CHAPTER 2
LITERATURE REVIEW

Hepatitis C Virus

History of Hepatitis C virus

The hepatitis C virus (HCV) was discovered in 1989 by Choo et al. as a single stranded RNA virus found in the serum of patients with post-transfusion non-A-non-B (NANB) hepatitis (Choo et al, 1989).

It is well known that an acute non-A, non-B hepatitis (NANBH) is characterized by a high incidence of chronicity and lead to chronic liver disease such as cirrhosis of the liver and eventually, hepatocellular carcinoma (HCC). Recent advances in technology have made it possible to identify hepatitis C virus (HCV) infection by assaying antibodies to HCV (anti-HCV) and by a detection of HCV-RNA (Kiyasawa et al, 1994).

Although acute hepatitis type C is often anicteric and asymptomatic, it may progress to chronicity in a significant percentage of patients. Thus, the chronicity is the most characteristic clinical feature of hepatitis C. A study of chronic hepatitis established, the rate of spontaneous cure of the liver disease is very rare (below 2%). The duration from the onset of acute hepatitis until the time of diagnosis of cirrhosis and of HCC was about 20 and 30 years, respectively. The long-term clinical course of hepatitis C is divided into the three phases of acute, silent and reactivated. The acute phase lasts from the onset of disease until 2-3 years and the silent phase lasts for 10-15 years. In the silent phase, the serum transferase level remains relatively low, below 100 IU/L, and is sometimes within the normal range. In the reactivated phase, the level of serum aminotransferase increases and remains at high or moderate level until HCC develops. The mechanism of chronicity of hepatitis C is unknown. However, recent advances in molecular analysis may soon eludicate this (Kiyasawa et al, 1994).

Structure of HCV

Hepatitis C virus is considered in Flaviviridae family. It is a positive stranded RNA virus and enveloped virus. The size is less than 80 nm, and consisted of approximately 9,400 nucleotides (Choo et al, 1989, Takamizawa et al, 1991). Such a physical structure is consistent with early studies examining the size and sensitivity of infectious HCV particles to lipid solvents (Bradley, 1985). However, the HCV particles have never been visualized by electron microscope, and thus its exact physical appearance is not known. There is low level of nucleotide sequence related between HCV and the flavivirus, and even similarities in the hydrophathy profiles of the putative viral structural proteins. However, there is greater enetic relatedness with the pestiviruses, important veterinary pathogens that are also classified within the Flaviviridae family and that include bovine viral diarrhea virus, classic swine fever virus (previously known as hog cholera virus) and border disease virus (Choo, 1991, Miller, 1990).

The HCV genome contains a single large open-reading frame (ORF) that follows a relatively lengthy 5' nontranslated region of approximately 342 bases (Figure 1). The 5' nontranslated RNA appears to play a critical role in controlling virus translation and may be important in the pathogenesis of HCV infection (Tsukiyama, 1992, Yoo, 1992). The 3' nontranslated region of the genome appears to contain a unique polyuridylic acid tract, although the existence of a more typical polyadenylic acid tract has been reported as well (Matsuura, 1993). The large ORF encodes a polyprotein that undergoes post-translational cleavage mediated by both cellular and virus specified proteases (Hijikata, 1991, Grakoui, 1993). The amino third of the polyprotein contains a series of structural proteins that include a 21-kd core (nucleocapsid) protein (C) and two envelope glycoproteins, E1 and E2 (Figure 1). These proteins are cleaved from the polyprotein by a signal peptidase present within the endoplasmic, and appears to be an internal viral structural protein somewhat resembling the core protein of hepatitis B. Preliminary evidences suggest that it may undergo additional proteolytic processing during virus replication. E1 and E2 are translocated into the endoplasmic reticulum and subsequently become heavily glycosylated during transport through the Golgiapparatus (Hijikata, 1991).

These glycoproteins are thought to be presented in the lipid envelope of the HCV particle. The falviviruses possess only a single major envelope protein, but E2 may be analogous to the NS1 protein of flaviviruses. In contrast, the pestiviruses have three major envelope proteins (Grakoui, 1993).

The remainder of the viral polyprotein contains a series of nonstructural viral proteins involved in the replication of the virus. The processing of this region of the polyprotein is complex, and the functions of several of the individual proteins remain obscure. These functions include, however, at lease two viral proteases (NS2 and NS3) (Hijikata, 1993), a putative helicase NS4 (Suzich, 1993), and an RNA polymerase (NS5).

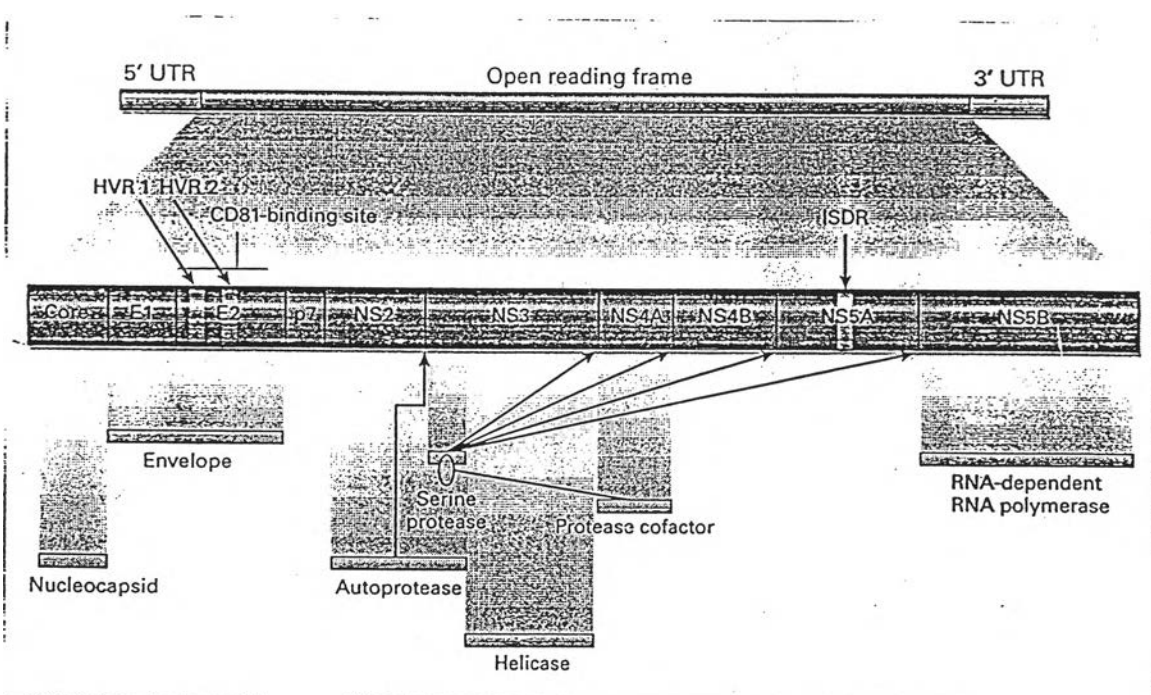


Figure 2.1 Organization of the RNA genome of HCV. The probable structure of the HCV particle is depicted on the left. NTR, nontranslated regions.

From : Lemon SM and Brown EA. Hepatitis C virus. In : Mandell GL, Bennett JE, Dolin R, editors. Princeples and Practice of Infectious Diseases. USA : 1995: 1474-86

Prevalence of HCV infection (Koff, 1991)

Studies of blood donors and pregnant women have suggested that the prevalence of anti-HCV antibodies is low in Northern Europe and Asia (0-1.9%), and highest in Africa (1.7-5.2%). In one Italian study, however, 10% of populations of factory workers were found to be anti-HCV-positive, which the authors suggest implies a relationship with socioeconomic variables. Furthermore, a Japanese study showed that the anti-HCV positivity rate increases with age, ranging from 0.2% in blood donors under 20 years of age to 3.9% in those over 51. In a French study, the prevalence of HCV infection among healthy blood and organ donors was generally low, but varied considerably among pregnant women depending on their country of origin (Table 2.2).

Table 2.2 Prevalence of anti-HCV positively in healthy Population by geographic distribution (Koff, 1991).

Countries	% of Anti-HCV positivity
Egypt	5.2
France	
Blood donors	0.3
Organ donors	0.9
Pregnant women from:	
France/French territories	1.6
North Africa	1.7-1.9
Sub-Saharan Africa	4.8
West Africa	4.1
Asia	0-1.8
Europe/USA	0
Southern Europe	1
Germany	0.5
Italy	0.9-1.1
Japan	0.7-1.9
Spain	1.2-1.5
USA	0.1

Epidemiology

WHO estimates of 170 million infected patients worldwide, and up to 90% of these will progress to chronic liver disease (Alter et al, 1992).

Pathogenesis and Pathology

Hepatitis C virus (HCV) is one of the viruses (A, B, C, D, E, G, TT and SEN) which together account for the vast majority of cases of viral hepatitis (Christopher, 2001).

Pathogenesis of hepatitis C has been unknown, but liver is the target organ of this disease. The untrastructural changes in hepatocytes were studied in chimpanzees and marmosets. Light microscopic examination of animal's liver biopsy specimens during the first episode of hepatitis revealed the presence of parenchyma lesions that were consistent with a diagnosis of acute viral hepatitis (Hadler, 1991, Bradley, 1983). Although the histological features of hepatitis C do not differ fundamentally from those of hepatitis B, there are some quantitative differences. Weak but constant necroinflamation and a strong lymphocytic reaction of the portal tracts appear to be relatively unique to chronic hepatitis C. Nearly all chronic hepatitis C cases do not improve during the natural course of infection (Uchida, 1994).

Worldwide epidemiology of HCV genotypes

Available evidence indicates that some HCV types are distributed worldwide, while others are confined to more restricted geographical areas. Genotypes 1, 2 and 3 are the most frequently encountered viral types worldwide. Thus, type 1a is most frequently found in Northern Europe and North America, whereas 1b is the most common genotype in Japan, Southern and Eastern Europe. The diffusion of genotype 3, which is endemic in South-East Asia, shows significant variability in different countries (Mario, 1999).

The distribution of the HCV genotype in Thailand was different from those found in other countries in Southeast Asia including Singapore, Indonesia, and the Philippines. HCV genotypes 1a and 1b were the most prevalent genotypes found in those countries, whereas in Thailand, genotype 3a was the most common genotype. The difference in the genotypic distribution patterns may reflect the difference in transmission routes and the origin of infection. Genotype 1a was also the major genotype found in patients receiving multiple transfusions, while genotype 3a was found primarily in intravenous drug abusers. HCV genotypes 3a, 1b, are predominant in Thailand (Kanistanon, 1997).

Severity of Hepatitis C

Acute infection

Acute hepatitis C is clinically indistinguishable from other types of acute viral hepatitis in the individual patient. However, the incubation period for acute hepatitis C averages about 6 weeks, based on studies of transfusion recipients (Aach, 1991), and in thus intermediate between type A and B hepatitis. Symptoms are usually mild and often subclinical or anicteric. The clinical symptoms are anorexia, abdominal pain, nausea, vomiting, itchiness, dark urine, jaundice, diarrhea, hepatomegaly and splenomegaly (Myint, 1985) and fever usually rises not more than 38.5 °C and acute hepatitis C is slightly less severe than hepatitis A or B (Hadler, 1991). For the ALT levels, 50% of patients have elevated ALT levels five times over the normal value with asymptomatic hepatitis (Pramoonsinsub, 1990).

Chronic Hepatitis C

Chronic hepatitis C is often but certainly not always found in individuals with prior risk factors involving potential exposure to blood (i.e., blood transfusion, injecting drug use, or occupational exposures). The typical picture is that of a relapsing, remitting infection with recurrent bout of hepatitis marked by periodic fluctuations in serum ALT activities. Specific symptoms and signs related to liver dysfunction, such as jaundice, ascitis, or gastrointestinal bleeding, are present only in far advanced disease. During quiescent periods, even the serum

ALT may be normal or near normal. Thus, the absence of ALT abnormalities does not preclude chronic HCV infection (Rumi, 1990).

There is a variable rate of fibrosis progression with a median time from infection to cirrhosis of approximately 30 years (range 13-42 years). Independent factors associated with an increased rate of fibrosis progression include age at infection greater than 40 yers, daily consumption of 50 g or more of alcohol, and male sex. There was no association between fibrosis progression and genotype (Poynard et al, 1997).

In HCV associated compensated cirrhotics, five year survival is over 90% and 10 year survival 80%. A five year follow up showed that the risk of developing HCC was 7% (1.4% per year) and 18% decompensated. After decompensation, prognosis is poor with 50% survival at five years (Fattovich et al, 1997).

Hepatocellular carcinoma (HCC)

The duration from acute to chronic hepatitis and HCC has not been clear, however some reports had documented the mean interval developing of chronic hepatitis, cirrhosis and HCC were 10, 20, 30 years (Pramoonsinsub,1990, Hollinger, 1990, Katkov et al, 1991). In Thailand, hepatitis C virus infection was not a major cause of HCC but many studies indicated a strong association between HCV and the development of HCC. The frequent of anti-HCV in patients with HCC was 13% in USA (Adrian et al, 1991), 30% in South Africa (Kaklamani et al, 1991), 60% in Japan and 74% in Italy (Colombo et al, 1989). In Spain 75% (Bruix et al, 1989), but the study in Thailand showed that some of HCC patients were also alcoholic or had been exposing to HBV. It has generated the hypothesis that HCV may operated as a cofactor with other causative agents and substances in the development HCC (Katkov et al, 1991, Choo et al, 1990).

In 1995, Tong et al published a study of 131 PTH cases referred to a centre between 1980 and 1994. A total of 101 patients underwent liver biopsy a mean of 22 years post transfusion. Twenty seven (20.6%) had chronic hepatitis, 30 (22.9%) had CAH, 67 (51.1%) had cirrhosis, and seven (5.3%) had HCC after mean time intervals from transfusion of 14, 18, 20, and 28 years, respectively. During the follow up period, 20 (15.3%) patients died, 19 (95%) from complications of cirrhosis or the development of HCC (Tong et al, 1995).

Some symptoms of hepatitis

- Fatigue is the most common symptom. Nearly all people with hepatitis complain of some degree of tiredness.
- Stress
- Depression
- Muscle, joint aches and pains
- Anxiety and irritability
- Headaches
- Sleep disturbances
- Other less common symptoms include pain or discomfort in the abdomen on the right side, itching, nausea, appetite/weight loss, and mental fuzziness (Nelson, 2001).

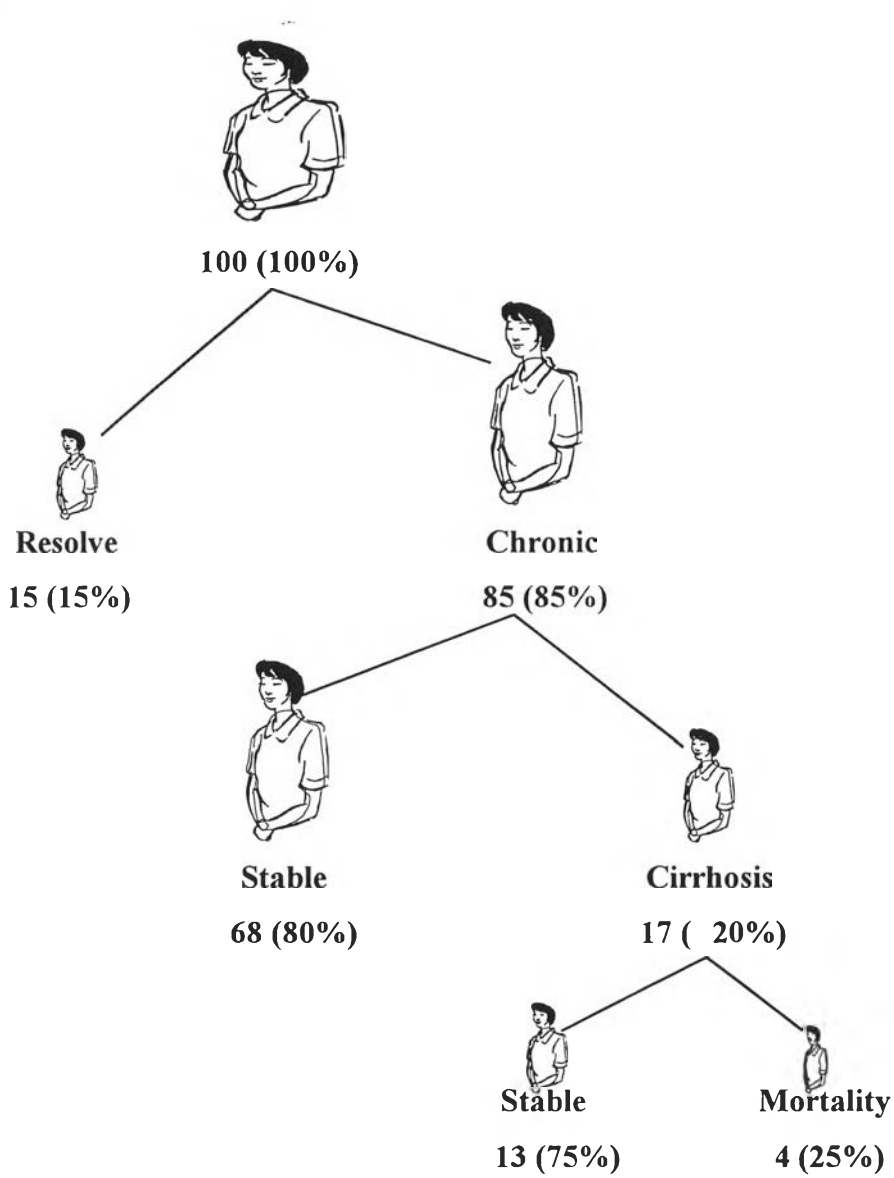


Figure 2.2 Outcomes in persons who develop hepatitis C infection. Harvey J. Alter, MD, Transfusion Service, National Institutes of Health.

Diagnosis of HCV infection

As our knowledge of the structure of HCV has increased, serum tests for the diction of HCV infection have become more sensitive. At present, there are no direct tests for HCV antigens. Rather, subjects are tested for the presence of anti-HCV antibodies. This usually involves an initial screening test with an enzyme-linked immunosorbent assay (ELISA), described below. Positive results are then checked with the more sensitive recombinant immunoblot assays (RIBAs). If available, tests for HCV-RNA (using PCR or the newer, branched DNA signal amplification method) may also be done to determine the presence or absence of virus in serum.

1. Diagnosis by using ALT level

For many years, a diagnosis of NANB hepatitis was necessity tentative. Such a diagnosis could only be based on exclusion of other etiological agents of hepatitis such as the viruses for hepatitis A and B, cytomegalovirus and Eptein-Barr virus. In 1981, the transfusion-transmitted virus study showed that ALT level in blood donors predicted the risk of NANB hepatitis in transfusion recipients (Aach et al, 1981, Alter et al, 1981). ALT screening was introduced as a surrogate for NANB hepatitis.

In 1986, blood bank throughout the United States was problematic for several reasons. The test was neither specific nor reproducible overtimes. There was no obvious cut-off that separated infection, blood donor from noninfection, and the advice given to donor was often confused and not medically useful. The implementation of ALT testing led to the discarding of approximately 2% of blood donation in the United States (Alter et al, 1981, Cable et at, 1997).

2. Diagnosis by using Enzyme-Linked Immunosorbent Assay (ELISA)

In 1989, an incision and extensive attack of this problem is now possible because of the elegant (and arduous) pioneering work of Chiron Laboratories who active milestone success by expressing in a recombinant system, an antigen after cloning part of the genome of what we know as hepatitis C virus. The first of such assay incorporated the C-100-3 polypeptide express in yeast. This protein was used to coat the solid phase of an antiglobulin-based assay, initially as a radioimmunoassay for antibody to HCV. Commercially, the assay is marketed worldwide in a microplate ELISA formatted by Ortho Diagnotics and is now also available as a bead-based ELISA from Abbott Diagnostics (Alter et al, 1989).

In 1992, on the basis of first-generation test was inadequately sensitive in patients with a prolonged window period and in patients who had lost HCV antibody (Kleinman et al, 1992). The sensitive of the first-generation HCV ELISA was 86-96% and specificity was 99-100% (Choo et al, 1990, Lim et al, 1991).

Anti-HCV was detected 6-18 weeks after the onset of hepatitis with the first-generation test (Mattson et al, 1992, Mattson et al, 1991), and 2-8 weeks with the second-generation test (Choo et al, 1990, Esteban et al, 1990, Donald, 1989). The second-generation test detected seroconversion more than one month before the first-generation test (Farci et al, 1992, Housein et al, 1991, Wang et al, 1992).

After cloning of hepatitis C virus has led to the development of several serologic assays for the detection of HCV infection. The successive addition of expressed antigen resulted in anti-HCV test of increasing sensitivity (Vrielink et al, 1995). In early 1996, a more study reported that with third-generation screening; only 1 in 103,000 donors would be in the seronegative window period of HCV infection (Schreiber et al, 1996).

Hepatitis C testing in patients with autoimmune chronic active hepatitis (AI-CAH) has been suggested to yield up to 65% false-positive results by using the first-generation (Lenzi et al, 1991). In the other patient groups beside AI-CAH, false-positive results haven't been a problem. The blood donors with positive results of an anti-HCV first generation and no risk factors and normal ALT levels have at least a 50% due to chance of having a false-positive result. By contrast, those with positive results and with a history of blood

transfusion or intravenous drug abusing or tattooing and in whom elevated ALT have over 95% likeihood of a truly positive result when the second-generation tests are involved.
The second-generation test appears to be remarkable reliable in excluding false-positive (Lenzi et al, 1991).

Third-generation ELISA now widely used in blood donor screening is even more sensitive and specific than the earlier ELISA, and is practically 100% effective in preventing transmission of HCV to recipients. However, HCV may still remain undetected in individuals who were infected less than 6 months previously and in immunosupressed patients. False-positive result also remains common among blood donors. All samples, which were positive on ELISA, should therefore be confirmed using supplementary tests (Schreiber et al, 1996).

3. Supplementary test: Recombinant Immunoblot Assay (RIBA)

A recombinant immunoblot assay (RIBA) for anti-HCV has proven to be a valuable research tool for elucidating the validity of the majority of ELISA-positives. First generation supplementary RIBAs have been succeeded by tests that detect antibodies to two viral antigens (RIBA-I, Table1). The second-generation RIBA (RIBA-II) has proven very useful in excluding false-positive ELISA results and also in identifying infectious patients. A close correlation has been reported between RIBA-II positive and viremia (HCV-RNA) based on polymerase chain reaction (PCR). The third generation RIBA (RIBA-III, Table1) has also been developed, with enhanced sensitivity and specificity compared to RIBA-II (Schering-Plough eds, 1996).

Table 2.1. Supplementary test: RIBAs (Schering-Plough eds, 1996)

Supplementary assays:	
1st generation RIBA	Anti-c 100/NS4, anti-5-1-1
2nd generation RIBA-II	Anti-c 100/NS4, anti-5-1-1
	Anti-c33/ns., anti-c22/c
3rd generation RIBA-III	Anti-c22/c, anti-c/NS3/NS4, NS5

The RIBA is the HCV confirmatory test that uses to determine the specificity of the HCV ELISA (Weiner et al, 1990, Alter et al, 1990). The full RIBA positively is associated with HCV infectivity, whereas an ELISA positive, RIBA intermediate result reflects a non-infectious anti-HCV positive (Estoban et al, 1990).

4. Detection of HCV-RNA: Polymerase Chain Reaction (PCR)

Direct tests for HCV antigens in serum are not yet available, so HCV-RNA is currently the best marker of viremia and infectivity, and possibly of disease activity. Although testing for HCV-RNA remains largely restricted to certain specialized centers, a commercially available HCV PCR assay has recently been introduced. Detection of HCV-RNA on PCR is not conclusive. PCR entails the use of oligonucleotide primers, which are homologous to known nucleic acid sequences to enzymatically amplify the DNA between the two primers. The method is sensitive enough to amplify a single DNA molecule to levels that are easily detected (Lucey and Traber, 1991). Detection of HCV-RNA may be useful in the diagnosis of acute hepatitis C, particularly in the absence of detectable anti-HCV (Christiano et al, 1990, Waxman et al, 1991) and for evaluating the sensitivity and PCR entails the use of oligonucleotide primers, which are homologous to known nucleic acid sequences to enzymatically amplify the DNA between the two primers. The method is sensitive enough to amplify a single DNA molecule to levels that are easily detected (Lucey and Traber, 1991). Detection of HCV-RNA may be useful in the diagnosis of acute hepatitis C, particularly in the absence of detectable anti-HCV (Christiano et al, 1990, Waxman et al, 1991) and for evaluating the sensitivity and specificity of other tests as they are developed

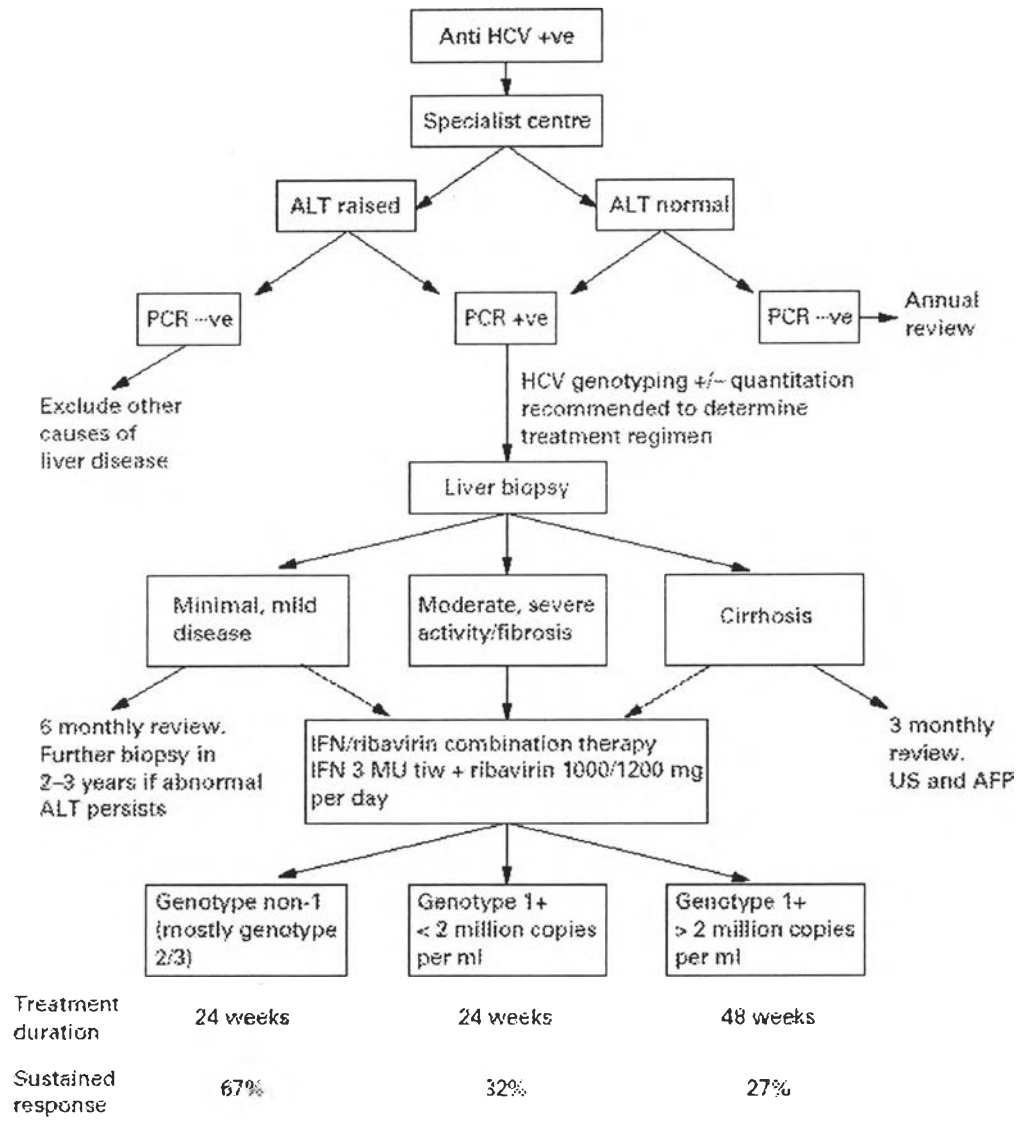
(Christiano et al, 1990). PCR and the new branched-DNA method for detecting HCV-RNA greatly facilitated the assessment of specific treatment efficacy (Lan et al, 1991).

During the acute phase of illness, HCV-RNA was detected 1-2 weeks after inoculation (Farci et al, 1992). It suggests that the virus is present in serum during the acute phase of the disease and that viremia may therefore correlate with disease activity (Waxman et al, 1991). The study in PT-NANBH patients in Taiwan found that 27 of 35 patients were positive for HCV-RNA, whereas 23 of them were positive for the first-generation ELISA and 28 of them were positive for the second-generation ELISA (Wang et al, 1992). The other studies found that HCV-RNA was detected in 45-93.8% of patients positive for anti c100-3 (Christiano et al, 1990, Hagiwara et al, 1992). The most important consideration for false-negative results is the existence of different strains or subtype of HCV. Significant mismatches between PCR primers and viral sequence could markedly diminish the sensitivity of the assay or completely eliminate amplification (Christiano et al, 1990).

In 1999, Food and Drug Administration U.S. Department of Health and Human Services Public Health Service (FDA) reported that they approved an improved, more specific, supplemental test to confirm screening test results for antibodies to the hepatitis C virus (HCV). The RIBA 3.0 Strip SIA is a three-stage test, which uses five genetically engineered HCV antigens -- proteins that react to HCV antibodies, was approved in June 1993 and was also manufactured by Chiron. The new supplemental test, called the RIBA HCV 3.0 Strip Immunoblot Assay (SIA), is used to test blood specimens that have already tested repeatedly reactive on licensed screening tests. This new test can detect one more type of antibody to the HCV virus than the previous supplemental test and is better at distinguishing truly positive from falsely positive test results.

In 1999, Lauren Neergaard, AP Medical Writer, reported that the new "nucleic acid testing", called NAT can detect can detect tiny amounts of a virus, such as the liver-destroying hepatitis C or the AIDS virus, before the blood donor's body has even recognized the infection. At first, NAT will hunt hepatitis C and HIV. But eventually, blood banks may test for other contaminants. However, the USA government hasn't mandated NAT-tested blood yet because technically it's still experimental: Genetic fingerprinting is commonplace in laboratories, where it's called PCR, for polymerase chain reaction testing.

In 2000, AcroMetrix, the privately held California corporation specializing in products and services that standardize and control molecular technologies, announced the release of their new Hepatitis C virus (HCV) nucleic acid controls for blood screening and medical diagnostic laboratories worldwide. Michael J. Eck, President of AcroMetrix said that "In continued support of the World Health Organization's declaration of the year 2000 as the 'Year of Blood Safety,' AcroMetrix is pleased to take an active role in assisting blood screening organizations and laboratories with new and innovative NAT controls for hepatitis C virus,". Industry experts anticipate that nucleic acid testing (NAT) will become commonplace in the blood screening industry by year-end.



Hepatitis C virus (HCV) algorithm. Sustained response defined as negative polymerase chain reaction (PCR) six months after treatment cessation. Data derived from Poynard and colleagues and McHutchinson and colleagues, as shown in the review by Weiland. IFN, interferon; ALT, alanine aminotransferase; US, ultrasound; AFP, Alphafetoprotein (Poynard et al, 1998).

Transmission

The transmission of HCV by blood transfusion and blood products, including factor VIII and immunoglobulin, has been fully documented. The long-term follow-up studies of recipients of contaminated blood or blood products indicate a high rate of infection and, of those infected, 60-70% may develop chronic viral carriage. In those with multiple exposures, for example haemophiliacs, virtually all who received factor VIII before the introduction of heat treatment in 1988 are anti-HCV positive (Bjorkander et al, 1996).

1. Transmission by blood and blood products

It is clear that transfusion of infected blood products is a particularly efficient route of HCV transmission. There is now clear evidence that approximately 80-90% of cases of PT-NANBH are due to HCV infection. Although blood transfusion is an efficient route of transmission, it can not account for the prevalence and maintenance of HCV in the population, most individuals do not receive a transfusion during their lifetime. However, transfusion can be a significant source of infection. Hemophiliacs, who are exposed to large amounts of single donor product or to product derived from large pool of plasma are a high risk group (Alter et al, 1992, Van et al, 1989, Contreras et al, 1991).

2. Transmission by injecting drug users (IDUs)

Individuals sharing syringes or needles for injecting drug use are at high risk of infection by parenterally transmitted blood-borne infectious agents consequently, the prevalence of anti-HCV in IDUs is high (Luksamijarulkul and Plucktaweesak, 1996, Alter etal, 1990).

3. Transmission by organ and tissue transplantation

HCV infection can be transmitted through organ and tissue transplantation. Post-transplantation liver disease is still an important cause of morbidity and mortality, especially in renal transplant recipients (Braun, 1990). Present data on HCV transmission by donated organ and tissue are limited but it is clear that the screening of potential organ donors for anti-HCV would be beneficial in minimizing any risks of post-transplantation HCV infection.

4. HCV Transmission by a history of imprisonment

High-risk behaviors for transmission of HIV and HBV (ie, IDUs and unprotected sex) appear to be widespread in prisons and young often institutions. It is not surprising, therefore, that the risk of HCV infection is also increased among prisoners (Stark et al, 1997).

5. HCV Transmission by hemodialysis

Transmission of HCV between hemodialysis patients may also occur, although the risk has been reduced by more stringent environmental control measures and screening of patients for anti-HCV antibodies (Schering-plough eds).

6. Mother-infant transmission

By comparison with HBV, maternal transmission would also seem likely. However, transmission from HCV carrier mother to their offspring has been reported only few studies (Vassiliki et al, 1998, Zanettti et al, 1995). A study of Giovannini M, et al.(Giovannini et al, 1990) documented that transmission to children increased when simultaneously infected with maternal HIV.

7. HCV infection in health care workers.

The prevalence of anti-HCV in health care workers was 0.7-2% (Fujiyama et al, 1991, Liaw et al, 1991, Hofman and Kunz, 1991). The persons having direct contact with the patients, such as doctors and nurses,, seem to be at a higher risk of infection than those with only indirect contact, such as laboratory technicians and cleaning personnel (Hofman and Kunz, 1991). However, the prevalence rates in this group didn't differ significantly from prevalence rates found among volunteer blood donors or general population (Liaw et al, 1991, Arguillas et al, 1994).

8. Transmission through non-human vectors

Transmission through non-human vectors, not ably arthropods, is a well-defined route for some infectious agents. Yellow fever virus, the prototype flavivirus, is transmitted by this route. Currently, however, there are no confirmed reports of non-human transmission of HCV (Hoofnagle, 1991).

9. Sexual transmission

At first sight, sexual transmission might appear to be one of the most likely cause of spreading HCV. The studies in homosexual males found that the HCV prevalence ranged from 1.3 to 7.8% (Stevens and Taylar, 1990), 10% of hepatitis patients with the only identifiable source of infection is heterosexual activity with multifiable partners or household or sexual exposures to a contact with hepatitis (Zuckerman et al, 1998) and in female sex workers were 3 to 12% (Wu et al, 1993, Gutierrez et al, 1992). Anti-HCV has been found in 11% of sexual partners of anti-HCV positive IDUs and correlates with the presence of anti-HIV (Tor et al, 1990).

10. HCV infection in post transfusion hepatitis (PTH)

HCV is the cause of PTH. PTH patients include the patients that receive blood or blood components during operation and hematologic diseases who receive multiple transfusions. The prevalence of anti-HCV in PT-NANBH was 40-76% in USA (Kuo et al, 1989, Jott et al, 1990), 47-85% in German and Spain (Esteban et al, 1989), 61-69% in Taiwan or Japan or China (Chen et al, 1991, Meng et al, 1991). In another study, in Thailand NANBH was reported as being the etiology of 62.5% of HCV (Poovorawan et al, 1991). Punyagupta concluded that NANBH was more common than hepatitis B virus in the etiology of PTH in Thailand (Nuchprayoon et al, 1993).

Epidemiological Variables

Personal Characteristics

1. Age:

Hepatitis C may occur in all age groups: however, most cases occur among young adult. Age distribution of disease is related to patterns of exposure such as drug abuse in young adult, transfusion in children and old adults (Hadler and Margolis, 1991, Novati et al, 1992). The studies in blood donors, there was no difference among age groups (Hadler et al, 1991).

2. Sex:

Hepatitis C virus infection is similar for both sex (Nakashima et al, 1992, Hadler and Margolis, 1991, Alter et al, 1990).

3. Race:

Parenterally transmitted NANBH occurs worldwide with no racial predilection (Hadler and Margolis, 1991, Alter et al, 1990) and higher prevalence in black race than other race (Hillard et al, 1993).

4. Occupation:

Health care workers with blood exposure and in particular, hemodialysis staff appear to be at some risk of NANBH (Kuo et al, 1989). Hepatitis C virus transmission to a health care worker by needlestick accident has been reported (Vander et al, 1994, Tao and Wang, 1991). Between 5-10% of sporadic NANBH cases in developed countries occur in this group (Kuo et al, 1989).

5. Socioeconomic factors:

There are limited studies in socio-economic factor that concerning with HCV infection. Some studies indicated that low socio-economic conditions have higher risk of HCV infection (Feinstone, 1990, Hollinger, 1990). However, the specific risk factors associated with low socio-economic level have not been elucidated (Steven and Taylor, 1990). The horizontal transmission of HCV among person under similar environmental

conditions is the predominant mode of transmission and improvements in sanitary conditions have likely been contributing significantly to the striking reduction of HCV infection rate (Tao and Wang, 1991).

6. Geography:

NANBH has been documented to be an important cause of acute and chronic hepatitis in all parts of the world (Nishioka, 1994).

7. Temporality:

No significant difference in the incidence of hepatitis C was detected, it occurs throughout the year (Kuo et al, 1989, Jawetz et al, 1991, Laskus et al, 1991).

8. Other factors:

The other factors of NANBH transmission, demonstrated or suspected, include tattooing, ear piercing, blood transfusion, history of STD in the last year, history of having sex equal or more than twice a month, number of sexual partners per month and condom use (Thomas et al, 1995, Nakashima et al, 1992, Hillard et al, 1993, Petersan et al, 1992, Stary et al, 1992). In one study found that liver disease patients with tattooing were higher anti-HCV positive (Hishioka, 1991). Other factors in sexually transmitted risk group found that coincidence of hepatitis C virus antibodies and other sexually transmitted disease such as gonorrhea the prevalence was 12.00%-13.60% (Hillard et al, 1993, Stary et al, 1992), syphilis was 2.70%-17.20% (Hillard et al, 1993, Stary et al, 1992) and anti-HIV positive was 50.00% (Stary et al, 1992).

Treatment of HCV infection

Therapy should not be started until a firm diagnosis of chronic hepatitis C is made. Chronic hepatitis C can be diagnosed based on finding persistent elevations of ALT, anti-HCV in serum and liver histology compatible with chronic hepatitis. Patients should have elevations of serum ALT for at least 6 months or for a shorter period if it clears from the history that the disease has longstanding. A liver biopsy is necessary to document that chronic hepatitis is present, to assess the severity of hepatocellular injury and fibrosis and to help rule out other diagnoses such as alcoholic liver disease, hemochromatosis and sclerosing

cholangitis. Patients should have firmed serological or epidemiological evidence of hepatitis C. Alpha interferon is currently licensed for use in chronic hepatitis C. The recommended regiment of alpha interferon is 3 MU given either subcutaneously or intramuscularly three times weekly for 6 months (24 weeks). Actually, the optimal dose and duration of therapy are controversial, with some investigators recommending higher dose (5 MU three times weekly) for more prolonged periods (12 months or 48 weeks) (Hoofnagle, 1991). Alpha interferon has many side effects, but must are self-limiting and tolerable, and almost all are rapidly and fully reversible when the drug is stopped (Renault and Hoofnagle, 1991). The fear of interferon's side effect should not cause avoidance of therapy. In randomized trial of alpha interferon, only 3-10% of patients were not able to tolerate the full 6 months of treatment (Davis et al, 1989, Marcellin et al, 1991).

Interferon Monotherapy

Numerous studies have now been published to evaluate different IFNs, dosing regimens and response definitions. The disparate study designs and data analysis make interpretation of the results and comparison with other studies difficult. Few trials have included more than 100 patients per treatment group (Poynard et al, 1996).

The goal of treatment is the achievement of sustained (24-48 weeks post treatment cessation) transaminase and virological response (PCR negative) with histological improvement. Most of the treatment trials have used similar doses of between 1 and 3 million units (MU) of IFN three times a week for periods of 3-6 months. A dose of 3 MU is more efficacious than 1 MU (Causse et al, 1991). In addition, only those patients receiving 3 MU had significant improvements in liver histology. Alberti et al have shown that 6 MU three times a week leads to a higher proportion of patients with normal ALT at the end of treatment compared with those treated with 3 MU three times a week (Alberti et al, 1993). Another study using 10 MU three times a week suggested that sustained response rates could be as high as 50% although there is a greater risk of treatment failures due to side effects (Iino et al, 1993).

Longer treatment regimens of 12 or 18 months also resulted in greater numbers of sustained responders. In one study with a three year follow up period, treatment for 48 weeks led to a sustained biochemical response in 57.1% of patients compared with 15.4% in patients treated with the same dose for 24 weeks (Saracco et at, 1993). One trial studied 329 patients treated initially with 3 MU three times a week for six months and then randomised to a

further one year of 3 MU or 1 MU three times a week or no further treatment (Poynard et al, 1995). A total of 303 patients were randomised and the study end points were normalisation of ALT at the end of treatment during a follow up period of 19-42 months and improvement in histology at the end of treatment. Patients treated with 3 MU for 18 months were more likely to have normal ALT at the end of treatment ($p=0.008$), during follow up ($p=0.02$), and to have improved histological activity scores at the end of treatment ($p=0.02$).

The majority of patients (>90%) with sustained response seem to maintain normal ALT with negative HCV-RNA in prolonged follow up (1-6 years) (Boyer et al, 1995). The histological appearances also improve and in some patients the liver becomes normal.

Ribavirin Monotherapy

Initial pilot studies with ribavirin revealed encourageing results with significant biochemical responses during treatment but there was always relapse following treatment withdrawal. There was no effect on HCV viraemia (Reichard et al, 1991 and Di Bisceglie et al, 1994).

More recently, randomised, double blind, placebo controlled trials of ribavirin therapy have been reported. Once again there were biochemical responses in most patients treated with ribavirin but no patient became persistently PCR negative (Di Bisceglie et al, 1994 and Dusheiko et al, 1996).

Prevention and control of HCV infection

To interrupt transmission and reduce the incidence of hepatitis C, the prevention and control measures should be included:

a) Proper selection and screening of blood donors for anti-HCV

Because parenteral exposure to blood is the predominant mechanism of transmission, so screening of donors for anti-HCV with a sensitive test now is possible to identify most carriers (Kuo et al, 1989) and it should greatly reduce the risk of transfusion associated NANBH about 60-85% (Kuo et al, 1989, Estaban et al, 1990). However, this test can not identify all serum samples infected with HCV. The lack of antibodies in donors may still transmit the disease. Thus, the further improvement of prevention of PT-NANBH but also for diagnosis of HCV infection (Jott et al, 1990, Kuo et al, 1989, Hishioka, 1991). Besides these, the elimination of commercial blood and the person at risk donors is the major factor that results in the decrease in the rate of –post-transfusion hepatitis (Kuo et al, 1989, Feinstone, 1990, Hollinger, 1990). Data from the National Blood Center, Bangkok and blood donors in Northeastern Thailand showed high anti-HCV prevalence in donate blood (Songsivilai et al, 1997). The study suggested that preventive measures against post-transfusion HCV should be further continued advocating routing blood screening of donors for the anti-HCV.

b) Health education about hepatitis C in hospital and Community

General measures used to prevent hepatitis in hospital settings including non-reuse or sterilization of needles and sharp instruments, blood precautions when dealing with patients or their body secretions and basic procedures to minimize the potential of percutaneous or mucosal blood contact in all settings are important in preventing NANBH transmission. In hepatitis C patients, the physician should inform their infections and give the knowledge about hepatitis C to them in order to control their diseases and delay becoming chronic hepatitis; moreover, they may be monitored for the development of chronic hepatitis and treated early in their course with hope for improvement in quality of life and survival, avoid exposure to hepatotoxins and change their lifestyle to decrease the likelihood of infecting other (Takamatsu et al, 1998).

In the community, prevention will depend on measuring the risk associated with sexual lifestyle, sharing private wares, percutaneous doing, and person-to-person contact with hepatitis patients (Alter, 1990). The recent study of HCV-RNA in saliva suggested that the saliva of patients infected with HCV should be a source of HCV infection (Foucett, 1991). It wants further investigation to improve the strategy of HCV prevention.

c) Specific prevention

There is no specific prevention for PT-NANBH (Poovorawan, 1992, Feinstone, 1990, Hollinger, 1990), but the expression of antigens associated with HCV will allow for the possible preparation of vaccine in the future (Feinstone, 1990). The efficacy of passive immunoprophylaxis by immune serum globulin (ISG) for prevention of transfusion associated hepatitis give mixed results, however at this time using of ISG is not recommended and can not be adequately ascertained (Kuo et al, 1989, Feinstone, 1990, Hollinger, 1990).

Summary of recommendation

Patients infected with HCV should be referred to a clinician with a particular interest in the infection. Patients must have access to adequate counselling from a health care with knowledge and experience of chronic HCV infection. All patients must have access to the appropriate diagnostic and therapeutic options available in the management of HCV infection.

DIAGNOSIS (Booth et al, 2001)

- Patients with suspected of HCV infection should be tested for anti-HCV by an up to date (currently third generation) ELISA test.
- All patients with positive antibody tests and those patients thought to be at risk of HCV infection despite negative or indeterminate serological tests should undergo PCR testing of serum. A positive result confirms current viraemia whereas a negative test suggest non-viraemic infection, transient absence of viraemia or recovered infection, a level of viraemia below the detection limit of the assay, or may reflect a non-specific ELISA result.

- Patients with positive ELISA but negative PCR should therefore be tested with recombinant immunoblot assay to confirm antibody status.
- A qualitative PCR test is recommended in immunodeficient patients with suspected HCV infection.
- The results of routine liver tests correlate poorly with both necroinflammatory and fibrosis scores found on liver biopsy.
- Liver biopsy is valuable for assessing status of liver inflammation, potential progression of fibrosis, and the presence or absence of cirrhosis. To clarify these, and to assess suitability for treatment, liver biopsy is recommended for patients found to be viraemic, whether or not liver function tests are abnormal. Standard histological scoring systems by a suitably experienced pathologist should be used to encourage uniformity of histological reports. The risks and benefits of liver biopsies must be fully discussed with the patient.
- Measurement of HCV RNA concentrations in serum and determination of HCV genotype are recommended and should be used to determine the duration of treatment.

COUNSELLING REGARDING TRANSMISSION

- Patients should be counseled on the implications of HCV positivity and advised on the risks of infectivity.
- The natural history is slowly progressive (median time to cirrhosis 28-32 years).
- HCV positive patients should not donate blood, organs, tissues, or semen.
- The risk of sexual transmission is small (maximum 5% but possibly much less). There is insufficient evidence to firmly recommend barrier contraception in stable monogamous relationships but is strongly advised for HCV infected patients with multiple sexual partners.
- Transmission from mother to child is rare (maximum of 6%) but transmission rates are higher in HIV positive mothers.
- Breast feeding is not contraindicated.
- Household contacts should avoid third party contact with blood by not sharing toothbrushed and razors, and by covering open wounds.

- Standard precautions for the prevention of transmission to medical personnel and patients is mandatory in health care settings.
- Needle exchange programmes in drug addicts may help reduce parenterally transmitted infection.
- Current IVDUs should not be treated although in selected cases ex-IVDUs taking regular oral methadone may be considered for treatmeant.

TREATMENT MEASURES

- Patients should be advised that excess alcohol consumption (>50g/day) appears to hasten the progression of disease.
- Consideration should be given to entering patients with established cirrhosis into surveillance programmes for HCC, if their general state of health is sufficiently good that emerging cancers could be appropriately treated.
- Patients must be screened for their suitability to receive IFN and ribavirin, with criteria which includes proven viraemia and abnormal liver histology.

- IFN and ribavirin are currently the only licensed treatments for HCV in the UK.
- IFN and ribavirin comination is the treatment of choice for IFN naïve patients.
- IFN and ribavirin combination is also recommended for those patients relapsing after IFN monotherapy.
- IFN monotherapy should be considered for those patients in whom ribavirin is contraindicated.
- The role of pegylated interferon remains unknown.

TREATMENT INTERFERON MONOTHERAPY

- We recommend IFN monotherapy should be initiatd at a dose of 3 MU three times per week by injection.
- IFN monotherapy should be continued for 12 months unless there is evidence of failure to respond.
- There is no evidence to suggest that one type of alfa-IFN is superior to another (alfa-2b, alfa-2a, alfa-n1, and consensus interferon (CIFN).

TREATMENT-INTERFERON -RIBAVIRIN COMBINATION THERAPY

- Recent results of large randomized controlled studies have shown improved response rates for IFN / ribavirin combination therapy in IFN naïve and relapsers compared with IFN monotherapy.
- Combination therapy consists of IFN at standard doses (usually MU three times per week) with ribavirin 1000 mg/day for patients weighting 75 kg or less and 1200 mg for those weighting more than 75 kg.
- In viraemic patients, the decision to offer treatment should be influenced by the histological findings.
- Treatment can be reasonably withheld in patients with mild disease but they should be followed to see if there is evidence of progressive liver disease by the use of repeated biopsy after an interval.
- Treatment should be offered to those patients shown to have moderate disease.
- Cirrhotic patients respond less well to IFN monotherapy but sustained responses have improved with IFN/ ribavirin combination treatment. There is no conclusive evidence that treatment in this group of patients delays progression of liver disease or the development of HCC.
- Treatment should not be withheld on the basis of genotype analysis or the measurement of HCV RNA levels.

- The duration of combination treatment depends on the genotype and level of viraemia.
- Patients infected with non-HCV 1 (mostly genotype 2 or 3) should be treated for six months irrespective of the level of viraemia.
- Patients infected with genotype 1 and low level viraemia (<2 million copies per ml) should be treated for six months whereas 12 months' treatment is recommended for those infected with genotype 1 and high level viraemia (>2 million copies per ml). (Recommendation grade A.) If HCV quantitation is not available treatment is recommended for 12 months in HCV 1 infected patients.
- Patients unlikely to respond to IFN monotherapy can be identified at three months by persistent elevation of serum transminase levels and the persisting presence of

HCV RNA by PCR in serum. (Recommendation grade B.) If ALT levels are normal or HCV RNA negative (or both) at three months, treatment should be continued for the full duration (12 months). (Recommendation grade B.) In patients with initially normal ALT levels, failure to become RNA negative at three months suggests longer treatment will be ineffective.

- The recommendation that early treatment response can be used to predict sustained response does not apply to patients receiving 12 months of IFN/ribavirin combination therapy a positive PCR at six months is an indication to stop treatment.
- Although transient or mild side effects are common during IFN monotherapy, serious toxicity requiring reduction in dose or cessation of treatment occurs in 5-10% of patients during treatment.

- Withdrawal from IFN/ribavirin combination therapy occurs more often with 10-20% of patients requiring a reduction in dose or cessation of combination therapy.
- Patients with a combined biochemical and virological response at the end of IFN monotherapy, who relapse in follow up over the next year, have a significant chance of a sustained response after further treatment with IFN/ribavirin.
- Patients with a biochemical but not virological respons during initial treatment with IFN monotherapy are unlikely to have a sustained response to further treatment with IFN/ribavirin.
- There is continuing development in the treatment of patients with HCV infection. In particular, the role of pegylated interferon and re-use of weight adjusted doses of interferon will shortly be established. The guidelines will need regular and frequent review.

In 1999, Vogt, studied about the Hepatitis C infection in Children who underwent cardiac surgery before the implementation of Blood-Donor screening. It was found that sixty-seven (14.6 percent) of the 458 patients who had undergone cardiac surgery had anti-HCV, as compared with 3 (0.7 percent) of the control subjects. At a mean interval of 19.8 years after the first operation, 37 (55 percent) of the 67 patients who were positive for anti-HCV had detectable HCV RNA in their blood. The infection had cleared in the other 30 patients, as evidenced by negative results on three polymerase-chain-reaction analyses performed at six-

month intervals. Only 1 of the 37 patients who were positive for HCV RNA had elevated levels of liver enzymes; that patient had severe right-sided congestive heart failure. Of the 17 patients who underwent liver biopsies, only 3 had histological signs of progressive liver damage. These three patients had additional risk factors: two had congestive heart failure, and the third had also been infected with hepatitis B virus.

It could be concluded that children who had undergone cardiac surgery in Germany before the implementation of blood-donor screening for hepatitis C had a substantial risk of acquiring the infection. However, after about 20 years, the virus had spontaneously cleared in many patients. The clinical course in those still infected seems more benign than would be expected in people infected as adult.

In 1996, Cathy Conry-Cantilena, studied 481 donors, among who 248 were positive for HCV by RIBA, 102 had indeterminate results, and 131 were HCV-negative. In a logistic-regression analysis, significant risk factors for HCV infection among the HCV-positive participants were a history of blood transfusion in 66 (27 percent); for the comparison with RIBA-negative donors), intranasal cocaine use in 169 (68 percent), intravenous drug use in 103 (42 percent), sexual promiscuity in 132 (53 percent), and ear piercing among men. Nine of 85 sexual partners of HCV-positive donors were anti-HCV–positive; 8 had used intravenous drugs or received transfusions. HCV RNA was found in 213 HCV-positive donors (86 percent), 3 who had indeterminate results by RIBA (2 of these 3 tested positive with a more specific, third-generation RIBA), and none who were HCV-negative. Of the HCV-positive donors, 69 percent had biochemical evidence of chronic liver disease; among 77 donors positive for HCV by RIBA, who underwent liver biopsy, 5 had severe chronic hepatitis or cirrhosis, 66 had mild-to-moderate chronic hepatitis, and 6 had no evidence of hepatitis.

It could be concluded that among volunteer blood donors, prior blood transfusion, intranasal cocaine use, intravenous drug use, sexual promiscuity, and ear piercing in men are risk factors for HCV infection. The high frequency of intravenous drug use was unexpected, because these donors had denied such use when questioned directly at the time of their blood donations.

In 1996, Worman studied 179 patients in the United States with chronic hepatitis C to determine how genotype related to epidemiology, pathogenicity and response to therapy. Fifty-eight percent of patients had genotype 1a, 21% had 1b, 2% had 2a, 13% had 2b, 5% had 3a and 1% had 4a. There was no association between genotype and mode of acquisition of infection. Patients with genotypes 1a and 1b had more severe hepatitis. Twenty-eight percent of patients with genotype 1a and 26% of patients with genotype 1b had a complete biochemical response to treatment with interferon-alpha for six months. In contrast, 71% of patients with genotype 2a or 2b had a complete response to interferon therapy. This study confirms that 1a and 1b are the most predominant hepatitis C virus genotypes in the United States and that patients infected with these viral genotypes generally have more severe liver disease and lower rates of response to interferon therapy than patients infected with genotypes 2a or 2b.

In 1996, Kurtzberg found that twenty-four of the 25 donors–recipient pairs were discordant for one to three HLA antigens. In 23 of the 25 transplant recipients, the infused hematopoietic stem cells engrafted. Acute grade III GVHD occurred in 2 of the 21 patients who could be evaluated, and 2 patients had chronic GVHD. In vitro proliferate responses of T cells and B cells to plant mitogens were detected 60 days after transplantation. With a median follow-up of $12^{1}/2$ months and a minimal follow-up of 100 days, the overall 100-day survival rate among these patients was 64 percent, and the overall event-free survival was 48 percent.

It could be concluded that HLA-mismatched placental blood from unrelated donors is an alternative source of stem cells for hematopoietic reconstitution in children.

In 1999, Pornthip Khemnak, studied 200 patients to determine the prevalence of HCV infection and risk factors were interviewed and their blood specimens were collected for testing anti-HCV antibody by Chemiluminescent technique. The results showed that the prevalence in patients with tattooing or patients having sexual relations two or more times per month was higher than in those without tattooing or patients having sexual relations less than two times. Quantitative risk analysis found that domicile was significant risk factors.

In 1990, Sukhontha Kongsin, studied about the cost - benefit analysis of screening HIV-Antibody (AIDS) by using ELISA method. The cost and benefit analysis was applied to two models, the first was routine screening model and the other was the expert's judgment model. The cost was calculated from additional cost incurred by making every routine screening. Benefit in the first model was estimated from predictable prevented HIV-positive cases and resources saving in the symptomatic treatment. Benefit in the other was calculated from predictable prevented full-blown AIDS cases and the earning income foregone.

It was found that the routine screening test is much more cost-effective than the expert's judgment in every aspects. Similarly, the additional cost per 1 unit could save the treatment resources about 350 units and could prevent the loss of income foregone by 0.22 percent to make every routine screening feasible.

In 1982, Hornbrook, studied a relation between elevated alanine aminotransferase levels in donor blood and incidence of non-A non-B hepatitis in recipients of such blood, defined cost as the direct costs of testing and indirect costs associated with loss of blood product, additional recruitment, and informing donors of their abnormal aminotransferase level; costs ranged from $3,151 to $4,003 per 1,000 units. The results suggest that if prospective studies demonstrate that exclusion of blood with elevated aminotransferase levels decreases non-A,non-B hepatitis in recipients, the net economic impact may be positive.

In 1999, Leal P, study cost utility of the prevalence round of a screening programme for HCV in intravenous drug users (IVDUs) in contact with services in the south and west health region of the UK. A simple spreadsheet model was used to estimate cost utility (cost/quality adjusted life year (Qaly). The cost of the prevalence round of screening in IVDUs would be about 700,000 pounds and was identify about 1400 people and eligible for treatment 270 and 20 would respond to IFN alpha. This gives a cost/Qaly of 9300 pound for the screening programme. Although cost effective and many of important uncertainties and the assumption used to estimate the long term effectiveness of screening and treatment but there is not enough evidence to inform the policy development and requirement for further research.

In 2000, Pereira A, Sanz C, studied cost-effectiveness analyses needed to decide the value of further expansion of the screening protocols for HCV in blood donors. The calculation method for cost-effectiveness ratio by the simulation of a Markov model representing the outcomes of patients transfused with HCV infective blood used to estimate health and economic impact of PTHC. Overall 12.3 percent patients receiving HCV infective blood will develop to chronic HCV, 9.3 percent will progress to liver failure, and 9.25 percent will eventually die of liver disease after a median time of 20.75 years (rang 6-70). Ninety-one percent of the infected blood recipients had no reduction in life expectancy due to PTHC, and average loss per patient was 0.754 years. The present value of the life time health cost with PTHC is $6330 per case. HCV antibody testing increase patient's life expectancy 20.4 hours. Adding HCV NAT increase patients life expectancy by 0.08 hours per blood collection tested at cost effective ratio of $1,829,611 per Qaly gained. By adding HCV Nat just help additional gain at a very high cost.

In 1999, Gordon FD, found the benefits and drawbacks of public health screening for hepatitis C, its cost effectiveness, and the various strategies to identify individuals infected with the hepatitis C virus (HCV). The estimation of estimation of 4 million people infected with hepatitis C in the United States and approximately 50% unaware of their infection. Both the high incidence and the recent improvement with the treatment of HCV would be beneficial to the patients, their family and to the public to have a screening program for this disease.

Focusing for the screening and improved the treatment the outcome will result cost effective for HCV in the future. The United States and in Europe have issued guidelines for hepatitis C screening. Each of these calls for screening of high-risk populations, which include individuals who have received blood products and intravenous drug users. Targeted screening and improved treatment outcomes will likely show identification of those with hepatitis C to be cost effective in the future.

Blood Donors with Hepatitis C

The first-generation test for antibody to HCV (anti-HCV) was introduced into donor screening in 1990.(Alter, 1997) The first-generation test for antibody to HCV (anti-HCV) was introduced into donor screening in 1990.(Alter, 1997) Cathy Conry-Cantilena, in 1996, mentioned that total of 954,316 volunteer blood donors were screened between March 1991 and August 1994 for HCV+. Results showed 4,585 (0.5%) were HCV+ (ELISA and RIBA). From this group, 248 (0.026%) who were confirmed HCV+.

At Thai Red Cross reported that that total of 221,409 volunteer blood donors were screened between 1998 and 2000 for HCV+. Result showed 1,165 (0.53 %) were HCV+ (Elisa).

Cost –Benefit Analysis

Cost-benefit analysis (CBA) is an evaluate technique for the comparing the value of all resources consumed (costs) in implementing a program or intervention. In essence, CBA may be thought of as the "yield" of an "investment". Will the benefits of a program exceed the cost of implementing it? Which program. Will produce the greatest net benefit? (Prommeenate, 2000) .

Cost-Benefit Analyses (CBA) requires programmed consequences to be valued in monetary units, thus enabling the analyst to make a direct comparison of the programmes incremental consequences incommensurate units of measurement, be they dollars, pounds, or yen. .(Drummon, 1997) Thus, CBA is an important tool that can be used to guide the decisions-making process in the allocation of funds for health and other program. CBA allows researchers to answer questions such as should a program be funded or should a program be continued based on a comparison of its costs and benefits. (Prommeenate, 2000) .

CBA requires that the costs and benefits both be valued in the same nits. If a particular pharmaceutical regimen decreases the need for serum concentration monitoring, the dollar value of the eliminated tests is the benefit. (Prommeenate, 2000) The results of such analyses might be stated in the form of ratio of dollar costs either to dollar benefits, or as a simple sum (possibly negative) representing the net benefit (loss) of one program over another. (Drummon, 1997) Similarly, if the benefit is lives saved, a dollar value can be assigned to those lives. (Prommeenate, 2000).

Costs

Economists define cost as the value of resources used to produce something, including a specific health service or a set of services (as in a health program). (Creese and Parker, 1994).

In determining costs, the first step is to decide from whose perspective the analysis is to be taken. A program which looks uninteresting from one perspective may look significantly better when other perspectives are considered. In addition, perspective of the study outlines the scope of relevant costs. Perspectives or points of views that can be used in economic evaluation are patient perspective, provider prospective, payer perspective, and society perspective. (Prommeenate, 2000).

A good classification scheme depends on the needs of the particular situation or problem. (Creese and Parker, 1994) In a study about costs, many of the issues surrounding costing are context specific and the analyst's options are often limited by the available of data. For example, some studies used patient charges as a measure of cost rather than determining economic costs. The choice between them depends on the purpose and perspective of the study. However, charges can be converted to cost using cost-to-charge ratios, which vary among hospitals. (Prommeenate, 2000).

Santerre and Neun wrote in "Health Economic Theory, Insights, and Industry Studies" that the total cost imposed on society by a medical condition or health behavior is generally one of three major types:

1. Direct medical care costs
2. Direct non-medical cost
3. Indirect cost.

1. Direct medical care cost

Direct medical care costs are the amount spent on medical services to treat the illness, including hospital care, professional services, drugs and supplies.

2. Direct non-medical cost

Direct non-medical costs are out-of-pocket expenses for items outside the medical care sector, such as transportation, hotel rent for family airing treatment.

3. Indirect cost

Indirect costs are the earning lost as a result of temporary or permanent disabilities occurring because of the illness. All of these direct medical costs are the most important costs in assessing costs of alternative medical treatment. (Santerre and Neun, 2000)

Waraporn Prommeenate mentioned in "Cost- Benefit Analysis of Adverse Drug Reaction Monitoring Program at Lerdsin Hospital in 1999" that cost can also be classified by inputs as :

1. Capital costs: these costs include opportunity costs of land and depreciation costs of building and depreciation costs of durable goods. The total costs were spread over their useful lifetime by straight-line depreciation method.

2. Operating cost: includes labor cost and material cost.

- Labor costs are defined as incentives of work such as salaries, wages, overtimes, income supplement, health benefits and other benefits such as travel allowances.
- Material costs are costs of consumed materials in an organizational operation. They are drug and medical supplies, utility such as electricity, telephone, mailing, office materials, and materials such as household material, fuel, kitchen goods.

Waraporn Prommeenate (2000) categorized cost of adverse drug reaction into three categories:

1. Labour Costs, which is the wages/salary of pharmacists.

2. Material Costs, which is the sum of cost of material use in the program: adverse drug reaction report form, stickers for labeling adverse drug reaction, the budget supported for the adverse drug reaction activities, etc.

3. Capital Costs, which is the building, land and facilities, use in the program.

Sanga Intajak (1996) used the incremental approach in the cost and benefit analysis of the contracting out primary medical care under social security scheme, total incremental cost classification by input:

1. Capital Costs which is building and equipment.

2. Recurrent Costs which is personal, promotion, vehicle, supply, utility: telephone, post – mail, electric and other: miscellaneous, meeting.

3. Treatment Charges Paid to Networks Costs which is private network, supra-contractors, IPD expenditure and OPD expenditure.

Shamim Ara Begum (1995) determined the cost in the study of Cost Analysis of Childhood Diarrheas Inpatients into two categories:

1. Direct Cost, which is the registration fee, bed cost, medical cost, laboratory cost and food cost of the patient.

2. Indirect Cost which is the food cost (attendants), wage lost (parent) and total conveyance cost (parents).

2.3.2 Benefit

Health programmer benefit to be broadly defined; some may be improvements in health status while other maybe attributes such as the value of information or the value associated with the process of care. (Drummon, 1997)

Woraporn Prommeenate (2000) mentioned in "Cost-Benefit Analysis of Adverse Drug Reaction Monitoring Program at Lerdsin Hospital in 1999 that the economic benefits of health program or intervention typically are classified as direct, indirect, and intangible.

Direct benefits

Direct benefits are defined as that portion of averted costs currently borne that are associated with spending for health services; they represent potential savings in the avoided use of health resources. Savings may occur in care avoided prior to diagnosis and hospitalization, during hospitalization or treatment, during convalescent care, and during continued medical surveillance.

Indirect benefits

Indirect benefits represent potential increased earnings or productivity gains that would not have been possible without the particular healthcare program. They are often calculated from the avoidance of earnings and productivity losses that would have been borne without the health program in question.

Intangible benefits

Intangible benefits of health or a particular intervention are difficult to measure. These include the psychological benefits of health, such as satisfaction with life or health.

Sanga Intajak (1996) referring the incremental benefit into two categories:

1. Monetary Benefits due to the contracting out are the increasing capitation payment from the National Social Security Office, for health services given to insures workers registered with the private clinics compared with the capital payment received, if the contracting out was not implemented, and cost saving because of implementing the contracting out.

2. Non-monetary Benefits are the achieved benefit from if the contracting out programmed beyond monetary benefits. Most of them can be assessed by looking at various indicators that include:

- Equity in utilization and access to health care
- Service provision improvements
- Quality of service improve