of *viremia. In patients with *genotype 2 or 3, the duration is 24 weeks, while patients with genotype 1 need 48 weeks of treatment. [4, 65, 69]

Combination therapy, approved in many countries, increases the proportion of patients who have a sustained viral response (SVR), reaching 40%-50%, compared with response rates of 15%-25% with *interferon alone.[17, 31, 56, 94, 101]

Infections with *genotype 1 strains of HCV are less responsive to *interferon than infections with other *genotypes of HCV.[3, 4, 41, 52, 65] The *genotype should not be used as a reason to deny treatment.[5] In 2003, combination therapy with pegylated *interferon and ribavirin is the therapy of choice for naïve patients. SVRs of 42 to 46 percent were achieved for genotype 1 using pegylated interferon and ribavirin for 48 weeks. Patients with genotypes 2 and 3 achieved SVRs of 76 to 82 percent after 24 weeks of treatment.[4, 65]

Combination therapy with pegylated *interferon and ribavirin for 24 or 48 weeks should be the treatment of choice for patients who relapse after **interferon treatment. A relapse rate of less than 20% occurs in relapse patients treated with combination therapy for a year. [16] Nonresponders are sometimes refractory to** retreatment and do not necessarily benefit from escalating the dose.[3, 4, 17, 31, 39, 41, 52, 65, 101]

The sooner in the evolution of the infection the treatment is started, the better the chances of responding to *interferon-a therapy.[9, 34, 60, 72] A few studies suggest that treatment of acute hepatitis C with *interferon-a results in a reduction in the proportion of patients who progressed to chronic disease, but this approach requires further studies.[31, 39, 52]

Persistent *viremia at week 4 of therapy provides an accurate identification of nonresponders to *interferon treatment. In these patients, interruption of treatment or other therapeutic options should be considered.[20]

Transplantation is an option for patients with *cirrhosis who manifest clinically evident end-stage liver disease. After transplantation, however, the donor liver almost always becomes infected, and the risk of progression to *cirrhosis reappears.[41, 79]

If chronic hepatitis inflammation is an important factor in the development of HCC, then a therapeutic approach to lessen the extent of chronic hepatic inflammation should have important implications for the management of patients with chronic hepatitis C.[52]

There are no licensed treatments or guidelines for the treatment of infants or children infected with HCV.[77, 94]

Patients with chronic hepatitis C and concurrent HIV infection may have an accelerated course of HCV disease. Therefore, although there are no HCV therapies specifically approved for patients co-infected with HIV, these patients should be considered for treatment.[65]

Corticosteroids, ursodiol, thymosin, acyclovir, amantadine, and rimantadine are not effective.[44]

To protect their liver, people with HCV infection should avoid alcohol consumption, not start any new medicine (not even herbal) without a physician's knowledge, and get *vaccinated against hepatitis A and B .[24, 94]

The absence of *cirrhosis, young age, and a short, known duration of *serum transaminase elevations are associated with a better response to *interferon therapy.[31]

Response to *interferon-a therapy is also influenced by the iron content of the liver.[31] However, iron depletion improves *ALT levels, but is ineffective in achieving *viral eradication in patients retreated with *interferon-a.[36]

Response to therapy is influenced by duration of therapy, dosage, infecting *viral load and disease stage. The strain of the infecting *virus may also affect the clinical response.

The treatment strategy to be adopted depends on availability of drugs and cost.[3]

Patient adherence is critical to the success of HCV treatment.

Currently, there is no rationale to treat patients with chronic hepatitis C and normal *ALT levels, since they are usually asymptomatic and rarely develop *cirrhosis, although the definition of a "normal" ALT varies from center to center.[90]

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Click here for: Types of response (LINK TO PAGE 50)
Click here for: Management of treatment failures (LINK TO PAGE 51)
Click here for: Contraindications to interferon therapy for chronic hepatitis C (LINK TO PAGE 52)
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Click here for: Liver transplantation (LINK TO PAGE 57)

Monitoring[5, 103]

It is recommended that progression of liver disease be monitored every 6 months by checking blood counts and liver *enzymes. In patients with more advanced liver disease, level of α-fetoprotein and ultrasonography should be added.[4]

Patients with chronic hepatitis C should be examined, questioned about side effects, and have blood tested for *ALT/*AST every 1 to 4 weeks while on therapy. Evaluation should continue for at least 6 months after stopping therapy to assess whether the response to therapy is sustained.[31]

Early response is assessed at 3 months by evaluating the patient's *ALT and/or HCV RNA response.

End-of-treatment response is assessed by *ALT and/or HCV RNA estimation when therapy is completed.

Sustained response is assessed by *ALT and/or HCV RNA estimation 6-12 months after completion of treatment.

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Types of response[103]

Sustained response: clearance of HCV RNA from the blood and persistent normalization of *serum *ALT levels observed 6-12 months after therapy has ended (virological and biochemical response).

Patients with a sustained virological response will remain HCV RNA negative for at least 5 years after stopping therapy and experience a long-term biochemical and histological outcome with a decrease in total inflammatory activity and a decrease in the reversible components of fibrosis. These parameters may yet not mean that patients are cured from HCV since they may not reflect definitive *viral clearance.: HCV RNA may still be detectable in the liver of *serum HCV RNA negative patients showing ongoing inflammatory change. Nevertheless, sustained virological responders have a highly reduced risk of disease progression.[13]

Transient (relapsing) response: Complete virological and biochemical response at end of treatment followed by the re-emergence of *virus and /or elevation of *ALT levels during follow-up.

Breakthrough response: Temporary virological and biochemical response occurring during therapy followed by reappearance of HCV RNA and/or an abnormal *ALT level before the end of treatment.

Nonresponse: HCV RNA remains detectable and/or *ALT fails to normalize throughout the treatment phase. When a discordant virological and biochemical response occurs, the virological response should take precedence when interpreting the response to therapy.

*Interferon treatment and more so combination therapy significantly reduces *viral load, *serum *ALT activity, improves histological activity and blocks progression of fibrosis in patients who have not cleared HCV compared to the natural history of the disease. Patients who still have a positive HCV PCR after treatment should therefore no longer be called nonresponders to *interferon. *interferon might even reduce the *incidence of HCC and mortality.[71]

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Management of treatment failures

Transient (relapsing) responders, who were treated initially for 6 months, can be considered for re-treatment with combined pegylated *interferon-a and ribavirin for 6-12 months. Transient responders already treated for 12 months have a low probability of achieving a sustained response.

Treatment should be discontinued when a breakthrough response occurs. Patients' inclusion in trials of new treatment regimens should be considered.[103]

Treatment should be considered for discontinuation in patients who are not responding after 3 months of therapy (detectable HCV RNA and abnormal *ALT). Inclusion into controlled clinical trials looking for alternative new treatment regimens should be considered. Patients who fail to achieve a virologic and/or biochemical response following 6-12 months of therapy are unlikely to respond to additional treatment regimens.[94, 103]

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Contraindications to interferon therapy for chronic hepatitis C

Hepatic decompensation
  albumin <3.0 g/l
  **bilirubin* >51.3 µ mol/l (30 mg/l)
  prolonged prothrombin time >3.0 s
Portal hypertension
  variceal bleed
  ascites
  encephalopathy
Hypersplenism
  leukopenia (<2 x 10^9/l)
  *thrombocytopenia (<7 x 10^7/l)
Psychiatric depression
  severe, suicide attempt
Autoimmune disease
  polyarteritis nodosa, rheumatoid arthritis
Major system impairment
  cardiac failure
  obstructive airways disease
  uncontrolled diabetes
Pregnancy
Current intravenous drug abuse
Organ transplantation except liver

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Side effects of interferon therapy

Constitutional
 flu-like illness
 fever
 **rigors*
 **arthralgia*
 **myalgia*
 fatigue
Hematologic
 **leukopenia*
 **thrombocytopenia*
**Alopecia*
Neuropsiachiatric
 depression
 insomnia
 irritability
Weight loss
Ocular
Autoimmune
 **hypothyroidism*
 diabetes

In the currently recommended doses for the treatment of chronic hepatitis C, *interferon causes side effects that are generally mild and well tolerated. With prolonged therapy, the occurrence of late and severe side effects should lead to the discontinuation of *interferon.[31]

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Contraindications to ribavirin

end-stage renal failure
anemia
hemoglobinopathies
ischemic heart disease
severe heart disease
pregnancy
no reliable method of contraception
uncontrolled arterial hypertension

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Side effects of ribavirin

Ribavirin can induce hemolytic anemia and can cause problems to patients with preexisting anemia, bone marrow suppression, or renal failure. In these patients, if combination therapy cannot be avoided, attempts should be made to correct the anemia.[94]

Hemolytic anemia caused by ribavirin can be life-threatening for patients with ischemic heart disease or cerebral vascular disease.[94]

Ribavirin is teratogenic, and there are contraindications to consumption during pregnancy.[94]

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Liver transplantation

Liver transplantation is indicated in patients with life-threatening *cirrhosis or HCC.[5]

Patients with *cirrhosis who have a life expectancy of 1-2 years without transplantation because of recurrent or refractory ascites, Child-Pugh C *cirrhosis, uncontrolled gastrointestinal bleeding, severe encephalopathy, or bacterial peritonitis, should be considered for liver transplantation, where this is possible.[5, 79]

Patients with HCC can be considered for transplantation if there are less than 3 nodules of 3-5 cm and if there is no extrahepatic spread.[5, 22, 27, 32, 61, 75]

After liver transplantation, HCV reinfection is almost constant,[5, 79] and at

4 months:	- 75% of patients have acute hepatitis
2 years:	- 50% of patients have chronic hepatitis
3 years:	- 50% of patients have normal graft or mild lesions
	- 5% have develop severe lesions
4 years:	- 70% of patients have chronic hepatitis
5 years:	- 10% of patients have HCV-related *cirrhosis on the graft
	- 70% of patients have survived (in Europe)
10 years:	- 60% of patients have survived (in Europe)

These survival rates compare to the rates obtained after transplantation for other non-malignant liver diseases.[5, 22, 27, 32, 61, 75]

Liver grafts are rapidly infected since HCV *viremia increases as early as 3 days post-transplant. HCV RNA levels increase progressively, and at 1 month, the HCV RNA level may be dramatically increased compared to pretransplant values.[79]

Recurrent HCV infection after liver transplantation is currently treated with *interferon and ribavirin.[50]

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Guidelines for epidemic measures

1) When two or more cases occur in association with some common exposure, a search for additional cases should be conducted.

2) Introduction of strict aseptic techniques. If a **plasma* derivative like antihemophilic factor, fibrinogen, pooled **plasma* or thrombin is implicated, the lot should be withdrawn from use.

3) Tracing of all recipients of the same lot in search for additional cases.

4) Relaxation of sterilization precautions and emergency use of unscreened blood for transfusions may result in increased number of cases.

Future considerations

A better understanding of the host and *viral mechanisms that are involved in promoting the development of a persistently infected state will provide insights into the mechanisms of *viral evasion of host defences.[41]

Improvement in assessing disease severity and stage, predicting progression, predicting response before, and likelihood of relapse during treatment should be encouraged.[38]

The strengthening of regional and national centers of expertise for diagnosis, screening and therapy is to be encouraged.[94, 103]

Existing WHO guidelines for the safety and preparation of *plasma products should be implemented.[103]

The additive value of amantadine to *interferon or to *interferon-ribavirin combination in inducing sustained *viral clearance should be explored.[82]

Drugs that can normalize *serum *ALT, and thus reduce the progression of liver disease, such as *interferon, ursodeoxycholic acid, ribavirin and glycyrrhizin should be evaluated in the purpose of reaching persistent *ALT normalization in patients who are incapable of otherwise clearing the *virus.[82]

More effective and better tolerated therapies are central clinical research challenges.[38]

Glossary

alopecia loss of hair occurring at any site and from any cause.

ALT alanine aminotransferase, an **enzyme* that interconverts L-alanine and D-alanine. It is a highly sensitive indicator of hepatocellular damage. When such damage occurs, ALT is released from the liver cells into the bloodstream, resulting in abnormally high **serum* levels. Normal ALT levels range in man from 10 to 32 U/l; in women, from 9 to 24 U/l. The normal range for infants is twice that of adults.

amino acids the basic units of **proteins*, each amino acid has a NH-C(R)-COOH structure, with a variable R group. There are altogether 20 types of naturally occurring amino acids.

antibody a **protein* molecule formed by the **immune system* which reacts specifically with the **antigen* that induced its synthesis. All antibodies are **immune globulins*.

antigen any substance which can elicit in a vertebrate host the formation of specific **antibodies* or the generation of a specific population of **lymphocytes* reactive with the substance. Antigens are **protein* or carbohydrate, lipid or nucleic acid, or contain elements of all or any of these as well as organic or inorganic chemical groups attached to **protein* or other macromolecule. Whether a material is an antigen in a particular host depends on whether the material is foreign to the host and also on the genetic makeup of the host, as well as on the dose and physical state of the antigen.

arthralgia joint pain with objective findings of heat, redness, tenderness to touch, loss of motion, or swelling.

AST aspartate aminotransferase the **enzyme* that catalyzes the reaction of aspartate with 2-oxoglutarate to give glutamate and oxaloacetate. Its concentration in blood may be raised in liver and heart diseases that are associated with damage to those tissues. Normal AST levels range from 8 to 20 U/l. AST levels fluctuate in response to the extent of cellular necrosis.

bilirubin is the chief pigment of bile, formed mainly from the breakdown of hemoglobin. After formation it is transported in the **plasma* to the liver to be then excreted in the bile. Elevation of bile in the blood (>30 mg/l) causes **jaundice*.

carcinoma a malignant epithelial **tumor*. This is the most frequent form of cancer.

carrier is a person who has HCV (HBV, HDV) in his or her blood even if all symptoms have disappeared. Because the **virus* is present in the blood, it can be transmitted to others. The HBV carrier can be recognized by a specific blood test.

cirrhosis a chronic disease of the liver characterized by nodular regeneration of **hepatocytes* and diffuse fibrosis. It is caused by parenchymal necrosis followed by nodular proliferation of the surviving **hepatocytes*. The regenerating nodules and accompanying fibrosis interfere with blood flow through the liver and result in portal hypertension, hepatic insufficiency, **jaundice* and ascites. Cirrhosis is a more severe, irreversible process of liver inflammation, necrosis, and regeneration. In hepatitis C, cirrhosis occurs as a late stage sequela of chronic infection, and may take 20-30 years to develop.

codon the smallest unit of genetic material that can specify an **amino acid* residue in the synthesis of a polypeptide chain. The codon consists of three adjacent **nucleotides*.

cytopathic that kills the cells.

EIA *enzyme immunoassay

ELISA *enzyme-linked immunoassorbent assay

endemic continuously *prevalent in some degree in a community or region.

endoplasmic reticulum a network or system of folded membranes and interconnecting tubules distributed within the **cytoplasm* of eukaryotic cells. The membranes form enclosed or semienclosed spaces. The endoplasmic reticulum functions in storage and transport, and as a point of attachment of ribosomes during **protein* synthesis.

enzyme any **protein* catalyst, i.e. substance which accelerates chemical reactions without itself being used up in the process. Many enzymes are specific to the substance on which they can act, called substrate. **Enzymes* are present in all living matters and are involved in all the metabolic processes upon which life depends.

epidemic an outbreak of disease such that for a limited period a significantly greater number of persons in a community or region suffer from it than is normally the case. Thus an epidemic is a temporary increase in **incidence*. Its extent and duration are determined by the interaction of such variables as the nature and infectivity of the casual agent, its mode of transmission and the degree of preexisting and newly acquired immunity.

epitope also known as **antigenic* determinant. A localized region on the surface of an **antigen* which **antibody* molecules can identify and bind.

follicle a small, saclike depression.[1]

genome the total genetic information present .

genotype the genetic constitution of an individual.

hepatocytes are liver cells.

histopathology the study of the structural alterations of cells and tissues caused by disease.[1]

humoral pertaining to the humors, or certain fluids, of the body.

idiopathic pulmonary fibrosis chronic inflammation and progressive fibrosis of the pulmonary alveolar walls, with steadily progressive dyspnea, resulting finally in death from oxygen lack or right heart failure.[6]

IgG **antibodies* IgG is the most abundant of the circulating **antibodies*. It readily crosses the walls of blood vessels and enters tissue fluids. IgG also crosses the placenta and confers passive immunity from the mother to the fetus. IgG protects against bacteria, **viruses*, and toxins circulating in the blood and lymph.

IgM **antibodies* IgMs are the first circulating **antibodies* to appear in response to an **antigen*. However, their concentration in the blood declines rapidly. This is diagnostically useful, because the presence of IgM usually indicates a current infection by the pathogen causing its formation. IgM consists of five Y-shaped monomers arranged in a pentamer structure. The numerous **antigen*-binding sites make it very effective in agglutinating **antigens*. IgM is too large to cross the placenta and hence does not confer maternal immunity.

incidence the number of cases of a disease, abnormality, accident, etc., arising in a defined population during a stated period, expressed as x cases per 1000 persons per year.

interferon a **protein* produced in organisms infected by **viruses*, and effective at protecting those organisms from other **virus* infections. Interferons exert **virus*-nonspecific but host-specific anti*viral activity by inducing the **transcription* of cellular genes coding for anti*viral **proteins* that selectively inhibit the synthesis of *viral DNA and **proteins*. Interferons also have immunoregulatory functions. Production of interferon can be stimulated by *viral infection, especially by the presence of double stranded RNA, by intracellular parasites, by protozoa, and by bacteria and bacterial products. Interferons have been divided into three distinct types (a, ß, and ?) associated with specific producer cells and functions, but all animal cells are capable of producing interferons, and certain producer cells (leukocytes and fibroblasts) produce more than one type (both a and ß). Combination of pegylated a-interferon with ribavirin is the therapy of choice for treatment of chronic hepatitis C.

immune globulin (IG) is a sterile preparation of concentrated **antibodies* (immune globulins) recovered from pooled human **plasma* processed by cold ethanol fractionation. Only **plasma* that has tested negative for a) hepatitis B surface **antigen* (HBsAg), b) **antibody* to human immunodeficiency **virus* (HIV), and c) **antibody* to hepatitis C **virus* (HCV) is used to manufacture IG. IG is administered to protect against certain diseases through passive transfer of **antibody*. The immune globulins are broadly classified into five types on the basis of physical, **antigenic* and functional variations, labeled respectively **IgM*, **IgG*, IgA, IgE and IgD.

immune system our body's natural defense system, involving **antibodies* and a class of white blood cells called **lymphocytes*.

jaundice is a yellow discoloration of the skin and mucous membranes due to excess of **bilirubin* in the blood, also known as icterus.

leukopenia an abnormal decrease in the number of leukocytes in the blood.

lumen the cavity or channel between a tube or tubular structure.

lymphocyte a leukocyte of blood, bone marrow and lymphatic tissue. Lymphocytes play a major role in both cellular and **humoral* immunity, and thus several different functional and morphologic types must be recognized, i.e. the small, large, B-, and T-lymphocytes, with further morphologic distinction being made among the B-lymphocytes.

membranoproliferative glomerulonephritis chronic glomerulonephritis characterized by mesangial cell proliferation and irregular thickening of the glomerular capillary wall.[6]

microsome any of the vesicular fragments of *endoplasmic reticulum formed after disruption of and centrifugation of cells.[6]

microvesicular steatosis fatty change in which numerous small lipid droplets are present in the cytoplasm.[6]

myalgia pain in the muscles.

necrotizing vasculitis any of a group of disorders characterized by inflammation and necrosis of blood vessels, occurring in a broad spectrum of cutaneous and systemic disorders.[6]

nucleotide a molecule formed from the combination of one nitrogenous base (purine or pyrimidine), a sugar (ribose or deoxyribose) and a phosphate group. It is a hydrolysis product of nucleic acid.

nucleus a membrane-bounded compartment in an eukaryotic cell which contains the genetic material and the nucleoli. The nucleus represents the control center of the cell. Nuclei divide by mitosis or meiosis.

plasma the liquid matrix in which the blood cells and blood **proteins* are suspended in. It contains an extensive variety of solutes dissolved in water. Water accounts for about 90% of blood plasma.

polymerase an **enzyme* which catalyzes the replication of DNA (DNA polymerase) or RNA (RNA polymerase).

porphyria cutanea tarda familial or sporadic porphyria, characterized by liver dysfunction and photosensitive cutaneous lesions, with hyperpigmentation and scleroderma-like changes in the skin, and increased excretion of uroporphyrin; caused by a deficiency of uroporphyrinogen decarboxylase induced in sporadic cases by chronic alcoholism; autosomal dominant inheritance in familiar cases.[2]

polyarteritis nodosa a generalized arteritis characterized by necrosis of medium-sized and small arteries and involving many organs including the heart, gastrointestinal tract, muscles, and kidneys. It is one of the connective tissue disorders.[1]

prevalence is the number of instances of infections or of persons ill, or of any other event such as accidents, in a specified population, without any distinction between new and old cases.

prophylaxis is the prevention of disease, or the preventive treatment of a recurrent disorder.

protein large molecule made up of many **amino acids* chemically linked together by amide linkages. Biologically important as **enzymes*, structural protein and connective tissue.

reverse transcriptase an *enzyme that catalyzes the formation of DNA using an RNA template, and is thus an RNA-dependent DNA **polymerase*. The name refers to the fact that the *enzyme *transcribes nucleic acids in the reverse order from the usual DNA-to-RNA **transcription*.

RIBA™ recombinant immunoblot assay

rigors stiffness, inflexibility.

RT-PCR **reverse transcriptase* - **polymerase* chain reaction. A technique commonly employed in molecular genetics through which it is possible to produce copies of DNA sequences rapidly. **Qualitative RT-PCR for HCV** test to detect HCV RNA by amplification of *viral genetic sequences. **Quantitative assays for HCV RNA** tests to detect HCV RNA concentration (*viral load) by amplification of *viral genetic sequences or by signal amplification.

seroconversion the production in a host of specific **antibodies* as a result of infection or immunization. The **antibodies* can be detected in the host's blood **serum* following, but not preceding, infection or immunization.

serotype a subgroup within a species, defined by reaction of one or more *antigens with the corresponding anti*serum.[1]

serum is the clear, slightly yellow fluid which separates from blood when it clots. Sera containing **antibodies* and antitoxins against infections and toxins of various kinds (antisera) have been used extensively in prevention or treatment of various diseases.

sialadenitis inflammation of a salivary gland or glands.[1]

Sjögren's syndrome a symptom complex of unknown etiology, usually occurring in middle-aged or older women, marked by the triad of keratoconjunctivitis sicca with or without lacrimal gland enlargement, xerostomia with or without salivary gland enlargement, and the presence of connective tissue disease, usually rheumatoid arthritis but sometimes systemic lupus erythematosus, scleroderma, or polymyositis. An abnormal immune response has been implicated.[6]

thrombocytopenia a fewer than normal number of platelets per unit volume of blood, i.e. fewer than 130 x 10^9 platelets per liter.

titre a measure of the concentration or activity of an active substance.

transcription the process by which a strand of RNA is synthesized with its sequence specified by a complementary strand of DNA, which acts as a template. The *enzymes involved are called DNA-dependent RNA *polymerases.

translation the process of forming a specific **protein* having its **amino acid* sequence determined by the **codons* of messenger RNA. Ribosomes and transfer RNA are necessary for translation.

tumor a lump due to uncontrolled cell division, may be benign or malignant. Malignant tumors cause cancer. Tumors are able to spread to other parts of the body (metastasize) and begin secondary growths at these other sites.

vaccine an **antigenic* preparation used to produce active immunity to a disease to prevent or ameliorate the effects of infection with the natural or "wild" organism. Vaccines may be living, attenuated strains of **viruses* or bacteria which give rise to inapparent to trivial infections. Vaccines may also be killed or inactivated organisms or purified products derived from them. Formalin-inactivated toxins are used as vaccines against diphtheria and tetanus. Synthetically or genetically engineered **antigens* are currently being developed for use as vaccines. Some vaccines are effective by mouth, but most have to be given parenterally.

viremia the presence of *viruses in the blood, usually characterized by malaise, fever, and aching of the back and extremities.[6]

virion a structurally complete *virus, a *viral particle.[1]

virus any of a number of small, obligatory intracellular parasites with a single type of nucleic acid, either DNA or RNA. The nucleic acid is enclosed in a structure called a capsid, which is composed of repeating **protein* subunits called capsomeres, with or without a lipid envelope. The complete infectious *virus particle, called a *virion, must rely on the metabolism of the cell it infects. *Viruses are morphologically heterogeneous, occurring as spherical, filamentous, polyhedral, or pleomorphic particles. They are classified by the host infected, the type of nucleic acid, the symmetry of the capsid, and the presence or absence of an envelope.

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