VIRAL HEPATITIS

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CME Program For Health Professionals

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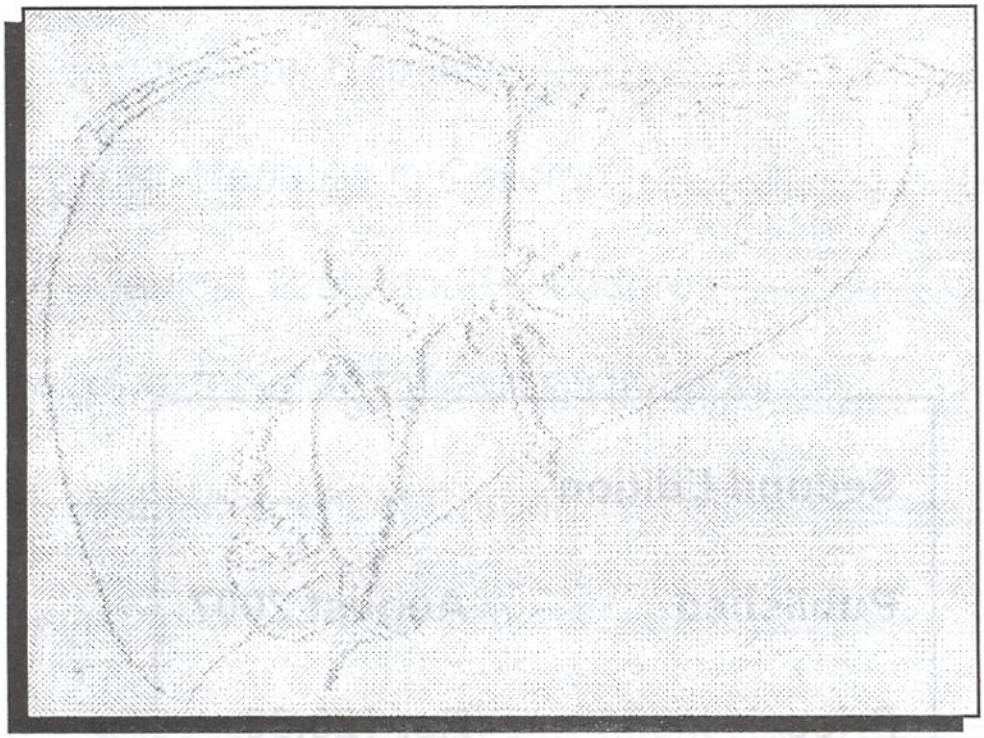

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PREFACE

Viral Hepatitis is one of the commonest diseases in Pakistan. Although, basically handled by gastroenterologists or medical specialists, it is of interest to nearly all the specialities. The surgeon may see it as bilary obstruction or acute abdomen. The gynecologist as a serious problem in pregnancy. They may even land up with a psychiatrist.

It has a varied etiology and equally varied clinical presentation, course and eventual outcome. It may present as a flu like illness or with no symptoms at all.The clinical course similarly may be with severe jaundice, fever , vomiting and encephalopathy or a very mild illness in which all symptoms disappear in matter of days. It could confer life long immunity or may lead to chronic hepatitis , cirrhosis and even hepatocellular carcinoma.However, inspite of all their eitiological and clinical diversity and perplex behavior, they do share a number of promising features.

1. Although afflicting the mankind since antiquity, It is a group of diseases about which little was known until about 50 years ago. Since then the dizzying progress which has been made is truly remarkable. It is a tribute to modern medicine and thousands of dedicated researchers all over the world, including Pakistan, that we are aware of the some its causative agents and how they damage the liver.

2. The break through in prevention by vaccination ,especially in HBV, has been a ray of hope for suffering millions all over the world. Indeed it has been rightly said that hepatic carcinoma may be the first malignancy which may be controlled by using a vaccine.

3. Viral diseases have been notorious as hardly any curative therapy is available. The advances being made in treatment of chronic hepatitis promise that they may not be so invulnerable any more.

The progress in understanding the epidemiology, clinicopathological features and therapy of hepatitis has thus been pheromenal. However, barring a few notable exceptions, this body of knowledge has not been available to the bulk of our health professionals. We therefore decided to compile this monograph.

An effort has been made to provide basic facts about the viruses without becoming overly technical.The types of hepatitis and their distinguishing features have been presented. The diagnosis and the serlogical tests for the diagnosis have also been dealt with. To put a proper perspective , the picture in Pakistan and the local situation has been described.The management of hepatitis is still in a fluid state. A number of latest consensus conferences which were held to resolve these issues are also covered.

The emphasis has been on the practical aspects rather pure academics. For those who may be interested to further probe the issues, a long list of references, some given at the end, is available.It is hoped that this monograph will be equally useful for the specialist and for those in general practice.

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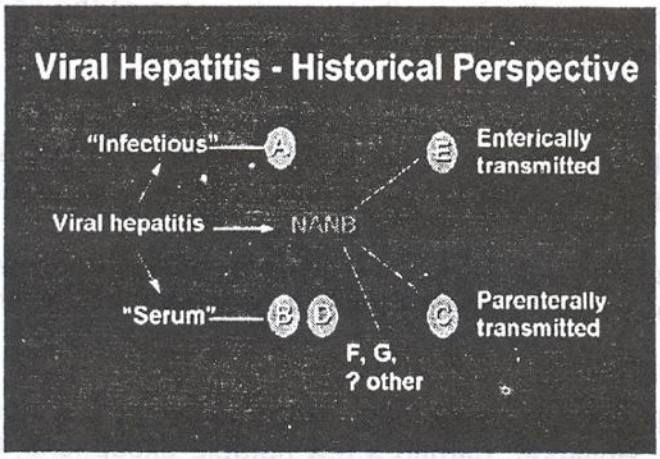
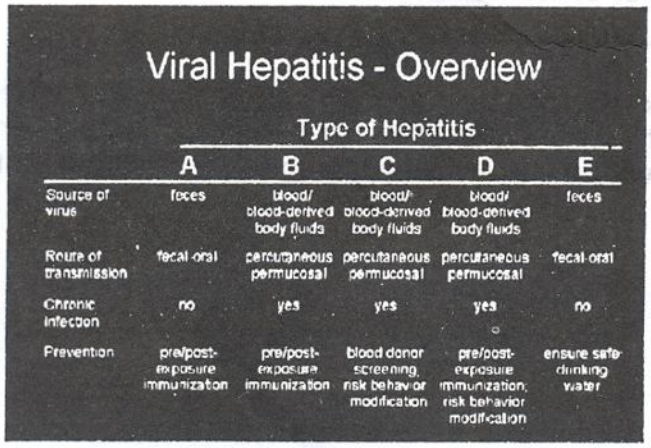
CHAPTER-1

THE ABC OF HEPATITIS

Viral hepatitis is the most common and most important public health problem facing us today. It is a fascinating group of diseases. The progress made in understanding these conditions in recent years has been unmatched by any other disease. If one were to recall one's student days during fifties, things were much simpler. There used to be the infectious hepatitis, spread through oral faecal route and serum hepatitis transmitted by parenteral means. Even this progress was achieved due to work carried out during the war and a decade prior to that. It was the work of Blumberg in sixties, which opened the floodgates of research. It is curious that he was not trying to isolate hepatitis virus. He was actually working on protein polymorphism. The presence of an antigen in the serum of an Australian aborigine led to the discovery of hepatitis B virus.



We now have a plethora of viruses that cause viral hepatitis. They range from A to G with the position of F being questionable. There may be a canidate in the newly described transfusion associated virus for H also. The new millenium, who knows, may take us to the end of alphabet. Actually there are a large number of viruses and even other agents that may affect the liver and cause similar clinical problem. However the hepatitis causing viruses are dealt separately.



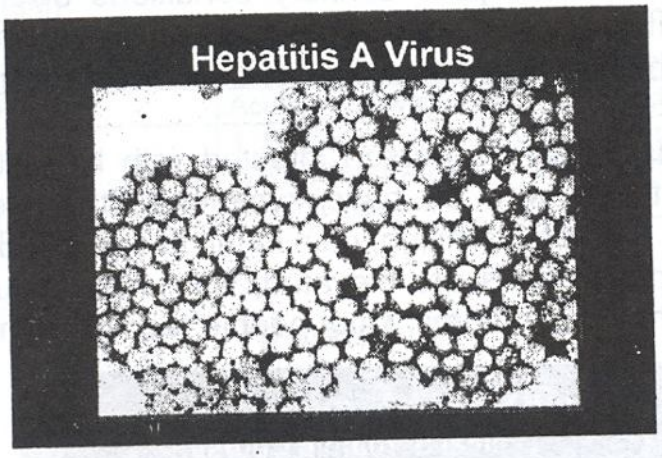
	Type of Hepatitis				
	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	no
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening, risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water

Although there is great advancement in our knowledge, there are a few features that are relevant even today. For example, notwithstanding the various types, all could be still be divided into the original groups of parenteral spread and the oral faecal spread groups. Their behavior is also distinct.

A brief account of various types is given.The description refers to the conditions as they occur abroad. However the relevant information about Pakistan, as far as is known is given in the main text or separately.

THE TYPES OF HEPATITIS

Hepatitis A



HAV causes 'infectious/epidemic hepatitis'.It has been known for centuries and was (wrongly) believed to be spread by aerosols. It is spread by faecal-oral route.

Clinically,it is very variable; more than 90% childhood infections are asymptomatic, 25-50% adult infections (as usual, the older you get, the worse it is). Incubation period varies from 10-50 days. Fever and jaundice are main symptoms. 99% cases recover completely, very few cases experience permanent liver damage. Fatalities are less than 0.1%.

The virus was first isolated by Purcell in 1973. In vitro, it grows in a variety of cell lines, but rather poorly. HAV is a Picornavirus, formerly classified in the genus Enterovirus. Genome studies (sequence homology) showed that it did not belong in this genus and it has been reclassified in a genus of its own: Hepatovirus.

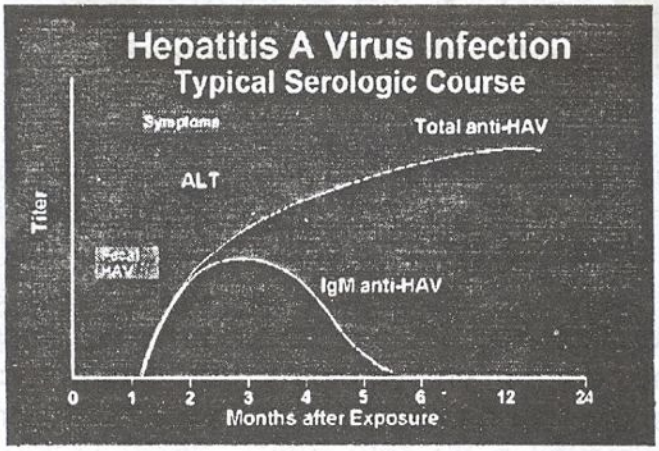
Both inactivated and attenuated vaccines are available, the inactivated form being more widely used. The availability of assays for and vaccines against HAV means that the incidence is likely to decrease in future. In Pakistan most people acquire it as asymptomatic infection during chilhood and are immune.

Transmission is usually by drinking water or eating food that has been contaminated with fecal matter containing the virus. Unlike the hepatitis B and C viruses, the hepatitis A virus remains stable when liver cells secrete it into bile, which then enters the digestive tract. **Fecal matter from an infected person has a high concentration of the virus during a certain period of infection**, whereas saliva and other bodily fluids have a low concentration. **The virus can survive in this contaminated fecal matter on a person's**

hand, for example, or on a surface for three to four hours at normal room temperatures. Thus, an eating utensil contaminated with the virus could be a way to transmit the infection to a person. Direct contact with an infected person is another confirmed transmission route, as are kissing on the mouth. Contamination of needles used for intravenous administration of drugs is a suspected route of transmission. In over 40% of the reported cases it is not known how these people were infected.

The risk of being infected with the hepatitis A virus generally depends on the hygienic and sanitary conditions in an area. Globally high risk geographic areas are the Middle East, South America, Eastern Europe, Central America, Africa and Southeast Asia. There are also areas in the United States where poor sanitary conditions or hygiene have resulted in outbreaks of hepatitis A.It is two to three weeks before the symptoms appear that the patients shed the virus in high concentration in feces and thus are most infectious to others.

As with the other hepatitis viruses a person infected with hepatitis A may not have any symptoms. However, in those who do have symptoms, they resemble the flu. These symptoms include fatigue, nausea, vomiting, pain in the liver area, dark urine or light colored stools and fever. Liver function tests are elevated, with many adults developing jaundice. Children under two rarely have symptoms. Most people recover within six months



A very small percentage of people infected with hepatitis A risk serious complications. These include people with alcoholic hepatitis, chronic hepatitis with cirrhosis or the elderly over 60 years old. These patients may suffer liver failure after becoming infected with hepatitis A.

Patients with hepatitis A may show improvement in their symptoms and liver function tests only to suffer a relapse, usually after four weeks. A relapse can occur more than once and there is no way to predict who will suffer a recurrence of acute symptoms. In rare cases, jaundice lasts for two or more months. It is rare for pregnant women who are infected with hepatitis A to suffer serious complications to themselves or their newborn children unlike Hepatitis E.

Hepatitis A is diagnosed by a blood test that is positive for the antibody to the virus, which appears about four weeks after the infection. There are no false positives or negatives with this test. Liver function tests (serum alanine aminotransferase [ALT] and asparate aminotransferase [AST]) are elevated above normal, often to very high levels. Symptoms will normally appear during the first four weeks of infection.

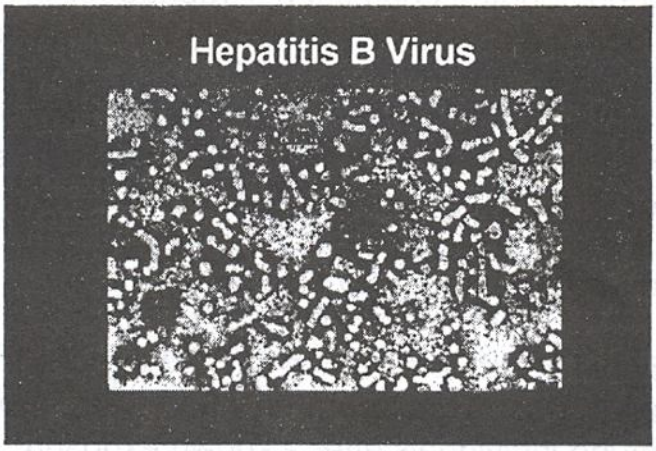
How Is Hepatitis A Treated?

There is no specific treatment for hepatitis A. Most patients are told to rest for one to four weeks after a diagnosis is made, to avoid intimate contact and to consume foods high in protein. People who have come into contact with the patient should be given temporary immunization with immune serum globulin within two weeks of exposure

Table II: Hepatitis A -Serology Results and Interpretation

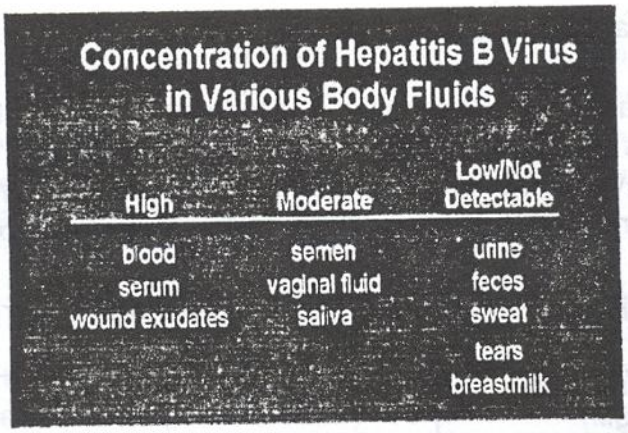
Anti-HAV (total)	Anti-HAV (IgM)	Possible Interpretations
-	-	1.Negative for HAV infection 2. Incubation period of HAV infection
+	+	Acute or convalescent HAV infection
+	-	1. Past HAV infection and immunity to HAV 2. Passive transfer of HAV antibody through receipt of gamma globulin

Hepatitis B



The Hepatitis B Virus (HBV)

HBV is a mostly double-stranded DNA virus in the Hepadnaviridae family. HBV causes hepatitis in humans and related virus in this family cause hepatitis in ducks, ground squirrels and woodchucks. The HBV genome has four genes: pol, env, pre-core and X that respectively encode the viral DNA-polymerase, envelope protein, pre-core protein (which is processed to viral capsid) and protein X. The function of protein X is not clear but it may be involved in the activation of host cell genes and the development of cancer.

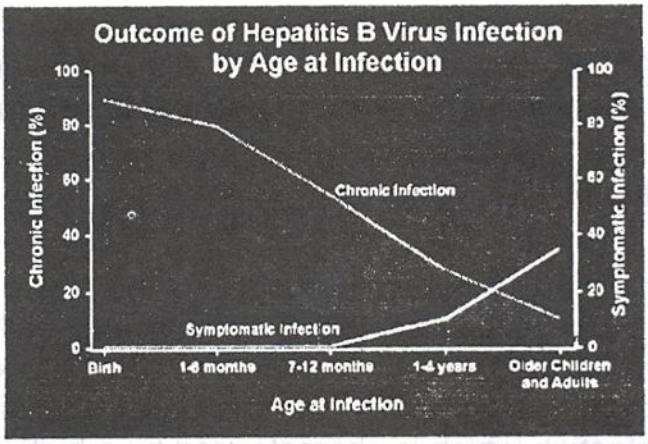


Risk Factors for HBV Infection

Hepatitis B is endemic in parts of Asia where hundreds of millions of individuals may be infected. HBV is transmitted horizontally by blood and blood products and sexual transmission. It is also transmitted vertically from mother to infant in the perinatal period which is a major mode of transmission in regions where hepatitis B is endemic.

The blood supply in developed countries has been screened for HBV for many years and at present transmission by blood transfusion is extremely rare. Major routes of transmission among adults in Western countries are intravenous drug use and sexual contact. The risk of HBV infection is notably high in promiscuous homosexual men but it is also transmitted sexually from men to women and women to men. Transmission is probably prevented by correct use of condoms. Health care workers and patients receiving hemodialysis are also at increased risk of infection.In countries like Pakistan , a lot has to be done to exercise control over blood transfusions. Other risk factors may also be significant.

Effective vaccines are available for the prevention of HBV infection. All individuals at risk for infection should be vaccinated. Post-exposure prophylaxis with hepatitis B immune globulin is also effective for non-immune individuals after a known exposure (e. g. needle stick).



The outcome of HBV Infection

HBV causes acute and chronic hepatitis. The chances of becoming chronically infected depends upon age. About 90% of infected neonates and 50% of infected young children will become chronically infected. In contrast, only about 5% to 10% of immunocompetent adults infected with HBV develop chronic hepatitis B. In some individuals who become chronically infected, especially neonates and children, the acute infection will not be clinically apparent.

Acute hepatitis B can range from subclinical disease to fulminant hepatic failure in about 2% of cases. Many acutely infected individuals develop clinically apparent acute hepatitis with loss of appetite, nausea, vomiting, fever, abdominal pain and jaundice. In cases of fulminant hepatic failure from acute HBV infection, orthotopic liver transplantation can be life-saving. About 90% to 95% of acutely infected adults recover without sequelae. About 5% to 10% of acutely infected adults become chronically infected.

The natural history of chronic HBV infection can vary dramatically between individuals. Some will develop a condition commonly referred to as a chronic carrier state. These patients, who are still potentially infectious, have no symptoms and no abnormalities on laboratory testing. Nonetheless, some of these patients will have evidence of hepatitis on liver biopsy.

Some individuals with chronic hepatitis B will have clinically insignificant or minimal liver disease and never develop complications. Others will have clinically apparent chronic hepatitis. Some will go on to develop cirrhosis. Individuals with chronic hepatitis B, especially those with cirrhosis but even so-called chronic carriers, are at an increased risk of developing hepatocellular carcinoma (primary liver cancer). Although this type of cancer is relatively rare in the United States, it is the leading cause of cancer death in the world, primarily because HBV infection is endemic in the East.

Chronic infection with HBV can be either "replicative" or "non-replicative." In non-replicative infection, the rate of viral replication in the liver is low and serum HBV DNA concentration is generally low and hepatitis Be antigen (HBeAg) is not detected. HBeAg is an alternatively processed protein of the pre-core gene that is only synthesized under conditions of high viral replication. In "replicative" infection, the patient usually has a relatively high serum concentration of viral DNA and detectable HBeAg. Patients with chronic hepatitis B and "replicative" infection defined by the presence of detectable HBeAg have a generally worse

prognosis and a greater chance of developing cirrhosis and/or hepatocellular carcinoma than those without HBeAg. In rare strains of HBV with mutations in the pre-core gene, "replicative" infection can occur in the absence of detectable serum HBeAg.

Diagnosis of Hepatitis B

The diagnosis of HBV infection is generally made on the basis of serology. Virtually all individuals infected with HBV, either acutely or chronically, will have detectable serum hepatitis B surface antigen (HBsAg). In acute infection, HBsAg is detectable several weeks after infection and its appearance coincides with the onset of clinical symptoms. HBeAg is also detectable in acute infection which is characterized by a high rate of viral replication. At around the same time, IgM antibodies against core antigen are detectable in serum. Subsequently, IgG antibodies against core are produced. As acute infection resolves, IgG antibodies against core antigen persist and IgM antibodies and HBsAg become undetectable. Subjects who develop an immune response against HBV develop antibodies against HBsAg. Such antibodies are also produced by vaccination. Most people who have had acute infection that resolves continue to have IgG antibodies against core antigen for life. Some remain immune with antibodies against HBsAg but some lose these antibodies and may be susceptible to future infection.

Acutely infected individuals who do not clear HBV continue to have serum HBsAg. In most cases, the chronic infection becomes "non-replicative" and the subjects lose serum HBeAg and develop antibodies against HBeAg. In some cases, "replicative" infection persists along with detectable serum HBeAg. In chronically infected individuals, infection can switch from "non-replicative" to "replicative" and vice-versa. One goal of treatment (see below) is to convert patients with chronic hepatitis B from a "replicative" (HBeAg positive) to "non-replicative" (HBeAg negative) state.

Diagnosis of hepatitis B is confirmed, and prognosis is assessed, by liver biopsy. Most people who are chronic carriers (no symptoms, HBsAg positive and normal serum aminotransferase activities) generally have little or no inflammation on biopsy. In such patients, you can often see "ground glass cells" on liver biopsy which are liver cells in which large amounts of HBsAg is being synthesized. Other individuals with chronic hepatitis B will have various degrees of liver inflammation on biopsy. Others will have fibrosis or cirrhosis. The amount of inflammation, and the presence of fibrosis or cirrhosis, correlate with a worse prognosis.

Table III: Hepatitis B Serologic Profiles and Their Interpretations

HBsAg	HBeAg	Anti-HBc (IgM)	Anti-HBc (total)	Anti-HBe	Anti-HBs	Interpretation
-	-	-	-	-	-	1. No exposure to HBV 2. Early incubation period of HBV infection
+	+/-	-	-	-	-	Late incubation period or early acute HBV infection
+	+	+	+	-	-	Acute HBV infection with high infectivity
+	+	-	+	-	-	Chronic HBV infection with high infectivity
+	+/-	+	+	+/-	-	1 Late acute HBV infection 2. Chronic HBV infection
-	-	+	+	+/-	-	Convalescent HBV infection "core window" period
-	+/-	-	+	-	+/-	1. Low level HBsAg carrier 2. Past HBV infection
-	-	+	+	+	+/-	Early recovery from acute HBV infection
-	-	-	+	+/-	+	Late recovery phase of HBV infection
-	-	-	-	-	+	Immunity to HBV due to: 1. HBV vaccination or passive transfer of HBIG 2. Remote past HBV infection

In individuals suspected of having chronic hepatitis B, the appropriate screening test is for serum HBsAg. Individuals who may have chronic hepatitis B who should be considered for testing include:

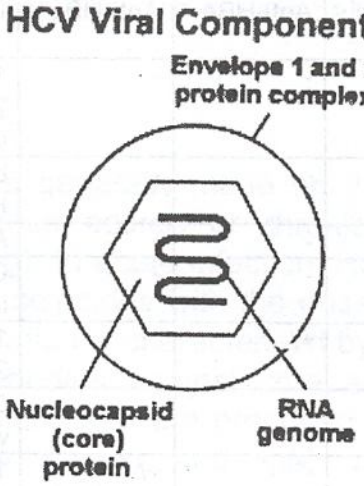
Those with symptoms of chronic liver disease
Those with abnormal laboratory tests suggesting liver disease

Those with risk factors such as past transfusions, intravenous drug use or unprotected promiscuous sex
Children of HBV infected parents or household contacts
Health care workers
Patients on hemodialysis
Individuals in the above groups who do not have chronic hepatitis B should be offered vaccination as most remain at increased risk of acquiring infection.

Cancer in HBV infected individuals

Individuals with chronic hepatitis B are at increased risk for the development of hepatocellular carcinoma. Although precise recommendations do not exist, it is reasonable for such individuals to undergo periodic screening for cancer. Screening procedures include measurement of serum alpha-fetoprotein (a tumor marker that is elevated in about 85% of individuals with hepatocellular carcinoma) and ultrasound examination. The optimal frequency of such screening examinations has not been determined.

Hepatitis C



Hepatitis C Virus

Hepatitis C virus (HCV) was first definitively identified by molecular cloning of the virus genome in 1989. The virus cannot be cultured in vitro and this has hampered investigations. The HCV genome consists of a positive-sense RNA molecule approximately 9.5kb in length:

Transmission of HCV

Not enough work has been done in Pakistan to determine the epideiology of HCV. However the factors already known to be significant ,like transmission through blood transfusion, may be responsible. It is unfortunate that no effective survilence is imposed on blood transfusion and its screening. In institutios in Pakistan where this is carried out ,there is a feeling that HCV, in place of HBV,is emerging as a major threat.

Other means of transmission may be important.There is need to carry out serious epidemiological studies in our population to understand and counter this serious problem.

In countries like USA where control measures are enforced,the relative importance of the two most common exposures associated with the transmission of HCV has changed over time. Blood transfusion, which accounted for a substantial proportion of HCV infections acquired more than 10 years ago, accounts for only a small proportion of recently acquired infections. In contrast, illegal (primarily injection) drug use has accounted for a substantial proportion of HCV infections during both the remote and recent past, and currently accounts for 60% of HCV transmission in the United States. Sexual exposures have been poorly ascertained particularly among patients with chronic hepatitis C, but recent data suggest sexual contact has accounted for 10% to 20% of HCV transmission. Other known exposures, including occupational (health care) and perinatal, account for a small proportion of all HCV infections. Thus, approximately 90% of HCV infections can be attributed to specific exposures. An additional nine percent appear to be associated with low socioeconomic levels, which may be a surrogate for high-risk exposures. Only one percent

of patients have no distinguishing characteristics and are classified as having an unknown source for their infection.

Acute HCV Infection

Persons with acute HCV infection typically are either asymptomatic or have a mild clinical illness; 60%–70% have no discernible symptoms; 20%–30% might have jaun-dice; and 10%–20% might have nonspecific symptoms (e.g., anorexia, malaise, or abdominal pain). Clinical illness in patients with acute hepatitis C who seek medical care is similar to that of other types of viral hepatitis, and serologic test-ing is necessary to determine the etiology of hepatitis in an individual patient. In 20% of these patients, onset of symptoms might precede anti-HCV seroconversion. Aver-age time period from exposure to symptom onset is 6–7 weeks, whereas average time period from exposure to seroconversion is 8–9 weeks. Anti-HCV can be detected in 80% of patients within 15 weeks after exposure, in 90% within 5 months after exposure, and in 97% by 6 months after exposure .Rarely, seroconversion might be delayed until 9 months after exposure 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 .Fulminant hepatic failure following acute hepatitis C is rare

Chronic HCV Infection

After acute infection, 15%–25% of persons appear to resolve their infection without sequelae as defined by sustained absence of HCV RNA in serum and normalization of ALT levels develops in most persons (75%–85%)with persistent or fluctuating ALT elevations indicat-ing active liver disease developing in 60%–70% of chronically infected persons .In the remaining 30%–40% of chronically infected persons, ALT levels are normal. No clinical or epidemiologic features among patients with acute infection have been found to be predictive of either persistent infection or chronic liver disease. Moreover, various ALT patterns have been observed in these patients during follow-up, and patients might have prolonged periods (12 months) of normal ALT activity even though they have histologic-confirmed chronic hepatitis .Thus, a single ALT determination cannot be used to exclude ongoing hepatic injury, and long-term follow-up of patients with HCV infection is required to determine their clinical outcome or prognosis.

The course of chronic liver disease is usually insidious, progressing at a slow rate without symptoms or physical signs in the majority of patients during the first two or more decades after infection. Frequently, chronic hepatitis C is not recognized until asymptomatic persons are identified as HCV-positive during blood-donor screening, or elevated ALT levels are detected during routine physical examinations. Most studies have reported that cirrhosis develops in 10%–20% of persons with chronic hepatitis C over a period of 20–30 years, and HCC in 1%–5%, with striking geographic variations in rates of this disease (.However, when cirrhosis is established, the rate of development of HCC might be as high as 1%–4%/year. In contrast, a study of >200 women 17 years after they received HCV-contaminated Rh factor IG reported that only 2.4% had evidence of cirrhosis and none had died .Thus, longer

term follow-up studies are needed to assess lifetime consequences of chronic hepatitis C, particularly among those who acquired their infection at young ages.

Although factors predicting severity of liver disease have not been well-defined, recent data indicate that increased alcohol intake, being aged >40 years at infection, and being male are associated with more severe liver disease .In particular, among persons with alcoholic liver disease and HCV infection, liver disease pro-gresses more rapidly; among those with cirrhosis, a higher risk for development of HCC exists. Furthermore, even intake of moderate amounts (>10 g/day) of alcohol in patients with chronic hepatitis C might enhance disease progression. More severe liver injury observed in persons with alcoholic liver disease and HCV infection possibly is attributable to alcohol-induced enhancement of viral replication or in-creased susceptibility of cells to viral injury. In addition, persons who have chronic liver disease are at increased risk for fulminant hepatitis A.

Extrahepatic manifestations of chronic HCV infection are considered to be of immunologic origin and include cryoglobulinemia, membranoproliferative glomer-ulonephritis, and porphyria cutanea tarda Other extrahepatic conditions have been reported, but definitive associations of these conditions with HCV infection have not been established. These include seronegative arthritis, Sjögren syndrome, autoimmune thyroiditis, lichen planus, Mooren corneal ulcers, idiopathic pulmonary fibrosis (Hamman-Rich syndrome), polyarteritis nodosa, aplastic anemia, and B-cell lymphomas.

Hepatitis D

The hepatitis D virus

The hepatitis D virus (also called delta virus) is a small circular RNA virus. The hepatitis D virus is replication defective and therefore cannot propagate in the absence of another virus. In humans, hepatitis D virus infection only occurs in the presence of hepatitis B infection.

Hepatitis D virus infection is transmitted by blood and blood products. The risk factors for infection are similar to those for hepatitis B virus infection. The hepatitis D virus most often infects intravenous drug users.

Hepatitis D - Clinical Features

- Coinfection
  - –severe acute disease
  - –low risk of chronic infection
- Superinfection
  - –usually develop chronic HDV infection
  - –high risk of severe chronic liver disease

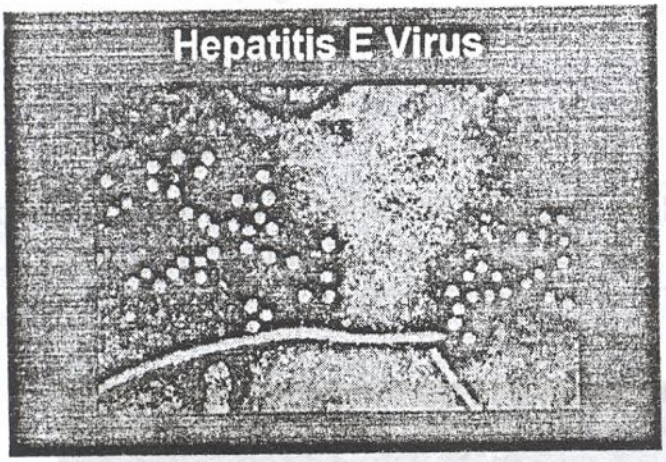
A patient can acquire hepatitis D virus infection at the same time as he/she is infected with the hepatitis B virus. This is called co-infection. A patient with hepatitis B can be infected with hepatitis D virus at any time after acute hepatitis B virus infection. This is called super-infection.

Hepatitis D virus super-infection should be suspected in a patient with chronic hepatitis B whose condition suddenly worsens. There is usually an obvious history of continued exposure to blood or blood products (eg. an active intravenous drug user). A particularly aggressive acute hepatitis B infection could suggest hepatitis D co-infection. Co-infection or super-infection with hepatitis D virus in a patient with hepatitis B is diagnosed by the presence of antibodies against the hepatitis D virus. IgM antibodies indicate acute infection.

Interferon-alpha is used to treat patients with chronic hepatitis B and hepatitis D infection. Some studies have suggested that a dose higher than that usually used for hepatitis B infection may be beneficial.

Hepatitis E

Hepatitis E Virus (HEV):



HEV has now been cloned and sequenced. The virion is a 30-32nm non-enveloped particle containing a s/s (+)sense RNA genome of ~7.5Kd. Genetic organization similar (not identical) to Caliciviruses:

Phylogenetic analysis of the genus Calicivirus in the family Caliciviridae based on the nucleotide and amino acid sequences of human and animal calicivirus 3D RNA-dependent RNA polymerase (approximately 470nt) and capsid hypervariable regions (approximately 1,200nt) to generate phylogenetic trees indicates that there are five separate genogroups:

Primate studies indicate faecal-oral (waterborne) transmission of the virus. HEV is endemic in S.E. Asia, ex 'USSR', India, Mid-East, Africa and C. America. ~1% of US blood donors have anti-HEV antibodies. Large epidemics with person to person spread have been known to occur. Normal course of infection seems to be an acute but relatively benign illness (c.f. HAV), except during pregnancy - 15-30% mortality. Recombinant vaccines are currently being prepared.

A closely related virus, swine hepatitis E virus (swine HEV), was recently identified in pigs. Swine HEV crossreacts with antibody to the human HEV capsid antigen & is a ubiquitous agent in pigs. The putative capsid gene (ORF2) of swine HEV shares about 80% sequence identity at the nucleotide level and 90-92% identity at the amino acid level with human HEV strains. The possible medical significance of this finding remains unclear at present.

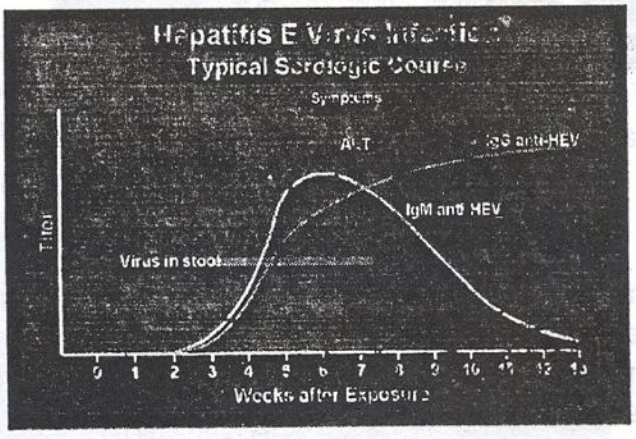
Hepatitis E - Clinical Features

Incubation period:	Average 40 days Range 15-60 days
Case-fatality rate:	Overall, 1%-3% Pregnant women, 15%-25%
Illness severity:	Increased with age
Chronic sequelae:	None identified

Hepatitis caused by HEV is clinically indistinguishable from hepatitis A disease. Symptoms include malaise, anorexia, abdominal pain, arthralgia, and fever. The infective dose is not known.

Diagnosis

Diagnosis of HEV is based on the epidemiological characteristics of the outbreak and by exclusion of hepatitis A and B viruses by serological tests. Confirmation requires identification of the 27-34 nm virus-like particles by immune electron microscopy in feces of acutely ill patients.Anti HEV antibody test is also available.



Transmission

HEV is transmitted by the fecal-oral route. Waterborne and person-to-person spread have been documented. The potential exists for foodborne transmission.

Frequency of Disease:

Hepatitis E occurs in both epidemic and sporadic-endemic forms, usually associated with contaminated drinking water. Major waterborne epidemics have occurred in Asia and North and East Africa.

Usual Course of Disease and Some Complications:

The incubation period for hepatitis E varies from 2 to 9 weeks. The disease usually is mild and resolves in 2 weeks, leaving no sequelae. The fatality rate is 0.1-1% except in **pregnant women.** This group is reported to have a fatality rate approaching 20%.

Target Populations: The disease is most often seen in young to middle aged adults (15-40 years old). Pregnant women appear to be exceptionally susceptible to severe disease, and excessive mortality has been reported in this group.

Analysis of Foods:

HEV has not been isolated from foods. No method is currently available for routine analysis of foods.

History of Recent Outbreaks:

Major waterborne epidemics have occurred in India (1955 and 1975-1976), USSR (1955-1956), Nepal (1973), Burma (1976-1977), Algeria (1980-1981), Ivory Coast (1983-1984), in refugee camps in Eastern Suddan and Somalia (1985-6), and most recently in Borneo (1987). The first outbreaks reported in the American continents occurred in Mexico in late 1986. To date, no outbreak has occurred in the U.S., but imported cases were identified in Los Angeles in 1987. Good sanitation and personal hygiene are the best preventive measures.

In India a study of 10,500 cases of proven Hepatitis E (HEV) in Pediatric population was reported. Indian HEV strain has 97% nucleotide and 98% amino acid sequence identity with Chinese strains but much diversity with Mexican strain. More than 70% acute hepatitis occurring in Pediatric population in this subcontinent are caused by HEV and 80% of these are sporadic. 90% cases were enterically transmitted, spread primarily by fecally contaminated drinking water (70%) and by food (20%), in 9.5% case spread probably was because of person to person and household contact. HEV in urine, respiratory secretions was demonstrated. Interestingly HEV was found in insects like Flies, Cockroaches, and also in engorged Bedbugs and in Mosquitoes, apart from briefly boiled Mussels, and partially cooked cockles. Maternal-neonatal transmission could be seen if mother had HEV infection in third trimester of pregnancy. In 5 cases HEV could be demonstrated in breast milk. By studying on 10 volunteers, 40% had anicteric form only accompanied by anorexia, epigastric pain. HEV appeared in serum before the icteric phase. Shedding of virus in stool starts before the icteric phase and continued during the high levels of abnormal ALT. Hepatitis IgG anti-HEV persist up to 4 years. In 5 cases Transfusion associated Hepatitis (TAH) could be established. No chronicity could be documented. 5% cases had fulminant viral Hepatitis

(FVH)/Sub fulminant viral Hepatitis (SVH), alpha-interferon (IFN) has been proved beneficial in these cases, further use of intravenous PGEI could also be beneficial.It was felt that inadequate chlorination of drinking water was an important additional factor for causing epidemics. A free residual chlorine concentration of at least 0.5 mg/l for minimum of 30 minutes is considered adequate as quality of drinking water.

The Pakistani profile is given under "Viral Hepatitis In Pakistan."

Hepatitis F ?

In 1994 an investigator reported finding viral particles in the stool of post-transfusion, non-A, non-B, non-C, non-E hepatitis cases (J Virol 1994;6:7810). Injection of these particles to Indian rhesus monkeys presumably caused hepatitis, and they were named hepatitis F. Subsequently, this finding has not been confirmed, and it is generally assumed the viral particles were incidental findings.

Thus, there is no hepatitis F virus, but the position in the nomenclature for the time being has been occupied.

Hepatitis G

HGV infection was originally suggested to be connected with fulminant hepatitis, but recent studies have failed to prove a connection between HGV and clinical illness. Some studies have suggested that in contrast to HCV, the liver is **not** the primary replication site for HGV. Where does HGV grow? Virus circulating in the bloodstream is difficult precipitate with antibody to immunoglobulins, but can precipitated with antibody to apolipoproteins. Since no hypervariable regions have yet been identified in the envelope proteins of HGV, the lipoprotein coat may help the virus evade immune surveillance and contribute to its persistence.

In many countries, 1-2% of blood donors test positive for HGV RNA & the prevalence of HGV infection is up to 10-15% in West African children. How this high prevalence is maintained is unknown, but this does suggest that sub-clinical infection is common. Antibodies to E2, an envelope protein of HGV, can be detected in >50% IVDAs who are HGV RNA negative, but in relatively few IVDAs who have HGV RNA. Therefore, HGV infection is probably much more frequent than studies of the prevalence of HGV RNA suggest.

The virus is transmitted by the same routes as HCV & co-infection is common; however, this may represent a common source of infection rather than any clinical similarity between the two viruses. The clinical significance of HGV infection and HGV-HCV co-infection remains to be fully elucidated, but at present does not seem to be a major disease-causing factor. The majority of patients infected with HGV by blood transfusion do not develop chronic hepatitis, but viremia frequently persists without biochemical evidence of hepatitis. Given the high prevalence of HGV worldwide and the association with mild or no clinical

Patients who receive multiple blood transfusions may have less of a risk than previously thought of contracting a newly discovered hepatitis virus found widely in donated blood.

Although the new hepatitis G virus (HGV) is similar to the highly infectious hepatitis C virus (HCV), little is known of its origins or its significance in causing disease. But, researchers do know that a high proportion of the general population has been in contact with HGV.

Patients with hemophilia and other blood disorders are particularly vulnerable to blood-born infections as a result of their need for blood transfusions.

In a study of blood recipients and donors, Dr. Lisa Jarvis and colleagues from the University of Edinburgh in Scotland found that although a high level of HGV was found in donated blood, recipients did not appear to have persistent infection with the virus after their transfusions. Jarvis suggests that while HGV and HCV may both be equally infectious, the newer HGV may be transmitted without causing overt infection in people who have had multiple blood transfusions. The Scottish researcher said the fact that persistent infection with HGV is common in the general population, but not in recipients of unscreened donor blood requires further investigation.

In a related editorial appearing in the British Medical Journal, researchers in Britain are trying to ensure the safety of the blood supply by instituting a system modeled on one used in the United States.

The U.K.'s SHOT initiative, which stands for Serious Hazards of Transfusion, is based on the Food and Drug Administration's comprehensive monitoring system of transfusion hazards which makes reporting transfusion-related deaths mandatory.

The virus has been reported from Pakistan. However no transfusion related studies, any screening nor safety measures have been proposed.

TT Virus (Hepatitis H ??)

In 1997 a novel DNA virus was identified in a Japanese patient after transfusion. The virus has little sequence similarity with any known virus, thus it is presently not clear to which family it belongs, and it is likely that it represents a new family. These viruses have become known as TTV "Transfusion-Transmitted Virus", although it is not clear precisely by which means the virus can spread. These are dense, 40nm diameter particles. Individual genome sequences vary by up to 40%.

Distribution & Pathogenesis:

Since it's discovery, it has become clear that TTV infection is present worldwide among blood donors and is common in patients with liver disease, including cryptogenic cirrhosis and fulminant hepatic failure. Alternatively, TTV appears to be present in up to 70% of healthy prople in the Gambia and Ecuador. In some studies, TTV DNA has been found more frequently in patients with liver cirrhosis and hepatocellular carcinoma than in those with chronic hepatitis. However, virus DNA is not integrated in tumour cells, which may suggest that the virus is a passenger rather that causative of the tumour. Further studies are required to determine the role of TTV in the pathogenicity of acute and/or chronic liver disease. Therefore, the significance of TTV infection in liver disease is, at present, analagous to that of HGV.

CHAPTER-2
ACUTE VIRAL HEPATITIS

Acute viral hepatitis is the disease which we commonly confront in every day practice. Th chronic hepatitis cases, although far more serious, are much less in number. These patient present with the familiar story of jaundice with loss of appetite and vomiting. In this contex two points need to be remembered. Firstly, viruses of viral hepatitis are not the only cause o jaundice. Other viruses and agents are also hepatotropic. Secondly jaundice may be th presenting feature in a case of chronic hepatitis or cirrhosis. In most cases , however clinica history and examination should clinch the diagniosis

Acute Viral Hepatitis
The Clinicopathological Spectrum

Some features of acute viral hepatitis based on study of 200 cases at Karachi and Rawapindi are presented to provide insight into clincopathologic features of hepatitis as we see in this country. Gen Manzoor Ahmad and Gen Shuaib Quraishi jointly carried out the studies.

Clinical differences between various types of hepatitis.

Although minor clinical differences have been documented between various types, it will be virtually impossible to assign a case of acute hepatitis to the type of virus. We in our studies did find Hepatitis B to be more severe with higher mean bilirubin and enzyme values. These cases had more prolonged course and had enzyme and clinical relapses. Others have described arthralgia as well as rashes although we did not see them with any great frequency.

The clinical course of Acute Hepatitis

The preicteric phase lasts for about six days .The average case completely recovered in about 35 days. The appetite is first to recover followed by fall in bilirubin. The enzymes are last to become normal, sometimes long after the disappearance of jaundice. Enzymes in some continue to fluctuate for many months. The appetite is perhaps the best indicator of recovery.

Diagnosis of Hepatitis Types

Although hepatitis may be indistinguishable, it is important that they be differentiated. The clinical course and treatment especially in chronic hepatitis may be different.

It is not enough to only get Hepatitis B surface antigen done.

What Tests to order for Acute Hepatitis Screen?

Most people will be baffled about what tests to include in "Hepatitis Profile" when a case of jaundice has to be investigated. This is because of availability of numerous markers for various hepatitis viruses. A simple asking for Hepatitis B surface antigen does not solve the problem and may even be misleading. It has now been proposed that the following tests will be appropriate.

Anti-HAV
HbsAG
Anti-HBc IgM and
Anti-HCV

This battery of tests will distinguish between infections caused by HAV, HBV and HVC.

Who should do the hepatitis serology?

It is not only important that the serology should be done it is perhaps even more important to ascertain as to who is doing them. Hepatitis is too serious a business to be left to quacks or poorly qualified. It is unfortunate that in our country there is hardly any control over Pathology Laboratories. One has come across a number of cases that were labeled as Hepatitis B or C by outfits who had no business to be reporting them. The results were catastrophic for the poor patients.

An Elisa test is the minimum required to be done for these cases. It demands a certain degree of training and expertise. Most are done as two-minute latex agglutination tests that fall short so far as sensitivity is concerned. In another bizarre twist some Labs are considered to have performed latex tests but reported them as Elisa.

How is a Physician to find out which test is being used ?

Stay with the lab where you know the Pathologists are Well Qualified.
Demand to know the type of test employed.
Be wary of the establishment where report is given in 5 minutes.

YOU OWE IT TO YOUR PATIENTS

LFT'S in Acute Hepatitis.

They vary in wide range. In our cases, which comprised ALL cases of hepatitis and not the serious ones, on admission serum bilirubin was 3.9mg(range upto 11.4). In Hepatitis B it was 4.6 (range upto 15mg). It reached its maximum on12.5 days and returned to normal in 30.4 days (34 days in HB). ALT mean was 1027 (range 100-2500) It attained maximum level in 12.2 days and returned to normal in 43.3 days (65.7 days in HB). 33% cases showed clinical or biochemical relapse (61.5% HB) In most cases it was clinically insignificant.

The degree of elevation of bilirubin or enzymes was not related to eventual recovery. This means that if the patient had enzyme level of 2500, it did not mean that he would take longer to recover.

Histological Features

Liver Biopsy is not indicated in acute disease. As a research effort, biopsies were carried out in 100 cases. No correlation was found between various histological features and recovery. There are minor differences in various types. The ground glass change of cytoplasm, however, is distinctive for HBV.

How to predict imminent Fulminant Hepatitis

It is difficult to predict imminent failure from LFT'S. Some of these cases may not even reveal clinical jaundice. The continued poor appetite should be a cause for concern. Fall of enzymes with continued rise of bilirubin is a grave sign.A high prothrombin time also indicates serious disease.

CHAPTER-3
VIRAL HEPATITIS IN CHILDREN

Children represent a significant prortion of our population. Viral hepatitis is very common disease in them.In most cases the disease is benign lasting a few days. In the vast majority it is asymptomatic not even causing jaundice.However it can result in fulminant hepatitis and death.

Prevalence of serotypes

A survey of healthy children in Karachi showed that 94.1% had antibodies to HAV by the age of 5 years indicating the sad state of community sanitation . Anti HBs and Anti C were negligible (2% and 0.43% respectively)

An important area of interest is the prevalence of carrier rates in mothers and transmission to the newborn.It was found to be 7.8% in one study in Rawalpindi. All were e-negative. The risk of vertical transmission was noted. However it is felt that unlike Far East, in our cases. the spread is probably perinatal.

It has been reported that if infection occurs in perinatal period the carrier rate is extremely high(70-90%) while cliniclal disease is infrequent(5-10%).It is therefore extemely important that vaccination is carried out in the newborn.

Table I

EARLY CHILDHOOD HBV INFECTION	
RISK OF CHRONICITY	
Age at Infection (years)	Proportion who become carriers (%)
<1	70-90
2-3	40-70
4-6	10-40
>7	6-10

Chronic Hepatitis B in Children

The risk of chronicity in hepatitis B infections in newborns and early childhood is high (see table 1).In addition, most infants and young children infected with hepatitis B have normal aminotransferases and are not candidates for therapy. Children who are first infected at ages over 7 years of age have a low risk of developing chronic disease. The prognosis of hepatitis B in children is generally good, cirrhosis and hepatocellular carcinoma are only rarely seen in the childhood years. Spontaneous seroconversion from HBeAg to anti-HBe antibody occurs in between 6-12% of infected children per year. In randomized controlled trials treatment with alpha-interferon in children resulted in 35% clearance of HBV DNA and HBeAg(11% in controls) and 7% clearance of HBsAg (1% in controls). Optimal treatment is between 3-6 Mu/m2 of interferon TIW for 6 months. The indications for treatment are similar

to those in adults. There is no information on the use of lamivudine in children. Normally treatment should not begin before two years of age, because of the side effects of alpha-interferon. In older children the side effects of interferon appear to be well-tolerated.Weight loss can be offset by dietary interventions.

Hepatitis C Infection in Children

In past years, hepatitis C was found with high prevalence in children who received multiple transfusions of blood derived products before testing for hepatitis C was introduced. Currently, age-related distribution of infection is likely related to different patterns of exposure. Vertical transmission in infants and body piercing, tattooing and drug abuse in adolescents are the most common routes of infection. The rate at which the initial infection becomes chronic in infants is still unknown. Up to 30% of these children appear to have spontaneous resolution of their infection. Although progression of the disease seems to be more benign in children than in adults, some children do develop significant fibrosis. Uncontrolled trials suggest that the response rate to interferon may be as high as 33-50%. The response to combination therapy (interferon and ribavirin) is unknown.The indications for treatment in children with hepatitis C have not been adequately defined.Chronic hepatitis C in children should not be treated except in controlled trials.

The neonates can also contract hepatitis B and C as in utero infection. A number of conditions have therefore to be distinguished in the newborn with the longer term jaundice. They range fromBilary atresia (43.4% in a Karachi study) to such diseases as Hepatitis A and B (8% each), galactasemia and cytomegalovirus infection. It may be kept in mind that the commonest cause in newborn is haemolytic jaundice due to ABO andRh incompatibility.

Hepatitis A encephalopathy can occur in childern. A prolonged jaundice and high prothrombin time are grave signs in these cases.

CHAPTER-4

MEDICAL TESTS AND PROCEDURES.

LIVER FUNCTION TESTS (LFT'S)

The term "liver function tests" and its abbreviated form "LFT's" is a commonly used term that is applied to a variety of blood tests that assess the general state of the liver and biliary system. Routine blood tests can be divided into those tests that are true LFT's, such asserum albumin or prothombin time, and those tests that are simply markers of liver or biliary tract disease, such as the various liver enzymes. In addition to the usual liver tests, physicians may order more specific liver tests such as viral serologic tests or autoimmune tests that, if positive, can determine the specific cause of a liver disease. Liver function tests measure various chemicals present in the blood and can be useful in determining the extent of liver disease.

There are two general categories of "liver enzymes." The first group includes the alanineaminotransferase (ALT) and the aspartate aminotransferase (AST), formerly referred to as the SGPT and SGOT. These are enzymes that are indicators of liver cell damage. The other frequently used liver enzymes are the alkaline phosphatase that indicate obstruction to the biliary system, either within the liver or in the larger bile channels outside the liver.

ALT OR SGPT

ALT, an enzyme appears in liver cells, with lesser amounts in the kidneys, heart, and skeletal muscles, and is a relatively specific indicator of acute liver cell damage. When such damage occurs, ALT is released from the liver cells into the bloodstream, often before jaundice appears, resulting in abnormally high serum levels that may not return to normal for days or weeks.

The purpose of this blood serum test is to help detect and evaluate treatment of acute hepatic disease, especially hepatitis, and cirrhosis without jaundice. To help distinguish between mytyocardial (heart) and liver tissue damage (used with the AST enzyme test). Also to assess hepatotoxicity of some drugs.

ALT levels by a commonly used method range from 10 to 32 U/L: in women, from 9 to 24 U/L. (There does exist differing ranges used by various laboratories.) The normal range for infants is twice that of adults.

Very high ALT levels (up to 50 times normal) suggest viral or severe drug-induced hepatitis, or other hepatic disease with extensive necrosis (death of liver cells). (AST levels are also elevated but usually to a lesser degree.) Moderate-to-high levels may indicate infectious mononucleosis, chronic hepatitis, intrahepatic cholestasis or cholecystitis, early or improving acute viral hepatitis, or severe hepatic congestion due to heart failure. Slight-to-moderate elevations of ALT (usually with higher increases in AST levels) may appear in any condition that produces acute hepatocellular (liver cell) injury, such as active cirrhosis, and drug-

induced or alcoholic hepatitis. Marginal elevations occasionally occur in acute myocardial infarction (heart attack), reflecting secondary hepatic congestion or the release of small amounts of ALT from heart tissue.

Many medications produce hepatic injury by competitively interfering with cellular metabolism. Falsely elevated ALT levels can follow use of barbiturates, narcotics, methotrexate, chlorpromazine salicylates (aspirin), and other drugs that affect the liver.

Serum liver enzymes can create confusion for both patients and physicians for these tests are highly sensitive, but very non-specific. Tests commonly referred to as liver function tests or LFT's do not actually determine liver function. Instead, they are static, primarily diagnostic parameters that serve to detect liver disease rather than quantitative liver function. Rather than liver function tests, it is more useful to refer to these tests as serum liver tests and to mentally categorise them according to the pathophysiologic processes they truly reflect.

AST

One of the two main liver function blood serum tests (the other being the ALT test). The purpose of this blood test is to detect a recent myocardial infarction (heart attack); to aid detection and differential diagnosis of acute hepatic disease and to monitor patient progress and prognosis in cardiac and hepatic diseases. AST levels by a commonly used method range from 8 to 20 U/L although some ranges may express a maximum high in the 40s. (Check with your physician.)

AST levels fluctuate in response to the extent of cellular necrosis (cell death) and therefore may be temporarily and minimally elevated early in the disease process, and extremely elevated during the most acute phase. Depending on when the initial sample was drawn, AST levels can rise- indicating increasing disease severity and tissue damage- or fall- indicating disease resolution and tissue repair. Thus, the relative change in AST values serves as a reliable monitoring mechanism.

Maximum elevations are associated with certain diseases and conditions. For example, very high elevations (more than 20 times normal) may indicate acute viral hepatitis, severe skeletal muscle trauma, extensive surgery, drug-induced hepatic injury, and severe liver congestion. High levels (ranging from 10 to 20 times normal) may indicate severe myocardial infarction (heart attack), severe infectious mononucleosis, and alcoholic cirrhosis. High levels may also occur during the resolving stages of conditions that cause maximal elevations. Moderate-to-high levels (ranging from 5 to 10 times normal) may indicate chronic hepatitis and other conditions. Low-to-moderate levels (ranging from 2 to 5 times normal) may indicate metastatic hepatic tumours, acute pancreatitis, pulmonary emboli, alcohol withdrawal syndrome, and fatty liver (steatosis).

BILIRUBIN

Bilirubin is the main bile pigment in humans which, when elevated causes the yellow discoloration of the skin and eyes called jaundice. Bilirubin is formed primarily from the

breakdown of a substance in red blood cells called "heme." It is taken up from blood processed through the liver, and then secreted into the bile by the liver. Normal individuals have only a small amount of bilirubin circulating in blood (less than 1.2 mg/dL). Conditions which cause increased formation of bilirubin, such as destruction of red blood cells, or decrease its removal from the blood stream, such as liver disease may result in an increase in the level of serum bilirubin. Levels greater than 3 mg/dL are usually noticeable as jaundice. The bilirubin may be elevated in many forms of liver or biliary tract disease, and thus it is also relatively non-specific. However, serum bilirubin is generally considered a true test of liver function (LFT), since it reflects the liver's ability to take up, process, and secrete bilirubin into the bile.

GGT (GAMMA GLUTAMYLTRANSFERASE)

The purpose of this blood serum chemistry test is to provide information about hepatobiliary diseases, to assess liver function, and to detect alcohol ingestion. Another purpose is to distinguish between skeletal disease and hepatic disease when serum alkaline phosphatase is elevated. A normal GGT level suggests such elevation stems from skeletal disease.

Normal results in females under age 45, range from 5 to 27 U/L; in females over age 45 and in males, levels range from 6 to 37 U/L. Serum GGT values vary with the assay method used (colorimetric or kinetic).

The sharpest increases in GGT levels indicate obstructive jaundice and hepatic metastasis. Elevations may indicate any acute hepatic disease, acute pancreatitis, renal disease, alcohol ingestion, postoperative status, and prostatic metastasis.

This test is non-specific, providing little data about the type of hepatic disease. GGT is particularly sensitive to the effects of alcohol in the liver, and levels may be elevated after moderate alcohol intake and in chronic alcoholism, even without clinical evidence of hepatic injury.

SERUM ALBUMIN

Albumin is a major protein which is formed by the liver, and chronic liver disease causes a decrease in the amount of albumin produced. Therefore, in liver disease, particularly more advanced liver disease, the level of the serum albumin is reduced (less than 3.5 mg/dL).

PROTHOMBIN TIME.

The prothrombin time, which is also called protime or PT, is a test that is used to assess blood clotting. Blood clotting factors are proteins made by the liver. When the liver is significantly injured, these proteins are not normally produced. The prothrombin time is also a useful LFT, since there is a good correlation between abnormalities in coagulation measured by the prothrombin time and the degree of liver dysfunction. Prothrombin time is usually expressed in seconds and compared to a normal control patient's blood.

PCR

This test uses the Polymerase Chain Reaction or PCR to amplify the amount of DNA or RNA present in a sample. The test is highly sensitive and can detect minute quantities of DNA or RNA. With regard to hepatitis B the test comes in two forms:-

QUALITATIVE PCR

This test tests for the presence of hepatitis B DNA, it is highly sensitive and gives a positive or negative result and is generally only used for research purposes. In someone who has never been exposed to hepatitis B a negative result would occur. In those with acute or chronic hepatitis B a positive result would be expected. In people who have successfully defeated a hepatitis B infection and developed antibodies to the surface antigen a negative result would be expected, however many positive results have been reported and this indicates that the hepatitis B virus is sometimes present, although in minute quantities, in those who have developed antibodies to the virus.

QUANTITATIVE PCR

This measures the quantity of hepatitis B DNA present in a sample. It is not as sensitive as qualitative PCR but does give an indication of the number of copies of the virus present. This result is used to determine what is known as "viral load" or the number of copies of the virus present.

This test is relatively expensive and generally only used for research purposes as other hepatitis B antigens can be used for diagnostic purposes. E.g. the presence of the "e" antigen indicates a high level of viral reproduction and so indicates a high viral load. However since mutant versions of hepatitis B do not always produce the "e" antigen this test can be used to determine viral load in those cases.

Tests for hepatitis and liver dysfunction in HCV infection

Early in HCV infection an elevation of the liver enzymes, especially the ALT or SGPT level reveals inflammation and hepatic injury.

ALT and AST

In hepatitis diagnosis, an elevated ALT or SGPT level is the most important liver enzyme abnormality observed rather than the AST level. The ALT is specific to the liver while AST is also found in red blood cells and muscles. Thus, things other than liver disease can cause an elevation of the AST level. Patients with significant liver disease may have very low platelets or white blood cells because the spleen often becomes enlarged. As the liver becomes injured and becomes fibrotic and scarred, the spleen enlarges and removes platelets and white cells from the blood. Regardless, the function of the platelets and the white blood cells remains good and there is not too much chance of increased bleeding or infection.

Biochemical Indicators of Hepatitis C Virus Infection

There are no biochemical; tests diagnostic of C infection. However sopme inkling about its presence may be suspected by the following tests. It must however be understood that demonstration of C virus or antibodies against it will clinch the diagnosis.

- In chronic hepatitis C, increases in the alanine and aspartate aminotransferases range from 0 to 20 times (but usually less than 5 times) the upper limit of normal.
- Alanine aminotransferase levels are usually higher than aspartate aminotransferase levels, but that finding may be reversed in patients who have cirrhosis.
- Alkaline phosphatase and gamma glutamyl transpeptidase are usually normal. If elevated, they may indicate cirrhosis.
- Rheumatoid factor and low platelet and white blood cell counts are frequent in patients with cirrhosis, providing clues to the presence of advanced disease.
- The enzymes lactate dehydrogenase and creatine kinase are usually normal.
- Albumin levels and prothrombin time are normal until late-stage disease.

Diagnostic tests

Tests used to detect HCV antibody are known as the enzyme immunosorbent assay (EIA) or the recombinant immunoblot assay (RIBA). Tests which look for virus in the blood are designed to detect the presence of the HCV RNA genome, the nucleic acid of the virus. These tests are called the branched DNA assay or bDNA assay and the polymerase chain reaction or PCR test.

How is HCV infection found?

Many HCV infected individuals are initially discovered when they go to their phyiscian for minor or unrelated problem.

Interpretations of a positive anti-HCV test

There are several possible interpretations of a positive anti-HCV antibody test. The test is unable to distinguish between an active current infection, which may be acute or chronic, or a past resolved infection. In a neonate born to an HCV-infected mother, a positive anti-HCV test may represent passively transferred HCV antibody that crosses the placenta from the mother. This reveals nothing about the child and the possible infection. A positive anti-HCV test also may be a false positive reaction. One way to rule out a false positive test is to do the RIBA test.

How the RIBA test works -

In the RIBA test, the diagnostic laboratory uses a plastic strip to which HCV proteins are bound. The patients serum is then added to the strip. The strip develops different visible bands based on the association of various viral proteins with their respective antibodies. A positive reaction exists if two or more unique bands are present. If one band is present, it is labeled an indeterminate response. Four bands are present at least 80% of the time in HCV infection. Again, this test does not separate an active infection from a previous infection but it can validate a positive EIA test.

HEPATITIS C TESTS

Tests		INTERPRETATION	RECOMMENDATION
anti-HCV	positive	chronic hepatitis, chronic hepatitis C recovered, recent acute hepatitis C, or false positive test	further evaluation
anti-HCV	positive	possible chronic HCV carrier, may have chronic hepatitis C	further evaluation
ALT	normal		
supplemental test (RIBA-2)	positive		
anti-HCV	positive	presume chronic hepatitis C	further evaluation/ consider interferon therapy
ALT	elevated		
supplemental test (RIBA-2)	positive		
anti-HCV	positive	presume false positive anti-HCV or recovered	further evaluation by HCV-RNA PCR test i RIBA2 negative or indeterminate
ALT	normal		
supplemental test (RIBA-2)	Negative / indeterminate		
anti-HCV	positive	presume false positive anti-HCV, false negative supplemental test unlikely	further evaluation for liver disease other than hepatitis C
ALT	elevated		
supplemental test (RIBA-2)	negative		
ALT (no other symptoms)	elevated	possible fatty liver, chronic viral hepatitis, alcoholic liver disease, hemochromatosis, drug induced liver injury, other liver diseases	further evaluation

How is active infection determined? How are bDNA and PCR tests different?

The presence of the HCV RNA genome determines active infection. The bDNA test has a high precision. High precision means that if you test the same sample of blood several times the results will be fairly close. The PCR test has moderate precision but a higher sensitivity meaning it will detect less virus. The bDNA assay has a lower limit of sensitivity of 200,000 copies of the viral genome (nucleic acid) per mL. If a person tests negative by the bDNA test, he/she could still have up to 200,000 copies/mL circulating in their blood. The PCR test can detect from less than 100 copies/mL up to several million or more without having to dilute the blood. However, lower sensitivity is the critical factor. In one series of 260 individuals, 7% had less than 100,000 copies of virus per mL. All of these samples were detected by PCR but only 5% were detected by the bDNA test. At higher levels (over one million copies per mL) detection rates were comparable. In a large multicenter clinical trial conducted by Amgen, sera from over 700 individuals were examined. About half had a viral load of over 3 million copies/mL while half were below 3 million. 25% had HCV viral concentrations below a million copies/mL, while 15% had HCV levels below 200,000 genomic equivalents/mL, the cut off level for the bDNA test. Conversely, 25% additional patients had a virus load above 6 million copies/mL. The PCR test is useful but may be subject to cross-contamination. Because PCR amplification can multiply one copy of virus a trillion fold up to detectable levels, cross-contamination of samples can result in false positive reactions if the laboratory is not careful.

Therefore choosing a high quality laboratory for PCR testing of samples is most important. When the proficiency of 21 laboratories was tested recently, 95% agreed the first time, while only 68% agreed the second time. On a third occasion, 92% agreed on a negative sample but that leaves 8% who incorrectly found a positive result. Another evaluation of a positive sample resulted in 75% who agreed and 25% which found the sample negative. Even more disconcerting was the fact that these were samples containing relatively large amounts of virus, which should have made detection easier.

What happens to the HCV-RNA level over time?

In a study of HCV RNA subjects bled 1) twice a day, 2) daily for a week, 3) weekly for six weeks, or 4) monthly for three months showed from two to threefold differences in the viral concentration over time when batch tested. To test in a batch means the samples were frozen when taken and then all were tested at the same time. It is anticipated that the amount of variation observed will be greater when testing is done in real time, the usual way that tests are done. Thus, differences observed between samples tested in real time may be several times as great. Therefore, unless results vary by 3-5 fold or more, the differences are probably not important. When evaluating samples from patients being treated with interferon, concentration of the virus in the blood is not important. What is important is whether the virus is no longer detected. If the virus has not disappeared from the blood when treatment ends, the patient will relapse. If virus is detected in the blood, it also will be present in the liver. However, if it is not in the blood, it might still be in the liver. Examination of liver tissue for the virus is the only way to determine this. HCV also may be extrahepatic,

in sites other than the liver, which is why we continue to treat people for long periods of time to eliminate the virus, not only from the blood, but also from the liver or the other sites.

Which is better, quantitative or qualitative tests?

If tests differ in sensitivity, then the most sensitive and specific assay should be used. The exact concentration of virus is not critical for monitoring therapy for it is the presence of virus in the blood which makes a difference. Quantitative assays are essential for clinical studies or for determining pathogenesis. HCV RNA testing can be used to resolve indeterminate RIBA results as well as for determining whether an infection is current or past for determining HCV from other liver diseases, and to determine if infants born to HCV positive women are infected. It also is appropriate for monitoring drug therapy and to study patterns of transmission.

Genotypes -

There are more than 3,000 amino acids (over 9,000 nucleotides) in the HCV genome. Genotypes differ from each other by about 1,000 nucleotides. The Amgen study examined over 700 individuals at 41 centers in the US and Canada for genotype distribution. Genotype 1a and 1b were the most common (55-60%). These genotypes also are among the most resistant to interferon as is type 4, which is most common in Egypt. Some patients appear to have many different quasispecies of HCV from the same genotype circulating in their blood. Quasispecies differ from each other by only about 50-60 amino acids and thus are very closely related.

Liver Biopsy

Liver biopsy is not necessary for diagnosis but is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage. Hematoxylin and eosin stains and Masson's trichrome stain are used to grade the amount of necrosis and inflammation and to stage the degree of fibrosis.

The liver biopsy can give a clue to the type of virus. The morphological features such as ground glass appearnce can point to HBV infection. Special stains are also available to demonstrate it. Specific immunohistochemical stains for HCV have not been developed for routine use so far.

Liver biopsy is also helpful in ruling out other causes of liver disease, such as alcoholic liver injury or iron overload.

Chronic hepatitis can cause the following changes in liver tissue:

Necrosis and inflammation around the portal areas, so-called "piecemeal necrosis" or "interface hepatitis."

Necrosis of hepatocytes and focal inflammation in the liver parenchyma.

Inflammatory cells in the portal areas ("portal inflammation").

Fibrosis, with early stages being confined to the portal tracts, intermediate stages being expansion of the portal tracts and bridging between portal areas or to the central area and late stages being frank cirrhosis characterized by architectural disruption of the liver with fibrosis and regeneration.

Grading and staging of hepatitis by assigning scores(like Knodell's Histological Activity Index) for severity are helpful in managing patients with chronic hepatitis. The degree of inflammation and necrosis can be assessed as none, minimal, mild, moderate, or severe. The degree of fibrosis can be similarly assessed. Scoring systems are particularly helpful in clinical studies on chronic hepatitis.

CHAPTER-5
PROTECTION AGAINST VIRAL HEPATITIS

The protection against Hepatitis requires an understanding of its various types, their mode of spread and epidemiology. Vaccines are available against Hepatitis A and B. The protection against water borne types like A and E essentially requires that fecal-oral chain be broken. The purity of water supply is of paramount importance. However in a developing country like Pakistan , it will remain a dream for a long time. Till that is achieved , boiling all drinking water should always be resorted to. Another sensible thing to do, but often neglected , is to wash hands thoroughly before eating.

Vaccine against Hepatitis C is still in the future mainly due the complex and variable structure of the virus.

IMMUNE GLOBULINS

Immune globulins are important tools for preventing infection and disease before or after exposure to hepatitis viruses Immune globulins used in medical practice are sterile solutions of antibodies (immunoglobulins) from human plasma. They are prepared by cold ethanol fractionation of large plasma pools and contain 10%-18% protein. In the United States, plasma is primarily obtained from paid donors. Only plasma shown to be free of hepatitis B surface antigen (HBsAg) and antibody to human immunodeficiency virus (HIV) is used to prepare immune globulins.

Immune globulin (formerly called immune serum globulin, ISG, or gamma globulin) produced in the United States contains antibodies against the hepatitis A virus (anti-HAV) and the HBsAg (anti-HBs). Hepatitis B immune globulin (HBIG) is an IG prepared from plasma containing high titers of anti-HBs.

There is no evidence that hepatitis B virus (HBV), HIV (the causative agent of acquired immunodeficiency syndrome (AIDS)), or other viruses have ever been transmitted by IG or HBIG commercially available in the United States. Since late April 1985, all plasma units for preparation of IGs have been screened for antibody to HIV, and reactive units are discarded. No instances of HIV infection or clinical illness have occurred that can be attributed to receiving IG or HBIG, including lots prepared before April 1985. Laboratory studies have shown that the margin of safety based on the removal of HIV infectivity by the fractionation process is extremely high .Some HBIG lots prepared before April 1985 have detectable HIV antibody. Shortly after being given HBIG, recipients have occasionally been noted to have low levels of passively acquired HIV antibody, but this reactivity does not persist.

Serious adverse effects from IGs administered as recommended have been rare. IGs prepared for intramuscular administration should be used for hepatitis prophylaxis. IGs prepared for intravenous administration to immunodeficient and other selected patients are

lactating women.

HEPATITIS A

Recommendations for IG Prophylaxis for Hepatitis A

Numerous field studies conducted in the past 4 decades confirm that IG given before exposure or during the incubation period of hepatitis A is protective against clinical illness. Its prophylactic value is greatest (80%-90%) when given early in the incubation period and declines thereafter. Recent tests have shown slightly decreased titers of anti-HAV in current IG lots compared with lots tested 8 years previously; however, no differences in IG efficacy have been noted.

Preexposure Prophylaxis

The major group for whom preexposure prophylaxis is recommended is international travelers to the areas where the disease is endemic.

Postexposure Prophylaxis

Hepatitis A cannot be reliably diagnosed on clinical presentation alone, and serologic confirmation of index patients is recommended before contacts are treated. Serologic screening of contacts for anti-HAV before they are given IG is not recommended because screening is more costly than IG and would delay its administration.

For postexposure IG prophylaxis, a single intramuscular dose of 0.02 ml/kg is recommended. IG should be given as soon as possible after last exposure; giving IG more than 2 weeks after exposure is not indicated.

The majority of our population is exposed to the virus during childhood and is immune. The utility of vaccination is therefore limited and has to be confined to special situations.

HEPATITIS B

A variable proportion of individuals infected with HBV will become chronically infected with the virus. The HBV carrier is central to the epidemiology of HBV transmission. **A carrier is defined as a person who is either HBsAg-positive on at least two occasions (at least 6 months apart) or who is HBsAg-positive and IgM anti-HBc negative when a single serum specimen is tested.** Although the degree of infectivity is best correlated with HBeAg-positivity, any person positive for HBsAg is potentially infectious. The likelihood of becoming chronically infected with HBV varies inversely with the age at which infection occurs. HBV transmitted from HBsAg-positive mothers to their newborns results in HBV carriage for up to 90% of infants. Between 25% and 50% of children infected before 5 years of age become carriers, whereas only 6%-10% of acutely infected adults become carriers.

Carriers and persons with acute infection have the highest concentrations of HBV in blood and serous fluids. A lower concentration is present in other body fluids, such as saliva and semen. Transmission occurs via percutaneous or permucosal routes, and infective blood or body fluids can be introduced at birth, through sexual contact, or by contaminated needles. Infection can also occur in settings of continuous close personal contact (such as in households or among children in institutions for the developmentally disabled), presumably via inapparent or unnoticed contact of infective secretions with skin lesions or mucosal surfaces. Transmission of infection by transfusion of blood or blood products is rare because of routine screening of blood for HBsAg and because of current donor selection procedures. Transmission of HBV from infected health-care workers to patients is uncommon but has been documented during types of invasive procedures (e.g., oral and gynecologic surgery). HBsAg-positive health-care workers need not be restricted from patient contact unless they have been epidemiologically associated with HBV transmission. Rather, they should be educated about the potential mechanisms of HBV transmission. Adherence to aseptic techniques minimizes the risk of transmission. HBV is not transmitted via the fecal-oral route.

Worldwide, HBV infection is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma. The frequency of HBV infection and patterns of transmission vary markedly in different parts of the world. In the United States, Western Europe, and Australia, it is a disease of low endemicity, with infection occurring primarily during adulthood and with only 0.2%-0.9% of the population being chronically infected. In contrast, HBV infection is highly endemic in China and Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and in the Amazon Basin. In these areas, most persons acquire infection at birth or during childhood, and 8%-15% of the population are chronically infected with HBV. In other parts of the world, including Pakistan, HBV infection is moderately endemic, with 2%-7% of the population being HBV carriers. Prevention strategies for populations in which HBV infection is highly endemic are directed at vaccinating infants with hepatitis B vaccine, usually beginning at birth, to prevent both perinatal and childhood transmission of infection. Recommendations for hepatitis B prophylaxis in other areas should be designed to maximize the interruption of HBV transmission in accordance with local patterns of transmission. The recommendations that follow are intended for use in the United States.It is unfortunate that no recommendations(at least we are not aware of any) have been formulated for Pakistan.

Hepatitis B Prophylaxis

Two types of products are available for prophylaxis against hepatitis B. Hepatitis B vaccines, first licensed in 1981, provide active immunization against HBV infection, and their use is recommended for both preexposure and postexposure prophylaxis. HBIG provides temporary, passive protection and is indicated only in certain postexposure settings.

HBIG

HBIG is prepared from plasma preselected to contain a high titer of anti-HBs. In the United States, HBIG has an anti-HBs titer of greater than 100,000 by radioimmunoassay (RIA). Human plasma from which HBIG is prepared is screened for antibodies to HIV; in addition, the Cohn fractionation process used to prepare this product inactivates and eliminates HIV

from the final product. There is no evidence that the causative agent of AIDS (HIV) has been transmitted by HBIG.

Hepatitis B Vaccine

Two types of hepatitis B vaccines are currently licensed in the United States. Plasma-derived vaccine consists of a suspension of inactivated, alum-adsorbed, 22-nm, HBsAg particles that have been purified from human plasma by a combination of biophysical (ultracentrifugation) and biochemical procedures. Inactivation is a threefold process using 8M urea, pepsin at pH 2, and 1:4,000 formalin. These treatment steps have been shown to inactivate representatives of all classes of viruses found in human blood, including HIV (28). Plasma-derived vaccine is no longer being produced in the United States, and use is now limited to hemodialysis patients, other immunocompromised hosts, and persons with known allergy to yeast.

Currently licensed recombinant hepatitis B vaccines are produced by Saccharomyces cerevisiae (common baker's yeast), into which a plasmid containing the gene for the HBsAg has been inserted. Purified HBsAg is obtained by lysing the yeast cells and separating HBsAg from yeast components by biochemical and biophysical techniques. These vaccines contain more than 95% HBsAg protein. Yeast-derived protein constitutes no more than 5% of the final product.

Hepatitis B vaccines are packaged to contain 10-40 ug HBsAg protein/ml and are adsorbed with aluminum hydroxide (0.5 mg/ml). Thimerosal (1:20,000 concentration) is added as a preservative.

The recommended series of three intramuscular doses of hepatitis B vaccine induces an adequate antibody response * in greater than 90% of healthy adults and in greater than 95%of infants, children, and adolescents from birth through 19 years of age. The deltoid (arm) is the recommended site for hepatitis B vaccination of adults and children; immunogenicity of vaccine for adults is substantially lower when injections are given in the buttock. Larger vaccine doses (two to four times normal adult dose) or an increased number of doses (four doses) are required to induce protective antibody in a high proportion of hemodialysis patients and may also be necessary for other immunocompromised persons (such as those on immunosuppressive drugs or with HIV infection)

Field trials of the vaccines licensed in the United States have shown 80%-95% efficacy in preventing infection or clinical hepatitis among susceptible persons. Protection against illness is virtually complete for persons who develop an adequate antibody response after vaccination. The duration of protection and need for booster doses are not yet fully defined. Between 30% and 50% of persons who develop adequate antibody after three doses of vaccine will lose detectable antibody within 7 years, but protection against viremic infection and clinical disease appears to persist .Immunogenicity and efficacy of the licensed vaccines for hemodialysis patients are much lower than in normal adults. Protection in this group may last only as long as adequate antibody levels persist.

Vaccines Available in Pakistan

The following vaccines /Immunoglobulins against hepatitis are available in Pakistan.

Immune globulins
Gamastan, Globuman ,Hepuman,Hyperhep and others
Vaccines against HBV
Engerix-B,H-B-VAX,Hepa-BVAC, Hepaccine-B, Heptis-B,Hevac B
Heberbiovac HB

Vaccine Usage

Primary vaccination comprises three intramuscular doses of vaccine, with the second and third doses given 1 and 6 months, respectively, after the first. Adults and older children should be given a full 1.0ml divided by dose, while children less than 11 years of age should usually receive half (0.5 ml) this dose. An alternative schedule of four doses of vaccine given at 0, 1, 2, and 12 months has been approved for one vaccine for postexposure prophylaxis or for more rapid induction of immunity. However, there is no clear evidence that this regimen provides greater protection than the standard three-dose series. Hepatitis B vaccine should be given only in the deltoid muscle for adults and children or in the anterolateral thigh muscle for infants and neonates.

For patients undergoing hemodialysis and for other immunosuppressed patients, higher vaccine doses or increased numbers of doses are required. A special formulation of one vaccine is now available for such persons .Persons with HIV infection have an impaired response to hepatitis B vaccine. The immunogenicity of higher doses of vaccine is unknown for this group, and firm recommendations on dosage cannot be made at this time.

Vaccine doses administered at longer intervals provide equally satisfactory protection, but optimal protection is not conferred until after the third dose. If the vaccine series is interrupted after the first dose, the second and third doses should be given separated by an interval of 3-5 months. Persons who are late for the third dose should be given this dose when convenient. Postvaccination testing is not considered necessary in either situation.

All hepatitis B vaccines are inactivated (noninfective) products, and there is no evidence of interference with other simultaneously administered vaccines.

Data are not available on the safety of hepatitis B vaccines for the developing fetus. Because the vaccines contain only noninfectious HBsAg particles, there should be no risk to the fetus. In contrast, HBV infection of a pregnant woman may result in severe disease for the mother and chronic infection of the newborn. Therefore, pregnancy or lactation should not be considered a contraindication to the use of this vaccine for persons who are otherwise eligible.

Vaccine storage and shipment

Vaccine should be shipped and stored at 2 °C-8 °C but not frozen. Freezing destroys the potency of the vaccine.

Side effects and adverse reactions

The most common side effect observed following vaccination with each of the available vaccines has been soreness at the injection site. Postvaccination surveillance for 3 years after licensure of the plasma-derived vaccine showed an association of borderline significance between Guillain-Barre syndrome and receipt of the first vaccine dose .The rate of this occurrence was very low (0.5/100,000 vaccinees) and was more than compensated by disease prevented by the vaccine even if Guillain-Barre syndrome is a true side effect. Such postvaccination surveillance information is not available for the recombinant hepatitis B vaccines. Early concerns about safety of plasma-derived vaccine have proven to be unfounded, particularly the concern that infectious agents such as HIV present in the donor plasma pools might contaminate the final product.

Effect of vaccination on carriers and immune persons

Hepatitis B vaccine produces neither therapeutic nor adverse effects for HBV carriers .Vaccination of individuals who possess antibodies against HBV from a previous infection is not necessary but will not cause adverse effects. Such individuals will have a postvaccination increase in their anti-HBs levels. Passively acquired antibody, whether acquired from HBIG or IG administration or from the transplacental route, will not interfere with active immunization .

Prevaccination serologic testing for susceptibility

The decision to test potential vaccine recipients for prior infection is primarily a cost-effectiveness issue and should be based on whether the costs of testing balance the costs of vaccine saved by not vaccinating individuals who have already been infected. Estimation of cost-effectiveness of testing depends on three variables: the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune individuals in the group.

Testing in groups with the highest risk of HBV infection (HBV marker prevalence greater than 20%), is usually cost-effective unless testing costs are extremely high. Cost-effectiveness of screening may be marginal for groups at intermediate risk. For groups with a low expected prevalence of HBV serologic markers, such as health professionals in their training years, prevaccination testing is not cost-effective.

For routine testing, only one antibody test is necessary (either anti-HBc or anti-HBs). Anti-HBc identifies all previously infected persons, both carriers and those who are not carriers, but does not differentiate members of the two groups. Anti-HBs identifies persons previously infected, except for carriers. Neither test has a particular advantage for groups expected to have carrier rates of less than 2%, such as health-care workers. Anti-HBc may be preferred to avoid unnecessary vaccination of carriers for groups with higher carrier rates. If RIA is used to test for anti-HBs, a minimum of 10 sample ratio units should be used to designate

immunity (2.1 is the usual designation of a positive test). If EIA is used, the positive level recommended by manufacturers is appropriate.

Postvaccination testing for serologic response and revaccination of nonresponders

Hepatitis B vaccine, when given in the deltoid, produces protective antibody (anti-HBs) in greater than 90% of healthy persons. Testing for immunity after vaccination is not recommended routinely but is advised for persons whose subsequent management depends on knowing their immune status (such as dialysis patients and staff). Testing for immunity is also advised for persons for whom a suboptimal response may be anticipated, such as those who have received vaccine in the buttock, persons greater than or equal to 50 years of age, and persons known to have HIV infection. Postvaccination testing should also be considered for persons at occupational risk who may have needle-stick exposures necessitating postexposure prophylaxis. When necessary, postvaccination testing should be done between 1 and 6 months after completion of the vaccine series to provide definitive information on response to the vaccine.

Revaccination of persons who do not respond to the primary series (nonresponders) produces adequate antibody in 15%-25% after one additional dose and in 30%-50% after three additional doses when the primary vaccination has been given in the deltoid. For persons who did not respond to a primary vaccine series given in the buttock, data suggest that revaccination in the arm induces adequate antibody in greater than 75%. Revaccination with one or more additional doses should be considered for persons who fail to respond to vaccination in the deltoid and is recommended for those who have failed to respond to vaccination in the buttock.

Need for vaccine booster doses

Available data show that vaccine-induced antibody levels decline steadily with time and that up to 50% of adult vaccinees who respond adequately to vaccine may have low or undetectable antibody levels by 7 years after vaccination. Nevertheless, both adults and children with declining antibody levels are still protected against hepatitis B disease. Current data also suggest excellent protection against disease for 5 years after vaccination among infants born to hepatitis B-carrier mothers. For adults and children with normal immune status, booster doses are not routinely recommended within 7 years after vaccination, nor is routine serologic testing to assess antibody levels necessary for vaccine recipients during this period. For infants born to hepatitis B-carrier mothers, booster doses are not necessary within 5 years after vaccination. The possible need for booster doses after longer intervals will be assessed as additional information becomes available.

For hemodialysis patients, for whom vaccine-induced protection is less complete and may persist only as long as antibody levels remain above 10 mIU/ml, the need for booster doses should be assessed by annual antibody testing, and booster doses should be given when antibody levels decline to less than 10 mIU/ml.

Groups recommended for preexposure vaccination

Persons at substantial risk of HBV infection who are demonstrated or judged likely to be susceptible should be vaccinated. They include the following:

TEST RESULTS AND INDICATIONS FOR VACCINATION

Checking To See If The Patient Needs Hepatitis B Vaccine. One must use a combination of two tests to truly determine if a patient is a carrier, already immune or still susceptible to the hepatitis B virus. The physician can use **HBsAg** and Anti-**HBc** or **HBsAg** and Anti-**HBs**.

HBsAg **Anti-HBc**	positive positive	the patient is a carrier.	DOES NOT NEED THE HEPATITIS B VACCINE.
HBsAg **Anti-HBc**	negative positive	the patient has been exposed and has probably developed natural immunity. Alternatively, he may be an individual with an isolated Anti-HBc result (HBsAg negative, Anti-HBc positive and Anti-HBs negative).	DOES NOT NEED THE VACCINE.
HBsAg **Anti-HBc**	negative negative	the patient is susceptible to hepatitis B.	GIVE THE FULL VACCINE PROTOCOL.
HBsAg **Anti-HBs**	positive negative	the patient is infected with hepatitis B and is probably a carrier.	DOES NOT NEED THE HEPATITIS B VACCINE.
HBsAg **Anti-HBs**	negative positive	the patient has already been exposedand has developed natural immunity or has been successfully vaccinated.	DOES NOT NEED THE VACCINE.
HBsAg **Anti-HBs**	negative negative	the patient is susceptible	SHOULD RECEIVE THE VACCINE.

Postexposure Prophylaxis for Hepatitis B

Prophylactic treatment to prevent hepatitis B infection after exposure to HBV should be considered in the following situations: perinatal exposure of an infant born to an HBsAg-positive mother, accidental percutaneous or permucosal exposure to HBsAg-positive blood, sexual exposure to an HBsAg-positive person, and household exposure of an infant less than 12 months of age to a primary care giver who has acute hepatitis B.

Various studies have established the relative efficacies of HBIG and/or hepatitis B vaccine in different exposure situations. For an infant with perinatal exposure to an HBsAg-positive and HBeAg-positive mother, a regimen combining one dose of HBIG at birth with the hepatitis B vaccine series started soon after birth is 85%-95% effective in preventing development of the HBV carrier state. Regimens involving either multiple doses of HBIG alone, or the vaccine series alone, have 70%-85% efficacy.

For accidental percutaneous exposure, only regimens including HBIG and/or IG have been studied. A regimen of two doses of HBIG, one given after exposure and one a month later, is about 75% effective in preventing hepatitis B in this setting. For sexual exposure, a single dose of HBIG is 75% effective if given within 2 weeks of last sexual exposure (56). The efficacy of IG for postexposure prophylaxis is uncertain. IG no longer has a role in postexposure prophylaxis of hepatitis B because of the availability of **HBIG and the wider use of hepatitis B vaccine.**

Recommendations on postexposure prophylaxis are based on available efficacy data and on the likelihood of future HBV exposure of the person requiring treatment. In all exposures, a regimen combining HBIG with hepatitis B vaccine will provide both short- and long-term protection, will be less costly than the two-dose HBIG treatment alone, and is the treatment of choice.

Perinatal Exposure and Recommendations

1. Transmission of HBV from mother to infant during the perinatal period represents one of the most efficient modes of HBV infection and often leads to severe long-term sequelae. Infants born to HBsAg-positive and HBeAg-positive mothers have a 70%-90% chance of acquiring perinatal HBV infection, and 85%-90% of infected infants will become chronic HBV carriers. Estimates are that greater than 25% of these carriers will die from primary hepatocellular carcinoma (PHC) or cirrhosis of the liver. Infants born to HBsAg-positive and HBeAg-negative mothers have a lower risk of acquiring perinatal infection; however, such infants have had acute disease, and fatal fulminant hepatitis has been reported. Based on 1987 data in the United States, an estimated 18,000 births occur to HBsAg-positive women each year, resulting in approximately 4,000 infants who become chronic HBV carriers. Prenatal screening of all pregnant women identifies those who are HBsAg-positive and allows treatment of their newborns with HBIG and hepatitis B vaccine, a regimen that is 85%-95% effective in preventing the development of the HBV chronic carrier state

Acute Exposure to Blood That Contains (or Might Contain) HbsAg

For accidental percutaneous (needle stick, laceration, or bite) or permucosal (ocular or mucous-membrane) exposure to blood, the decision to provide prophylaxis must include consideration of several factors: a) whether the source of the blood is available, b) the HBsAg status of the source, and c) the hepatitis B vaccination and vaccine-response status of the exposed person. Such exposures usually affect persons for whom hepatitis B vaccine is recommended. For any exposure of a person not previously vaccinated, hepatitis B vaccination is recommended.

Following any such exposure, a blood sample should be obtained from the person who was the source of the exposure and should be tested for HBsAg. The hepatitis B vaccination status and anti-HBs response status (if known) of the exposed person should be reviewed. The outline below summarizes prophylaxis for percutaneous or permucosal exposure to blood according to the HBsAg status of the source of exposure and the vaccination status and vaccine response of the exposed person.

For greatest effectiveness, passive prophylaxis with HBIG, when indicated, should be given as soon as possible after exposure (its value beyond 7 days after exposure is unclear).

DELTA HEPATITIS

Since HDV is dependent on HBV for replication, prevention of hepatitis B infection, either preexposure or postexposure, will suffice to prevent HDV infection for a person susceptible to hepatitis B. Known episodes of perinatal, sexual, or percutaneous exposure to serum or exposure to persons known to be positive for both HBV and HDV should be treated exactly as such exposures to HBV alone.

Persons who are HBsAg carriers are at risk of HDV infection, especially if they participate in activities that put them at high risk of repeated exposure to HBV (parenteral drug abuse, male homosexual activity). However, at present no products are available that might prevent HDV infection in HBsAg carriers either before or after exposure.

Concerns about possible adverse effects of hepatitis B vaccine are being taken seriously and carefully controlled scientific studies are underway to examine whether vaccination is associated with serious neurological disease in a small number of people. There is no confirmed scientific evidence that hepatitis B vaccine causes chronic illnesses (including multiple sclerosis, chronic fatigue syndrome, rheumatoid arthritis, optic neuritis or other autoimmune disorders.). Serious adverse events reported after receiving hepatitis B vaccine are very uncommon and may represent coincidence rather than causation. Given the frequency and severity of hepatitis B infection, the benefit of vaccination far outweighs the known and potential risks.

HCV prevention

There is no vaccine for HCV and no short-term preventive like gamma globulin. Non-therapeutic measures must be relied on for prevention, including screening blood, organs, and tissues, and high risk behavior modifications.

What do you tell HCV infected individuals?

Everyone who is antibody positive and carries the virus is potentially infectious although most won't transmit without large exposure to blood. An HCV infected individual should not donate blood, tissue, or organs. They should not share razors or toothbrushes. Any cuts or sores should be covered.

Prevention and control of HCV infection

In USA a broad nationwide prevention and control plan for hepatitis C is being developed that is aimed at early identification of persons with chronic HCV infection and reducing transmission in groups at high risk of infection. Three approaches are being used to identify and educate persons at risk of HCV infection: 1) verbal, written, and visual material directed to the public; 2) educational efforts directed to health care and public health professionals; and 3) development of community-based prevention programs. These educational programs are being developed through partnerships between government agencies, non-governmental voluntary organizations and professional societies.

We in Pakistan could opt for a similar program.Public service announcements have t potential to reach a broad population. The educational messages directed at the public v include information on who is at risk for HCV infection, the consequences of infection, th need for early diagnosis and possible treatment, and recommendations to prevent infectio and transmission. Educational efforts directed at physicians and other health ca professionals will include the appropriate medical management of HCV infected patient known and potential risks for HCV infection and transmission, need to ascertain complet risk factor histories from their patients, and appropriate evaluation of high risk patients fo evidence of infection. Community-based programs should include messages an interventions related to the prevention of hepatitis B and hepatitis C.

We are proud to state that we at Healthways have already initiated a modest progra of patient and physician education. We feel that this will be of some help in tackling this serious problem.

CHAPTER-6

MANAGEMENT OF CHRONIC VIRAL HEPATITIS

Treatment of Chronic Hepatitis B Infection

Lamivudine

Lamivudine (3TC) is an antivital drug developed in Canada, with wide use in the treatment of HIV infection. It was originally shown to dramatically reduce viral replication in Peking ducks infected with duck hepatitis virus. Although the virus almost always re-emerged on discontinuation of treatment, lamivudine's ability to suppress viral replication warranted trials in HBV infected patients.

Results of a one year study in Chinese patients with HBeAg positive chronic HBV infection were recently reported. This is the largest but most difficult group of patients with chronic HBV infection to treat: most were infected at birth, and tend to respond poorly to standard interferon therapy. In this study of 358 patients, 142 were randomly assigned to receive 25 mg of lamivudine, 143 to receive 100 mg and 73 were given placebo.

The parameters studied included transaminases, HBeAg seroconversion, HBV DNA levels, and hepatic inflammation and fibrosis (Knodell's score). The results, which are most encouraging, are shown in Table 1.

However, this is end of treatment data only and at present, we have no information on the sustainability of these responses. Unpublished data indicates that in patients with HBeAg and HBV DNA loss, the beneficial response is maintained 97% of the time.

The medication was well-tolerated, with no serious adverse effects observed. No patients had a significant deterioration in liver function. However, 14% of patients developed a mutation in the polymerase gene which makes the virus, although less virulent, 1000 times more resistant to lamivudine. Whether the mutation rate will change with longer duration treatment or whether these mutations will lead to significant clinical problems down the road, remains to be documented.

The results at 6 months or one year after stopping treatment are not given and whether worrisome flares in hepatic inflammation will occur in some patients on discontinuation of therapy remains a major concern. In fact, many of these patients continued on treatment for another year, with excellent results. However, three important questions arise: 1. Is life-long treatment required? 2. Is there risk to stopping lamivudine? 3. Will the rate of drug-induced mutants increase with prolonged therapy?

We do not have the answers to these questions at present and until we do we should not be treating all patients with chronic hepatitis B with lamivudine. At present we should certainly consider lamivudine treatment for patients with significant fibrosis or cirrhosis who are heading in the direction of needing a liver transplant. To the best of our knowledge, these patients must continue lamivudine therapy long-term once it has been started. Patients with

less advanced disease should still be initially considered for standard interferon treatmer which in carefully selected individuals has a 33% success rate. 2 Patients with mild diseas should continue to be observed until long-term data on lamivudine treatment are available An important concern with lamivudine therapy is the development of resistance, estimated t occur in 11% to 15% of patients after one year of therapy, and more than 30% after tw years.

Lamivudine is, without doubt, useful in the hepatitis B patient requiring a liver transplan Lamivudine, with or without hepatitis B immunoglobulin, has been shown to reduce th incidence of posttransplant hepatitis B infection and the associated severe cholestasis. Long- term studies are also required in this population, but the current results are mos promising. Some patients treated with lamivudine while waiting for a liver transplant have improved so much they were taken off the transplant waiting list.

Because of the development of lamivudine resistant mutants in both the transplant and non transplant settings, there is interest in combination therapy as is used in HIV infection. Thus far, lamivudine and penciclovir have been used successfully in treating duck hepatitis with the combination therapy showing synergy and better results than either agent alone.4 Studies in HBV infected patients are ongoing and such combination treatment looks promising.

Other Antiviral Agents

Several other nucleoside analogues with similarities to lamivudine are currently being investigated in both animal models and humans with HBV infection. Famciclovir, adefovir, dipivoxil and lobucavir are other nucleoside analogues which inhibit the HBV polymerase enzyme and have variable degrees of success in reducing the amount of closed circular DNA, often the cause of posttreatment rebound infection. These drugs induce mutations different from those observed in lamivudine-treated patients and offer the real possibility that combination therapy may be superior to single agent therapy.

Thymosin a1 (Ta) is an immunomodulatory peptide produced by the thymus and other cells. It stimulates T-cell maturation, antigen recognition, natural killer cell activity and the production of native interferons. Pilot studies showed some benefit in chronic HBV infection and as a result a therapeutic trial was undertaken in 98 Chinese patients to assess its efficacy and tolerability.5 Eighteen months after entry, 40.6% of patients receiving 1.6 mg sc bid for 26 weeks had cleared HBV DNA and HBeAg compared with 26.5% in the group receiving 52 weeks of the same treatment and 9.4% in the untreated control group. None cleared HBsAg. No significant side-effects were observed. Although this is only a single study, results are encouraging as they are significantly better than those observed with either lamivudine or IFN in this patient population.

Other Potential Therapies for Chronic HBV Infection

Several other lines of investigation are being taken in the approach to treatment of chronic HBV infection. As with other viral agents, vaccination with antigenic epitopes are being investigated. Antisense oligonucleotides and ribozymes have some theoretical potential and

are being studied.6 Recently, an inhibitor of the endoplasmic reticulum a-glucosidase, which prevents proper folding and transport of the hepadnavirus glycoproteins, has been reported to be successful in the woodchuck hepatitis model.7 Human studies are planned.

Ultimately, we may use a cocktail of antiviral drugs as is currently the norm in the treatment of HIV infection, with the hope of reducing resistance and improving response rates.

Treatment of Chronic Hepatitis C Infection

HCV infection is being called an epidemic which, while it has just been discovered, has been going on for a long time. Hepatitis C is the most common cause of infectious liver disease and of liver transplantation in adults. While therapy for hepatitis C is incomplete and still in its infancy, a therapy exists that cures some people which is unusual for a viral infection. While interferon's success rate is low, it creates a promise that the majority of hepatitis C cases will someday be treated and cured.

Alpha-interferon

Alpha interferon is the only licensed agent for HCV. Two forms have FDA approval, while several forms are in the process of becoming licensed. The standard dosage is 3 million units given three times a week by subcutaneous injection for 6 to 12 months. Interferon is a protein made by the immune system which acts to fight viral infections. For unknown reasons, hepatitis C does not stimulate the body to make interferon.

What does one hope to see while treating patients?

Sustained Response - A sustained response is defined as an improvement in a person's hepatitis after treatment. In this type of response, the ALT becomes normal and stays normal when treatment is stopped. 98% of the people with chronic HCV test positive by the PCR test. This test usually becomes negative within 6 - 12 weeks in people whose ALT eventually becomes normal during therapy and it remains negative in people with a sustained response. In a follow-up study of patients who had a sustained response, normal enzymes and a negative PCR remained for at least 10 years. Unfortunately, a sustained response is achieved in only 10-20% of people treated for six months with three million units of interferon three times a week. In over 50% of treated patients, the enzymes become normal and the PCR becomes negative at the end of therapy, but at least half relapse after treatment is stopped.

Nonresponders - Some patients are considered nonresponders. In these patients, the PCR test for HCV RNA remains positive and the liver enzymes fall slightly, if at all.

What is the difference between people who respond and those who don't?

Data suggests that the difference is in the virus, not the patient. Some strains are more resistant to interferon while other strains are very sensitive, disappearing immediately. In a meta-analysis - an examination of many studies which are then compared and summarized - 41-50% had a complete response during therapy while 22% had a sustained response. When interferon therapy was compared to no treatment, there was a chance of response with interferon, but without treatment patients don't spontaneously recover. A comparison of 6 months and 12 months of treatment from the meta-analysis showed that a higher sustained response rate occurs in patients treated for 12 months. Similarly, higher doses (5-6 million units three times a week) also seemed to result in better sustained responses.

How can we tell who will respond?

A response is more common in patients without cirrhosis, those who are young, and those who have had HCV infection for a short period of time. The strongest predictors of response are viral in nature: a low concentration of virus and genotypes other than genotype 1 are more often associated with a favorable response. However, these factors can't be used to decide whether to treat or not treat a patient because there are many exceptions. We can only use them to advise the patient of the chance of response. Ultimately, it is the patient who decides. From 3 to 7% of patients with genotype 1a and 1b respond to a six month course of interferon therapy compared to a 25 - 40% sustained response rate in patients with genotypes 2 and 3. Most Americans have 1a or 1b.

Interferon and Ribavirin

The use of interferon (IFN) monotherapy for chronic hepatitis C infection has been the subject of a great deal of research attention. However, even with the use of different types of interferon, different dosages, and different durations of treatment, sustained virological and biochemical responses were seen typically in less than a quarter of patients. These unsatisfactory long-term results with single-agent therapy led to the examination of combination therapy using ribavirin. Ribavirin, a guanosine analogue, had previously been shown to be ineffective in HCV infection when used as a solo agent, although a transient improvement in transaminases was often observed. In combination with interferon however, results are significantly better.

The first of the trials of combination therapy in the treatment of HCV infection was reported early in 1998. In a double-blind study, 50 naive patients (previously untreated with interferon) were treated with IFN a-2b 3 mu tiw plus placebo or ribavirin 1000 to 1200 mg orally, for 24 weeks. Follow-up was carried out at 24 weeks and 1 year posttreatment.

Of the 50 patients treated in this study, 33 had genotype 3a, which is quite rare in most of Canada. The sustained response in type 3a patients was 53% compared with only 13% in those with type 1b and 36% in those with type 1a. The side-effects observed were typical of IFN, with significant hemolytic anemia observed in the group receiving ribavirin. The anemia

is commonly seen with ribavirin treatment and responds well to dosage reduction, but close monitoring of these patients is required. This is especially true for patients with other conditions who could not tolerate significant anemia.

Two larger randomized trials, one from the United States and one from Europe, were recently published.These investigators compared IFN a-2b plus ribavirin, either for 24 or 48 weeks, with IFN a-2b plus placebo for 48 weeks (the American trial also had a 24-week IFN a-2b plus placebo arm). The American trial enrolled 912 naive patients, of whom 72% had genotype 1.9 In the European trial, with 832 patients, 59% had genotype 1, 36% genotype 2 or 3, and 6% had other genotypes.10 The primary outcome from the trials, virological response at end of treatment and 24 weeks later, is shown in Figure 1 (the American trial) and Figure 2 (the European trial).

More detailed analyses in these two large trials showed that in patients with genotype 1, sustained responses were much better after 48 weeks of combination treatment, than after 24 weeks of therapy (28% vs 16% in the American study, 31% vs 18% in the European study, which included genotypes 1,4,5, and 6 in a pooled analysis). However, for patients with genotype 2 or 3, there was no significant difference with the prolonged combination therapy compared with the shorter duration (66% vs 69% in one study, 64% and 64% in the other). This finding, along with similar results concerning viral load, raises the intriguing possibility that patients may be identified who do not require a full year of therapy in order to achieve good results.

Similar trials have been conducted to examine the use of combination therapy in chronic hepatitis C patients who have relapsed after previous successful interferon monotherapy. In one study, the response rate in the combination group was 42%, compared with a response rate in the IFN-only group of 3%.

The results of these large trials have now clearly established combination therapy, with IFN a-2b and ribavirin, as the standard of treatment for chronic hepatitis C. However, it remains to be determined as to whether the duration of treatment should be determined by the genotype of the virus.

Other Interferon Regimens

As the combination trials with IFN a-2b and ribavirin were being conducted, other investigators were working to clarify dosing regimens for IFN monotherapy. Although combination therapy is more effective than monotherapy, these trials offer some interesting information about the use of IFN.

Multiple interferon trials have shown that 1 year and 18 months of therapy with Intron® (interferon a-2b) is more effective in maintaining a long-term response than a 6 month course of treatment, but is less well tolerated. A recently published trial compared 6 months of lymphoblastoid IFN, a-n1 vs recombinant IFN a-2b in 1071 patients.12 At 48 weeks after treatment completion, the sustained ALT response was somewhat higher in the lymphoblastoid group (10.3% vs 6.5%) and 38/383 patients were HCV RNA negative in the lymphoblastoid group compared with 21/367 in the recombinant IFN group (p=0.04). Most of

the apparent benefit of the lymphoblastoid IFN was secondary to a 50% reduction in t posttreatment relapse. This finding remains unexplained.

Consensus interferon (CIFN), is a genetically engineered molecule designed to incorpora the most common amino acid structures of naturally occurring alpha-interferons. To reported the results of a randomized controlled trial of CIFN 3µg or 9µg tiw for 24 weeks 3 mu IFN a-2b in 704 chronic HCV patients.13 CIFN 9 µg was superior to the lower dose consensus interferon, but the results were virtually identical to that observed in the gro treated with recombinant IFN a-2b, with 20.3% normalizing ALT and 12.1% with a sustain negative HCV RNA. The side-effect profile was similar to that observed with oth interferons.

Another trial used CIFN in 337 patients who had either not responded to previous IF therapy or who had relapsed after treatment.14 The patients were treated with 15 µg CIFN for 48 weeks, a dose equivalent to 6 to 9 mu of standard IFN. The CIFN resulted in sustained ALT response in 17% (10/59) of previous non-responders, but a 52% (22/4 response in relapsers. The sustained HCV RNA response was 13% (9/69) in no responders but 58% (19/33) in relapsers. Whether these results reflect an intrinsic improv efficacy of CIFN itself or predominantly a response to higher dose and longer durati treatment, requires further assessment.

Investigation of a longer acting form of interferon, pegylated interferon, which only requir weekly injections, is underway. Because of its prolonged antiviral activity, it has the potent for enhanced efficacy and perhaps a reduction in the development of resistant virus.

Interferon and Thymosin a-1

Combination therapy using 26 weeks of thymosin a-1 and IFN a-2b showed improved en of-treatment results in the combination group compared with IFN treatment alone in a tr with 109 patients.15 The rate of normalization of ALT was 37% (13/35) in the combinati group vs 16.2% (6/37) in the IFN treated group and negative HCV RNA was observed 37% (13/35) and 19% (7/37) respectively. However, in this study relapsers were retreat and therefore the sustained response to treatment is not reported. The side-effect prof was similar in both groups.

Other Agents

There has been some interest in amantadine, an antiviral agent, sometimes used in t treatment of influenza A. Its exact mechanism of action is unknown, but in some viral mod it can interfere with viral uncoating or transcription. This year Smith reported the results her pilot study of amantadine 100 mg po bid for 6 months in 22 IFN nonresponders.16 Tw patients withdrew from the study because of side-effects. Of the remaining 20 patients, fo developed a sustained negative HCV RNA level and six normal transaminases. Howev two negative studies have also been reported, although only in abstract form. Th medication warrants further investigation, possibly in conjunction with IFN or other antivi agents.

As with hepatitis B, newer therapeutic agents such as ribozymes, antisense oligonucleotides and antigenic vaccines are potential agents. Protease and helicase inhibitors are being investigated as are dominant negative mutants but it will be several years before these agents are in clinical use. Research in HCV would be greatly expedited by an improved cell culture system for growing and manipulating the virus, or by an easier laboratory animal model such as we have in the woodchuck model of HBV infection. Currently, only chimpanzees can be infected with HCV, and they do not have the same high carrier rate observed in humans.

Treating Histologically Mild Chronic Hepatitis C:

Monotherapy, Combination Therapy, or Tincture of Time?

The recent National Institutes of Health Consensus Conference on hepatitis C solidified the justification for a selective approach to treatment. Nevertheless, the high profile of chronic hepatitis C has led to a sense of urgency about treating "all-comers" and thus has caused the variable natural history of this disease to be overlooked. The debate about whom to treat has failed to focus attention on the alternative approach of waiting for better emerging therapies for the subset of patients with histologically mild chronic hepatitis C. Practitioners should be more confident about postponing treatment in less symptomatic patients if liver biopsy specimens show no more than grade 1 necroinflammatory activity or stage 1 fibrosis. Patients with these lesions, in the absence of clinical signs of advancing disease, are much less likely than patients with higher grades or stages to progress to cirrhosis.

A "cure" for chronic hepatitis C remains elusive. End points of treatment depend on the achievement of sustained clearance of serum hepatitis C virus RNA, which is influenced, in turn, by the patient's viral replication and immune balance. Treatment of histologically mild chronic hepatitis C may ultimately mimic that of HIV infection.

Patients with chronic hepatitis C are burdened with both the fear of dying of this disease and the stigma of living with it. In the clinical setting, where physicians counsel patients with hepatitis C who are often beset with anxiety, we must keep the problem in perspective. Only 20% to 25% of the 3.5 to 4 million hepatitis C virus (HCV) RNA carriers in the United States develop cirrhosis. The risk is much lower in patients who are less symptomatic and have mild hepatitis without significant fibrosis on biopsy specimens. For this large cohort of patients, I urge clinicians to rely on prudent clinical reasoning and patience while awaiting the outcome of well-designed trials of emerging therapies.

New Therapeutic Developments

After a decade of disappointment with interferon-alpha therapy caused by frequent lack of response or relapse after this therapy is discontinued, specialists who treat patients with chronic hepatitis C have been encouraged in the past year by several pivotal developments. The first of these is the demonstration of the durability of HCV RNA clearance in patients (albeit less than 50%) who respond to 6 to 12 months of interferon-alpha monotherapy Second, the addition of a nucleoside analogue, ribavirin, to interferon-alpha has been shown to greatly improve the sustained virologic response rate in patients who have never been

treated and patients who have had relapse after a course of interferon monotherapy. Consensus interferon, a new synthetic type 1 interferon, is the only drug other than interferon-alpha that is approved by the U.S. Food and Drug Administration for the treatment of chronic hepatitis C, and it may be as helpful as interferon-alpha monotherapy for patients who have had relapse after a course of interferon .Results such as these account for a major change in our perception of the benefits of antiviral therapy for chronic hepatitis C.

The recent National Institutes of Health (NIH) Consensus Development Conference solidified an approach to the treatment of hepatitis C and gave us a road map with which to navigate the myriad therapeutic options for this disease. One key finding endorsed by the Conference Panel was the ability to predict, early in the course of therapy, which patients have a chance for a sustained response with prolonged treatment. Failure to clear viral load, as measured by sensitive HCV RNA assays within the first 12 weeks of treatment, indicates that sustained response is unlikely and that continuation of treatment is essentially futile. Others have chipped away at the 12-week decision point and have found that viral clearance as early as 4 weeks after the start of therapy may predict long-term response. Factors that have previously been associated with poor response to interferon, such as the presence of cirrhosis, high pretreatment viral burden, and genotype 1, were predictive only in certain therapeutic settings (standard interferon doses, 6-month treatment periods, or naive patients compared with patients who have had relapse or nonresponders) that reflect the circumstances in which the data were generated and may be less important as generic predictors, particularly if newer therapeutic approaches produce higher rates of sustained viral clearance. Prognostic factors may remain important but will require repeated reassessment in different patient groups receiving emerging therapies.

The Debate about Whom To Treat

It is often more appealing to treat a chronic disease, such as hepatitis C, with currently approved medication immediately after diagnosis than it is to wait for confirmation of potentially better therapies being evaluated in large clinical trials. The high public profile of hepatitis and the easy access we have to anecdotal information on the Internet adds to the sense of urgency about "doing something." Because of the breakneck pace of recent therapeutic advances, decision making has never been more in flux. In unscientific polls conducted at national meetings and in the practice community, it has been found that many of our colleagues are tempted to treat "all-comers" with an initial short course of interferon monotherapy in an attempt to eradicate HCV RNA, regardless of the presence or absence of predictive factors. Their argument is bolstered by the fact that such treatment may ultimately cut costs by distinguishing potential responders from nonresponders, allowing cessation of prolonged interferon therapy in the latter and reducing the incidence of interferon-associated side effects. Moreover, patients with mild hepatitis are more likely than those with more advanced histopathologic disease to respond to early treatment with viral clearance. A recent report of the use of decision modeling techniques in such patients showed an extension of life expectancy at reasonable cost. However, as Koff points out ,this report assumed that HCV RNA negativity at only 6 months of follow-up represents "cure" and restoration of life expectancy, which may not be the case. Further, the NIH Consensus Development Conference Panel report contradicts such decision-modeling logic; the Panel recognized that patients who have the greatest risk for progression to cirrhosis and most deserve treatment have evidence on biopsy of either portal or bridging fibrosis or moderate

degrees of inflammation and necrosis rather than mild hepatitis. The Panel recommends that decisions about treatment for mild hepatitis be made in consultation with each patient

The interest in the natural history of chronic hepatitis C and the importance of initial histopathologic findings was rekindled after more than 10 years of observation of some asymptomatic patients who were studied in 1970 .These patients had persistently elevated serum alanine aminotransferase (ALT) levels and subsequent HCV RNA positivity and negative findings on serologic tests for hepatitis B virus. Typical of such patients is a man, followed for 25 years, whose liver biopsy specimens at approximately 5-year intervals showed stable mild inflammation without significant fibrosis, or what is now considered grade 1-stage 1 disease. This new histologic classification of chronic hepatitis C based on grading (extent of necroinflammatory activity) and staging (extent of fibrosis) is widely accepted and provides insight that can aid in decision making. If patients do not have significant fibrosis ,the likelihood of progression to cirrhosis is remote. Predictions of stable disease can be made more confidently if the initial biopsy is done more than 10 years after onset of disease and shows no significant fibrosis—under these circumstances, subsequent fibrosis is unlikely to occur. The overall time to the appearance of cirrhosis (if it appears at all) in the absence of significant fibrosis on the initial biopsy specimen may be 20 to 50 years .For patients with grade 1 hepatitis and no unusual circumstances, one would wait for future therapies because of this condition's virtual lack of progression and the toxicity and relative lack of efficacy of the current therapy. If the first biopsy shows interface or lobular hepatitis (grade 2 disease), it may be more difficult to decide not to treat because few prospective studies have correlated clinical course with grade 2 disease. Clinical acumen may aid in decision making in such patients. If the patient has a palpable or firm liver (usually in the left lobe) or thump tenderness over the liver, a poor prognosis is more likely; if a liver biopsy specimen in that patient shows grade 2 disease, one is prone to strongly recommend therapy. Grade 3 and grade 4 hepatitis are most likely to progress to cirrhosis and should be treated in the absence of contraindications. Another reason to postpone therapy is the current difficulty in quantifying histologic improvement in treated patients with mild hepatitis. This measurement is rendered difficult because the principal criterion for meaningful improvement after therapy in most trials is a change of only two histologic activity points. However, histologic activity in biopsy specimens from these patients is in a narrow range of 0 to 4 points, leaving little room for measurable improvement. Interobserver error is also greatest when change is measured in scores of less than two points. This limitation is only important in grade 1 and grade 2 hepatitis without significant fibrosis, but it emphasizes the difficulty involved in interpreting histologic outcomes and highlights our need to rely solely on virologic markers in such patients.

The Patient with Persistently Normal Alanine Aminotransferase Levels

What do we do about the 25% of the population of HCV-infected patients who have detectable HCV RNA; persistently normal ALT levels; and, with few exceptions, minimal to mild hepatitis? Interferon monotherapy in these patients usually fails to produce sustained virologic clearance and may even be associated with an elevation in ALT levels that persists after treatment .Patients with persistently normal ALT levels have a slow rate of fibrosis progression; the expected median time to cirrhosis is 80 years.It has been postulated that nondrinking women younger than 40 years of age may be the "normal ALT" patients who are more responsive to interferon because heavy alcohol intake, usually in men, seems to

have a synergistic, deleterious effect on patients with this disease. The answer may come from an international study designed to determine the response rate in patients with repeatedly normal serum ALT levels who either receive no treatment or receive interferon for 12 months .Therapeutic experience is limited in patients with serum ALT levels less than 1.5 times the upper limit of normal because these patients have been excluded from most other clinical trials. For both of these cohorts that rarely progress to cirrhosis, I would delay monotherapy, except in the context of a formal clinical trial. In rare circumstances, treatment decisions can be made solely to eliminate viral infection per se, regardless of histologic findings (for example, to meet the desires of an active surgeon or a mother-to-be).

Future Therapeutic Options

New interferon regimens in the early 12-week induction period that have been or are being evaluated are higher-dose and daily dose therapy and, after induction, de-escalation and maintenance therapy. Consensus interferon reportedly causes greater reductions in HCV RNA levels in patients with higher pretreatment viral loads ,but this effect has yet to be confirmed. A variant mode of interferon delivery that has been touted to improve interferon's efficacy is pegylation using conjugated polyethylene glycol. Pegylation may augment the drug's duration of action by controlling the rate of absorption from the injection site, allowing less frequent injection (for example, only one injection per week). Because the NIH Consensus Development Conference Panel's recommendation to extend monotherapy from 6 to 12 months for early virologic responders will probably result in a more durable sustained virologic response and because the likelihood of gains from other permutations may be less than that from prolonged treatment, I have little enthusiasm for pursuing the other proposed regimens for mild hepatitis. To elucidate the possible deleterious role of increased hepatic iron levels (especially iron levels in portal tract cells on therapeutic response to interferon in chronic hepatitis C, iron reduction therapy plus interferon (compared with interferon alone) is being studied in two multicenter, randomized, controlled trials. Preliminary results from one of these important studies showed significant improvement in serum ALT levels but only a slight decrease in serum HCV RNA levels. Final results should be available soon. The limited success of vaccine strategiés has stimulated the search for adjunct therapies and antiviral medications that inhibit viral entry, replication, and assembly. Ribavirin has a synergistic effect with interferon; increases sustained virologic response two- to threefold; reduces relapse rates; and is being evaluated in controlled, randomized trials of therapy-naive patients. Another interesting approach is to correct deficiencies in the host immune response. Using interleukin-10,other cytokines, thymosin-alpha1, and nonsteroidal anti-inflammatory drugs for their immunomodulatory effects has been suggested.

Interfering with the function of serine protease by using combination therapy for HIV infection may provide an important model for the treatment of chronic hepatitis C. In many ways, HIV and HCV RNA are similar, although we do not know exactly how much of the experience with HIV therapy will eventually apply to HCV. Inhibition of serine protease, helicase, or RNA polymerase activity may be the most promising approach for antiviral treatment of HCV infection. The nonstructural 3/4A serine protease of HCV RNA is especially well characterized,It is required for viral replication and is the first molecular target for which new antiviral agents are being developed. A protease inhibitor would be likely to block both the establishment of viral infection and viral production in chronically infected

cells. Several candidate protease inhibitors are currently under intense preclinical study, and it would not be surprising if one or more of these prove to be clinically effective.

More speculative molecular strategies aim to block viral gene expression or function with antisense oligonucleotides and ribozymes (ribonucleic acid enzymes). Several of these interventions may eventually be both effective and well tolerated. Antisense nucleic acids for HCV RNA therapy could be designed to inhibit a specific RNA, resulting in the formation of RNA-DNA (antisense DNA) or RNA-RNA hybrids (antisense RNA) with an arrest of RNA replication or messenger translation. Ribozymes have been reported to eliminate HCV RNA in infected hepatocytes, and antisense drugs have reduced expression of HCV core protein in cell culture and have inhibited HCV-directed protein synthesis in hepatocytes

The Elusive "Cure" for Patients with Mild Histopathologic Findings

I believe that most patients with mild histopathologic findings and a concomitantly longer duration of disease (if that can be determined at the time of diagnosis) tend to have little progression. Delayed initiation of interferon monotherapy allows them to avoid the adverse effects and expense of therapy and the discouragement that can accompany treatment failure, which is frequent. For patients with borderline or mild grade 2 hepatitis and disconcerting clinical markers, as well as patients with more advanced histologic disease who do not respond to interferon, I support the NIH recommendation that they consider entering ongoing trials of combination therapy with ribavirin or other prospective antiviral agents and immunomodulators (with the caveat, of course, that the results of such trials could prove disappointing). On the basis of treatment experience with HCV, which resists eradication, the criteria for "cure" must certainly be extended beyond the usual 6-month definition of a sustained virologic response. Because HCV RNA has been found to recur even years after successful therapy, patients should ideally be followed and observed for at least one or two decades, although 2 to 5 years is more feasible in practice. "Cure" for chronic hepatitis C may prove to be elusive and, depending on the patient's viral replication and immune balance, treatment may ultimately mimic that for other chronic viral infections, such as herpes simplex, cytomegalovirus infection, and HIV infection.

Conclusions

We cannot yet confidently identify the patients most likely to benefit from interferon, but we do have tools for detecting nonresponse to this therapy (failure to clear HCV RNA early in the course of treatment) and nonprogression of disease (a liver biopsy specimen that shows no significant fibrosis). The lessons learned from therapy for HIV infection suggest that most patients may be successfully treated with combination therapy directed against HCV. For now, it is the informed patient, after discussion with his or her physician, who should decide on the timing and type of therapy. I will continue to advise a tincture of time for most of my patients with histologically mild chronic hepatitis C, both because I do not believe that their prognosis is as daunting as is often stated and because the outlook for new and more effective therapies is promising.

The above is an interesting set of observations by Dr Levine in a recent article in annals of internal medicine. In view of the great cost of treatment and lack of infrastructure facilities, there is need to formulate a policy guidelines for our patients as to who needs and who may not need treatment.

CHAPTER 7

RECENT CONCENSUS CONFERENCES

EASL (The European Association for the Study of Liver Disease) International Consensus Conference on Hepatitis C

Paris, 26-28 February 1999
Consensus Statement*
* This statement was drawn up by the Consensus Panel.

1. What are the Public Health Implications of Hepatitis C?

Hepatitis C is a major health problem. The global prevalence of chronic hepatitis C is estimated to average 3% (ranging from 0.1 to 5% in different countries): there are some 150 million chronic HCV carriers throughout the world, of whom an estimated 4 million are in the USA and 5 million in Western Europe. The prevalence seems to be higher in Eastern Europe than in Western Europe. In industrialized countries, HCV accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of hepatocellular carcinoma and 30% of liver transplants.

The incidence of new symptomatic infections has been estimated to be 13 cases/100000 persons annually. The actual incidence of new infections is obviously much higher (the majority of cases being asymptomatic). The incidence is declining for two reasons:

(a) Transmission by blood products has been reduced to near zero:
(b) Universal precautions have markedly reduced transmission in medical settings. Intravenous drug use remains the main mode of transmission; but, even here, the rate of transmission is diminishing due to a heightened awareness of the risk of needle sharing and, in some countries, the availability of needle-exchange, programs.

2. What is the Natural History of Hepatitis C? What are the Factors Influencing the Disease?

Hepatitis C is a disease with various rates of progression. In general, its course is slowly progressive. About 15% of HCV-infected individuals recover spontaneously; an additional 25% have an asymptomatic illness with persistently normal aminotransferases and generally benign histological lesions; hence, about 40% of patients recover or have a benign outcome. In those with biochemical evidence of chronic hepatitis, the majority have only mild to moderate necro-inflarnmatory lesions and minimal fibrosis:

Their long-term outcome is unknown and, probably, most of them will not succumb to the liver disease. About 20% of patients with chronic hepatitis C develop cirrhosis in 10-20 years, and may die of complications of cirrhosis in the absence of liver transplantation. Thus, hepatitis C is a dichotomous disease in which a subset of patients will die from liver-related causes, but in which the majority will probably live out their normal life span.

Several cofactors play an important role in the development of cirrhosis:

(a) The age at the time of infection, on average, patients who acquire the disease at an older age have a more rapidly progressing disease, while progression is slower in younger patients;
(b) Alcoholism (all studies show that alcohol is a very important co-factor in the progression of chronic hepatitis to cirrhosis);
(c) Co-infection with HIV;
(d) Co-infection with hepatitis B virus.

The incidence of hepatocellular carcinoma is 14% per year in patients with cirrhosis. This risk supports the necessity of regular monitoring by ultrasonography and measurement of alpha fetoprotein in patients with established or suspected cirrhosis. Development of hepatocellular carcinoma is rare in patients with chronic hepatitis C who do not have cirrhosis.

3. Diagnostic Tests

ELISA tests are easy to use and inexpensive, and are the best tests for initial screening. These tests are reliable in most immunocompetent patients who replicate HCV They are less sensitive in hemodialyzed and in immunocompromised patients.

In low-risk settings, such as blood banks and other general screening situations where approximately 25 of ELISA positive results may be false, a supplemental specificity test, such as a strip immunoblot assay, is recommended to avoid unwarranted notification of false positives. Then, a qualitative I-ICV RNA test should be performed if anti-HCV positivity is confirmed.

In high-risk populations and in clinical settings where hepatitis C is suspected, a positive ELISA should be confirmed by a qualitative HCV RNA test.

In patients with acute hepatitis of unknown cause, an ELISA test should be performed first. If hepatitis A and B tests are negative, then a qualitative HCV RNA test must be performed.

In ELISA-negative patients with chronic hepatitis of unknown cause, particularly in hemodialyzed and immunocompromised patients, a qualitative HCV RNA test should be performed.

Genotyping and quantitative HCV RNA tests are only recommended prior to the treatment of patients.

4. Who Should be Screened for Hepatitis C?

General screening is not advisable. Screening should be limited to risk groups:

(a) Persons who have (or might have) received blood products prior to initiation (1991) of second-generation ELISA test;
(b) Hemophiliacs;

(c) Hemodialyzed patients;
(d) Children born to mothers who have hepatitis C;
(e) Current or previous users of intravenous drugs;
(f) Donors for organ or tissue transplantation.

5. How Can the Transmission of Hepatitis C be Prevented?

The two main sources of Infection are intravenous drug use and administration of blood products. The latter source has almost completely disappeared since 1991.

Sexual transmission is very uncommon: the prevalence of HCV infection in stable partners of homosexual or heterosexual individuals infected with HCV is very low, but is higher in persons with multiple partners: The use of condoms in stable monogamous relationships is not justified; the use of condoms is strongly encouraged in patients with multiple partners.

Pregnancy is not contraindicated in HCV-infected women. Routine HCV screening is not recommended in pregnant women.

HCV vertical transmission is uncommon: the prevalence of transmission from mother to child is less than 6%. The risk of transmission appears to be greater in women with high levels of viremia or HIV co-infection. The mode of delivery (cesarean section/vaginal) does not appear to influence the rate of HCV transmission from mother to child.

There is no association between breast feeding and transmission of HCV infection from mother to child.

There are insufficient data concerning the risk of vertical transmission of in vitro fertilization in patients with hepatitis C to make recommendations at this time.

Nosocomial HCV infection is efficiently prevented by the observance of universal precautions.

6. Which Patients Should be Treated?

The decision to treat is a complex issue which must take into consideration numerous variables: age of the patients, general state of health, risk of cirrhosis, likelihood of response, and other medical conditions that may decrease life expectancy or contraindicate the use of interferon or ribavirin.

Does the decision to treat depend on the histologic lesions?

It is appropriate and important to obtain a percutaneous liver biopsy before beginning therapy. The liver biopsy provides an opportunity to grade the severity of necro-inflammation and to stage the progression of fibrosis, which may then be considered in relation to the supposed duration of the disease, clinical status and biochemical abnormalities to make therapeutic decisions. The biopsy also provides a baseline in individual patients. There is agreement that patients with moderate/severe necro-inflanimation and/or fibrosis should be treated.

Does the decision to treat depend on the age of the patient?

The physiological age of the patient is more important than the chronological age of the patient. Factors to be considered in older patients include overall health status with a special assessment of the cardiovascular system to determine the potential risk of a decrease in hemoglobin level if treatment with ribavirin is being considered.

Does the decision to treat depend on the clinical manifestations?

In the early stages, in the absence of advanced cirrhosis, there is a poor correlation between the clinical manifestations and the histological lesions of the disease. Overall, clinical status may affect the decision to treat with regard to quality of life. Studies have shown the abatement of symptoms in patients in whom treatment has induced sustained loss of HCV RNA.

Does the decision to treat depend on the level of viremia?

Only patients who have detectable serum HCV RNA are candidates for therapy It is widely recognized that patients who have higher levels of viremia (more than 2 million copies/ml) are relatively less likely to respond to therapy. However, the level of viremia should not be used as a reason to deny treatment.

Does the decision to treat depend on the genotype of the virus?

Although it is well-recognized that patients with genotype 1 respond to the treatment less well than patients with genotype 2 or 3, the genotype should not be used as a reason to deny treatment.

Should children be treated?

There are no large studies of the treatment of chronic hepatitis C in children. Available studies suggest that children have response rates to interferon monotherapy similar to adults. There are no data on combination therapy with interferon and ribavirin in children. The decision to treat a child must take into consideration the same factors as in adults. There may be additional factors that are unique to young children, in particular the effect of interferon on growth, which require further studies.

Should patients co-infected with HIV be treated?

Chronic hepatitis C is frequently found in HIV-infected subjects. It has been established that the progression of chronic hepatitis C is accelerated in co-infected patients. Treatment of hepatitis C may be indicated in those patients in whom treatment has stabilized the HIV infection. Consideration must be given to possible drug interactions and to additive blood abnormalities when treating these co-infected patients.

Should patients with compensated cirrhosis be treated?

Patients with compensated cirrhosis may be treated. Some potential benefits, such as the reduction in the development of hepatocellular carcinoma and decompensation, are not proven and should be assessed in future controlled studies.

Should patients with persistently normal aminotransferases be treated?

Patients who are HCV RNA positive and have persistently normal aminotransferase levels generally have mild disease and an uncertain response to therapy. At present, it is not recommended that these patients undergo therapy, but they should be followed up every 4-6 months or entered into clinical trials.

Should patients with HCV-related extrahepatic conditions be treated?

Consideration should be given to the treatment of HCV-related extrahepatic conditions, for example symptomatic cryoglobulinemia, glomerulonephritis or vasculitis. However, sustained remission is unlikely, and long-term maintenance therapy with interferon may be required. The efficacy of interferon and ribavirin combination therapy should be assessed.

Should patients with acute hepatitis C be treated?

Most experts are in favor of treating patients with acute hepatitis C. The timing and duration of the treatment have not been clearly established. Patients with acute hepatitis C should be informed of the 15% chance of spontaneous recovery, the 85% risk of chronic hepatitis C, and the side effects of therapy. Treatment decisions should be individualized and, ideally, patients should be entered into clinical trials. Combination therapy has not been evaluated.

Which patients should not be treated?

Given the relatively low efficacy and the side effects of the current treatment of hepatitis C, many patients with hepatitis C virus are not suitable candidates for therapy. In particular, patients with active heavy alcohol intake should not be treated because alcohol adversely increases viremia and interferes with the response to treatment. Active intravenous drug users should not be treated due to the risk of reinfection. In addition, compliance with treatment is poor in patients in whom alcoholism has not been interrupted and in whom drug addiction continues. It is potentially dangerous and there is no evidence that treatment is beneficial to patients with decompensated cirrhosis. The benefits of treating patients with histologically mild disease are uncertain, especially older patients, with co-morbid conditions.

7. What is the Optimal Treatment?

In naive patients, the combination of interferon and ribavirin should be offered to those without contraindications. The duration of therapy depends on the genotype and level of viremia. In patients with genotype 2 or 3, the duration is 6 months (regardless of the level of viremia). In patients with genotype 1, the current data suggest that 6 months is sufficient if

the level of viremia is low (less than 2 million copies/ml); 12 months of treatment is recommended if the level of viremia is high (more than 2 million copies/ml).

Preliminary data suggest that, with combination therapy, 5-10% of patients with detectable HCV RNA after 3 months of therapy may nevertheless clear HCV RNA after 6 months of treatment and develop a sustained response after treatment. There has been no consensus for recommending that therapy be discontinued if HCV RNA remains detectable after 3 months of treatment.

In naive patients in whom ribavirin is contraindicated, interferon monotherapy (3 MU or 9 pg thrice a week) should be administered for 12 months, with HCV RNA testing after 3 months of therapy. Therapy should be continued only in patients in whom HCV RNA has disappeared. It is not proven that an increased dosage of interferon, or daily administration, or high-dose induction increases the sustained response rate. Absolute contraindications to interferon are the following: present or past psychosis or severe depression; neutropenia and/or thrombocytopenia; organ transplantation except liver; symptomatic heart disease; decompensated cirrhosis; uncontrolled seizures. Relative contraindications to interferon are the following: uncontrolled diabetes; autoimmune disorders, especially thyroiditis.

Absolute contraindications to ribavirin are the following: end-stage renal failure; anemia; hemoglobinopathies; severe heart disease; pregnancy; no reliable method of contraception. Relative contraindications to ribavirin are the following: uncontrolled arterial hypertension; old age.

In patients who have relapsed after interferon mono-therapy-two options can be considered:

(a) Treat with a combination of interferon and ribavirin for 6 months if there are no contraindications to ribavirin;

(b) Treat with a high dose (more than 3 MU or 9 pg thrice a week) of interferon for 12 months. In both options, HCV RNA should be checked after 3 months and therapy should be discontinued if HCV RNA remains positive.

In patients who have failedto respond to interferon mono therapy or comhination therapy, there are no clear data to indicate that retreatment will be beneficial.

Liver transplantation is indicated in patients with life-threatening cirrhosis, and those with hepatocellular carcinoma on cirrhosis. Patients with cirrhosis should be considered for transplantation if they develop complications of their cirrhosis and have a life expectancy of 12 years without transplantation. This includes patients with recurrent or refractory ascites, Child-Pugh C cirrhosis, uncontrolled gastrointestinal bleeding after medical, endoscopical and TIPS (trans-jugular intrahepatic portacaval shunt) procedures, severe encephalopathy (spontaneous or after shunt), bacterial peritonitis.

Patients with hepatocellular carcinoma on cirrhosis can be considered for transplantation if there are less than 3 nodules of 3 cm and if there is no extrahepatic spread, including portal invasion.

After liver transplantation, HCV reinfection is almost constant. At 3 years, about 50% of the patients have a normal graft or mild lesions, 45% of the patients have chronic hepatitis and only 5% develop severe lesions. The 5-year rate of HCV-related cirrhosis on the graft is about 10%.

The 5 and 10 year patient survival rate in Europe is about 70% and 60%, respectively, which is comparable to that of patients transplanted for other non-malignant liver diseases. Patients should be informed of the risk of HCV recurrence and its potential consequences before transplantation.

THE CANADIAN CONSENSUS CONFERENCE ON THE MANAGEMENT OF VIRAL HEPATITIS (SEPT 1999)

INTRODUCTION

This report is the proceedings of a consensus conference on the management of viral hepatitis sponsored by the Canadian Association for Study of the Liver and Health Canada. This meeting was open to the public.Experts in various aspects of viral hepatitis were asked to present a review the medical literature on assigned topics.Three expert panels were convened, consisting of the speakers and other invited experts from the fields of hepatology, infectious disease, epidemiology, virology, medical microbiology and public health.The expert panels debated assigned topics, which corresponded to the reviews presented earlier.Audience participation was sought Attempts were made to reach consensus, on a number of recommendations about the management of viral hepatitis.A "rapporteur" group then synthesized the content of the literature reviews, and the debates and consensus statements into a preliminary document.This was presented to the audience, and additional comments sought to determine how well the document reflected the views expressed in the earlier discussions.The draft document was amended as necessary, and edited to produce this report.All participants were obliged to publicly declare any potential conflicts of interest.The report gives some background and offers recommendations aimed at both the general practitioner and the specialist in the text.The recommendations are summarized. Full text is available on request.

This report was written by a committee consisting of:-

Chairman - Eldon Shaffer, University of Calgary: Florence Wong, Susan King, Morris Sherman, University of Toronto; Fernando Alvarez, University of Montreal: William Depew, Queens University; Jutta Preiksaitis, University of Alberta.

SUMMARY OF RECOMMENDATIONS

Chronic Hepatitis B

Although acute hepatitis B continues to be an important clinical problem in Canada the majority of acute cases will resolve and clear HBsAg spontaneously.Chronic HBV infection, established when HBsAg is detectable for longer than 6 months with or without continuing liver enzyme abnormalities accounts for the greatest burden of disease.

Who should be tested?

Any patient with clinical or laboratory evidence for either acute or chronic liver disease should be considered as possibly infected with HBV.

HBV DNA Assays

It is important for the clinician to understand the type of assay methodology used, and its limitations, and that a consistent methodology be used for all assays..

HBV DNA testing should be limited to those patients being considered for treatment and to evaluate response to treatment.It is not indicated routinely in the evaluation of all HBsAg-positive patients.HBV DNA testing should be readily available to qualified practitioners regularly involved in the treatment of HBV.

Treatment of the Hepatitis B Carrier

In the HBeAg-positive patient with abnormal ALT levels liver biopsy is strongly recommended, but not mandatory.

Therapy may be with either interferon or lamivudine.Interferon is given at a dose of 27-35 mu weekly (5-6mu daily or 9-10 mu TIW) for 16 weeks.Lamivudine is given at a dose of 100 mg daily for 52 weeks. Lamivudine therapy for patients who are anti-HBe-positive and HBV DNA-positive is still considered experimental.The use of prednisone withdrawal prior to interferon therapy is contraindicated in the management of HBV-associated disease.There is insufficient information to recommend routine screening of immunosuppressed patients for HBV infection. There is also insufficient information to recommend lamivudine anti-viral prophylaxis for immunosuppressed patients who are known to be hepatitis B carriers.

Hepatitis D Virus

Patients with active hepatitis D should be treated in expert centres.

Decompensated Hepatitis B Cirrhosis

Low dose interferon is not recommended in decompensated hepatitis B cirrhosis.Patients with decompensated chronic hepatitis B should be referred to a liver transplant center, and treatment with lamivudine coordinated with the transplant center.

Glomerulonephritis

The indications for interferon therapy in patients with hepatitis B-induced membranproliferative glomerulonephritis are the same as for hepatitis B patients without glomerulonephritis. In membranous glomerulonephritis, the renal disease per se is an indication for interferon therapy. No recommendations for or against the use of lamivudine could be made.

Chronic Hepatitis B in Children

Optimal treatment is between 3-6 Mu/m2 interferon thrice weekly for 6 months.The indications for treatment are similar to those in adults.

Hepatitis C Virus

Patients who are anti-HCV-positive who have spontaneously developed negative HCV RNA by PCR should continue to be monitored at intervals for the presence of liver disease.

Factors that increase the risk of progression to cirrhosis include age over 40, consumption of even moderate amounts of alcohol, and increased age of acquisition of infection.

The risk of progression to cirrhosis also appears related to the degree of liver inflammation and fibrosis seen at the time of a biopsy.Patients with persistently normal ALT have a lower likelihood of progression to cirrhosis.

Use of HCV RNA testing

Qualitative HCV-RNA testing is not essential to make the diagnosis of hepatitis C in typical patients who are anti-HCV positive.

Quantitative HCV RNA testing is not routinely required for all patients.

Sexual transmission of the hepatitis C virus

HCV intra-spousal transmission appears to be rare in the absence of a parenteral risk in the partner.

The infected person should inform sexual partners.Testing should be offered to the sexual partner.Patients should be advised to avoid sharing items of personal hygiene.In short-term sexual relationships condom use is advised.Unprotected sex during menstruation should be avoided.Couples should be given information about the risks of transmission, and about precautions which may reduce the risk of transmission in stable monogamous relationships.The committee neither recommends nor recommends against the use of condoms.The choice belongs to the couple.

Mother-to-Infant Transmission of the Hepatitis C Virus

Rates of transmission of hepatitis C from mother to newborn infant vary between 0 and 3% according to different reports.

Breast feeding is considered safe and is not contraindicated

Testing for hepatitis C infection within the first 18 months of life should be by PCR assays.

Therapy for Chronic Hepatitis C

The prime indication for treatment in chronic hepatitis C is an ALT level more than 1.5 times the upper limit of normal on three consecutive occasions over more than three months.

A liver biopsy is recommended for grading and staging of the liver disease.

It is recommended that response to treatment be defined in virologic terms.

Successful treatment is indicated by clearance of hepatitis C virus RNA from serum (by sensitive PCR-based assays) 24 weeks after the completion of therapy (sustained response).

Dose and Duration of Treatment

The recommended treatment for chronic hepatitis C is with a combination of interferon alpha 2b and ribavirin. The dose of interferon is 3 mu TIW, and the dose of ribavirin is 1000 mg for patients weighing less that 75 kg. and 1200 mg daily for patients weighing more than 75 kg

Patients who carry genotypes 2 or 3 may be treated for 24 weeks.Patients carrying any other genotype should be treated for 48 weeks.

A positive HCV RNA assay after 24 weeks of therapy is an indication to stop treatment.

Interferon monotherapy should now be reserved for patients who cannot tolerate ribavirin

Contraindications to therapy

In assessing whether a patient is a good candidate for therapy with interferon and ribavirin, it is essential to consider the benefits and risks for that individual.

Absolute contraindications to therapy with interferon and ribavirin are decompensated liver disease, active alcohol abuse, pregnancy or lack of appropriate contraception and expected non-compliance.

Treatment Failures

Relapse after interferon monotherapy: - These patients should be offered treatment with interferon and ribavirin.

Non-responder to interferon monotherapy: -There is insufficient information to make a recommendation on the effectiveness of any of the therapeutic options for patients who were non-responders to interferon monotherapy.

Failure of combination therapy: - There are no proven treatment options for these patients at present

Hepatitis C Infection in Children

Chronic hepatitis C in children should not be treated except in controlled trials.

Acute hepatitis C

No recommendations can be made about the timing of therapy of acute hepatitis C

Healthcare workers or others subjected to needle-stick injury or equivalent exposure should be tested by anti-HCV at the time of the injury at 12 weeks to detect infection. Treatment should be with standard combination therapy of interferon and ribavirin for the standard duration despite the lack of prospective studies proving efficacy.Given the urgent need to gather data on such cases it is strongly recommended that patients with acute hepatitis C be treated in the setting of a clinical trial or a registry.

Combined Infections

In patients who are HBeAg-positive with detectable HBV DNA, undetectable HCV RNA and elevated aminotransferases, treatment is with interferon 27-36 mu weekly for 4 months.In patients who are HBeAg-positive with detectable HBV DNA undetectable HCV RNA and elevated aminotransferases, treatment is with interferon 27-36 mu weekly for 4 months.Chronic hepatitis B in HIV-infected patients must not be treated with lamivudine monotherapy. There are no recommendations about therapy in patients co-infected with hepatitis C and HIV.

Hepatitis Screening Patients with Chronic Hepatitis B and C for Hepatocellular Carcinoma

In the absence of documented benefit of mass screening, the committee makes no recommendations for or against screening for HCC in HBsAg-positive patients, nor for patients with chronic hepatitis C.Screening may be justified in high risk cases (presence of cirrhosis, long duration of infection, HBV/HCV co-infection, past curative resection for HCC family history of HCC [HBV only]).

Hepatitis B Vaccination

The vaccination strategy for Canada should be universal vaccination of all neonates, combined with screening of all pregnant women.Newborns of infected mothers should given hepatitis B immunoglobulin in addition to the vaccine.A catch up program should be instituted for all children and young adults who have not yet been vaccinated. There should be a standardized national policy, so that vaccination is assured for all children when their families move between provinces.

Serologic testing post-immunization is not recommended routinely

Hepatitis A Vaccination

Current recommendations by NACI with regard to populations in whom vaccination is appropriate remain pertinent.

Hepatitis G Virus

Routine screening of blood donors or wide spread testing for HGV is not recommended

Transfusion Transmitted Virus

No active attempt at diagnosing this infection is required.

Table-I: Initial investigation of the hepatitis B carrier

Tests of liver inflammation	AST ALT
Liver function tests	Bilirubin
	Prothrombin time/INR
	Albumin
Viral serology	HBeAg/anti-HBe
	Anti-HCV
Other important tests	BUN or creatinine
	CBC and differential

Table-II: Interpretation of hepatitis C virus RNA testing in anti-HCV-positive patients.

ALT Concentration	HCV RNA Result	Interpretation
Normal	Positive	Patient is infected. with undetectable liver disease
Normal	Negative	False-positive anti-HCV Spontaneous viral clearance False negative HCV RNA Dormant infection with no or minimal liver disease
Elevated	Positive	Infected with active liver disease,
Elevated	Negative	False-positive Spontaneous viral clearance False negative HCV RNA<O:P</O:P Dormant hepatitis C infection, but some other cause for liver disease

CHAPTER-8
THE QUESTIONS YOUR PATIENTS MIGHT HAVE

When a patient is informed by his doctor that he is suffering from chronic hepatitis, it usually is a nasty surprise. After the initial shock, most patients, even the uneducated ,would want to know more about the disease, the treatment and their prospects. Most people have heard about the disease and many have distorted notions about it. They are scared about even the "run of the mill" type of jaundice. It is the duty of the physcian to satisfy the curiosity and educate the victim. If the patient has an insight into his disease process, he or she is better able to cope with it.

We at Healthways have a patient education program. A number of books have been published to provide knowledge about common problems like diabetes and sterility in easy to understand language. A book for hepatitis patients in urdu is under process.

Some of the questions which the patients ask us when the collect their lab results are given below.

(1) What is Hepatitis?

Hepatitis is a viral illness that affects mainly the liver. There are many types. Some are conveyed through food and water. They are called A and E. B is transmitted through blood.In 1990 an antibody to the hepatitis C virus was identified but before that the illness was known as "non-A, non-B hepatitis".

(2) How great is the risk of hepatitis to me and my family?

Infection within the family can occur with hepatitis A, B, C or E. Prompt diagnosis and appropriate precautions with gamma globulin for hepatitis A, and with hepatitis B immune globulin (HBIG) and vaccination for hepatitis B are important for those who are exposed.

(3) My son has recovered from Hepatitis. Is he safe from hepatitis now?

Hepatitis is due to different viruses. One type does not confer immunity against the other.

(4) I have jaundice. What should I eat?

In the acute stage, appetite is poor. However small meals should be continued. A breakfast is usually tolerated better.

The food should be balanced and nutritious. No particular food is excluded.

(5) Should I remain in bed?

Again in the acute stage vigorous exercise is neither welcome nor advisable. However there is no need to be confined to bed especially after the acute stage is over. A good general rule is, "If you feel well, get up, but if you do not, take it easy."

(6) Doctor, Please put me on drip. I will recover sooner as it gives more "Taqa t."

There is no need to start a patient on IV drip if he can take nourishment by mouth.

(7) What is the difference between Acute and Chronic Hepatitis?

The term acute means that the virus has been present in the blood for less than six months. The term chronic means that a person has had the illness for more than six (6) months. If a patient has chronic HCV the virus will probably be with them throughout their life.

(8) I was told that I have hepatitis C or Kala Yarqan (Black Jaundice). But I have no Jaundice ?

Most patients with chronic hepatitis have no jaundice at least in early stages. The presence of jaundice is not necessary for diagnosis. Kala Yarqan perhaps refers to the serious nature of disease in popular perception.

(9) How does one get Hepatitis B or C?

Hepatitis B and C are spread by blood-to-blood contact. Therefore, anyway that one person's blood may be in contact with an infected person's blood will spread the virus .Some of the most common ways of spreading the virus are: transfusion of blood products, intravenous drug use, tattooing, body piercing, sharing razors. The risk of transmitting through transfusions of blood products decreases significantly if all blood donors are screened .

There are other ways they can spread in our country like after birth from infected mother. There may be other ways about which we do not know as yet.

(10) What are the symptoms of Hepatitis C?

Most people who have HCV do not know that they have the illness. Most are free of any symptoms. Interestingly, in many people the presence of the symptoms does not bear a direct relationship with the extent of the disease. In other words, someone with very mild HCV may have many of the symptoms, while another person who has much more advanced disease does not have any symptoms. It is very individual. Some of the more common symptoms of HCV include: extreme tiredness, itch, joint pain.

(11) How does one know if one has Hepatitis C?

Usually people with HCV are found because the liver enzymes in their blood are above normal limits, and their doctors do more blood tests to find the cause. Others are found

through testing positive while donating blood or because their doctor identified risk factors and requested the blood test.

(12) What are Liver Enzymes and what do they tell us?

Liver enzymes are proteins produced by the liver. Everyone has a low level in their blood but when the liver is injured in any way more liver enzymes are released into the blood stream. Elevated liver enzymes are a red flag to doctors to investigate the cause of this increase. The two most common liver enzymes that doctors check are the ALT(SGPT) and AST(SGOT).

(13) How can I prevent giving infection to someone else?

There is no need for anyone with HCV to be socially isolated. Because HCV is spread through blood-to-blood contact people with HCV should take some precautions. They include: - do not donate blood – let anyone who is contact with your blood know that you are HCV positive.
This includes dentists, blood technicians, nurses.
– Do not share razors or toothbrushes.

(14) What are the complications of hepatitis?

Fortunately, most people recover completely from hepatitis A, B, D, and E. Mild flare-ups may occur over a period of several months. Each flare-up is usually less severe than the initial attack and a relapse does not necessarily indicate that complete recovery will not take place. About. The mortality rate of hepatitis D and B is higher than for hepatitis B alone. Hepatitis E can cause serious illness in pregnant women. It however does not cause chronic disease About 5-10% of patients with hepatitis B and more than 80% of patients with hepatitis C develop chronic liver disease, which may be mild and slowly progressive, or may be serious and rapidly lead to cirrhosis. The terms "chronic persistent" and "chronic active" have been used for these two varieties, but we now know that the degree of activity varies with time and in different places in the liver at the same time. Cirrhosis is the final state of scarring which develops in chronic hepatitis. To determine how much scarring is present or how rapidly it may be progressing, a liver biopsy is usually necessary. Predicting who will develop chronic liver disease is not possible yet at the time of acute hepatitis.

(15) How can the spread of hepatitis be prevented?

Adequate sanitation and good personal hygiene will reduce the spread of hepatitis A and E. Water should be boiled prior to its use if any question of safety exists. Similarly, in areas where sanitation is questionable, food should be cooked well and fruits peeled. Washing hands with medicated soap, cleaning utensils, bedding and.clothing with soap and water is necessary for those involved in treating patients, especially in the first couple of weeks of illness.

To prevent spread of hepatitis B, avoid exposure to infectious blood or body fluids. Do not have intimate contact or share razors, scissors. nail files, toothbrushes or needles. If any risk is present, you should receive hepatitis B immune globulin and vaccine as soon as possible.

Blood banks must screen blood to insure the safety of the supply. Hepatitis B from transfusion can be largely prevented and hepatitis C greatly reduced, with prospects of even further reduction soon. Blood transfusion and injections are important modes of transmission in Pakistan. Always insist on disposible syringe for injection:There are unscrupulous people who recycle syringes. Pending some government regulation, satisfy your self that the syringe being used is safe.

Dentists, doctors, nurses, laboratory technicians, and others who may draw blood, perform surgical procedures or handle sharp instruments used on hepatitis patients or carriers must be informed so that adequate precautions can be taken. Family members and other intimate contacts must be advised to seek medical advice about immune globulin shots or vaccination.

(16) Are there vaccines and can the disease be prevented?

A vaccine for hepatitis A is currently available.

Two types of vaccine are available to prevent hepatitis B. The vaccine derived from yeast has replaced the plasma-derived vaccine in the U.S. Both are safe and effective and they seem to prevent infection if started within a few days of exposure. The normal vaccination schedule used in the United States is two injections, a month apart, followed by a third injection six months after the first one. Hepatitis B immune globulin may also prevent infection after exposure but it must be given within 48 hours to be useful.

Since both vaccination and immune globulin are expensive, rapid confirmation of the diagnosis of hepatitis B is needed. Hepatitis D is prevented by preventing hepatitis B. No vaccine or immune globulin is yet available for hepatitis C or E.

(17) Does hepatitis cause cancer?

A high incidence of liver cancer is found in some African and Asian countries where there are many hepatitis B carriers and appears to be related to the chronic hepatitis B carrier state. Research on this relationship is being pursued. The number of cases of liver cancer in patients with chronic hepatitis C is increasing, but whether the cancer rate will ever be as high as with hepatitis B is unknown.

(18) Should my family be tested for Hepatitis C?

The likelihood is small that HCV was spread to a family member. Treatment is not generally used for children with HCV. Testing may ease a person's concern if family members are tested.

Am I going to die if I have Hepatitis C?

Many people who have HCV may have a normal life span. However, there is still much information to be learned about HCV. In approximately 10% of people with chronic HCV, or, 10 people in 100 with HCV, their disease will gradually progress over 10 to 30 years to develop scarring, or cirrhosis of the liver. In a small number of these people HCV can lead to cancer of the liver and/or death.

(20) What should I eat if I have Hepatitis C?

People diagnosed with HCV can eat anything they want. The only recommendation is that they eat nutritiously. Avoidance of drinking alcohol in any form is recommended because studies have shown that the hepatitis C virus infection progresses more rapidly in people who drink alcohol. Some doctors believe that having no alcohol may stop HCV from progressing at all.

(21) Is there a treatment for HepatitisC?

Treatment for HCV varies depending upon the extent of a person's disease. Sometimes lifestyle changes such as stopping drinking alcohol is sufficient. For some people with more active disease doctors may recommend a treatment with alpha interferon alone or a combination of alpha interferon and Ribavirin.

(22) Can I give Hepatitis C to my wife?

Because hepatitis C is spread through blood the likelihood of spreading it to your wife is low..

(23) How HCV is not Transmitted ?

1. The Hepatitis C virus is NOT airborne.
2. It is NOT spread by:
   a. Sneezing and coughing
   b. Holding hands
   c. Kissing
   d. Using the same bathroom
   e. Eating food prepared by someone with HCV
   f. Holding a child in your arms
   g. Swimming in the same pool

(24) Can my wife give hepatitis to our child when she is pregnant or by breast feeding?

It is very unlikely that pregnant women with HCV can transmit the virus to their baby either in the womb or at childbirth. At the present time it is not known whether HCV can be spread from a mother to her baby through breast milk. However, the likelihood is very small and some liver specialists recommend that mothers if they want, breast feed their babies.

(25) Can I get vaccine for Hepatitis C?

Presently there is no vaccine for HCV. Recent studies show that people with HVC become much sicker and their liver becomes much more damaged if they develop another form of viral hepatitis. Doctors are now recommending that people with HCV receive the hepatitis A and/or the hepatitis B vaccine(s) if they have not been exposed to one, the other or both. That means if a person with HCV is immune to hepatitis B but not to hepatitis A then he/she should get the hepatitis A vaccine. If they are not immune to either than they should receive both the hepatitis A and B vaccine. There is a combination hepatitis A and B vaccine available. Checking for immunity involves a simple blood test.

CHAPTER-9

WHAT DO YOU TELL THE PATIENT AND HOW

A good physician must explain to his patient the nature of his illness and various options for treatment.. A sympathetic doctor who can explain the nature of the illness can be of immense relief required for a disease like chronic hepatitis. An added dilemma is that most of the patients in our country can not afford the treatment. The diagnosis is perceived as harbinger of financial ruin.

Problem

Counselling patients with hepatitis B or C viral infections is often the most difficult aspect of patient management for a number of reasons. Firstly, the natural history of these disorders remains unclear, particularly with respect to what percent and which patients will progress to cirrhosis and/or hepatocellular carcinoma. Secondly, patients often appear with preconceived notions of their ultimate course based on lay press, radio, and television accounts of the disease. Thirdly, many patients will have been seen by family practitioners who often counsel patients based on their recollection of viral hepatitis as it was understood during their medical school years, concepts that may not have withstood the test of time. Fourthly, the patient's level of anxiety often impairs or even precludes their ability to understand and retain much of what has been said. Finally, in a busy practice, time is a precious commodity, one that is often deemed lacking when counselling is required.

Approach

Despite the above limitations, important, useful, and relevant information can be transmitted to most patients within the final three to five minutes of the patient visit. For consistency, it is suggested that the following four aspects of the problem be discussed: 1) the disease itself, 2) impact of the disease on the patient, 3) transmission, and 4) family issues.

Table 1

Patient Counselling Topics
Disease itself
Prevalence
Natural history
Treatment

Impact of Disease on Patient's daily activities
Exercise/rest
Food
Alcohol
Further investigations

and that immunoprophylaxis given at birth is at least 95% effective in preventing postnatal transmission. As a result, breast feeding and other intimate contact between mother and child should be encouraged where appropriate. Female HCV carriers have an even lower risk of maternal-infant transmission (< 5%) and those infants who are infected may not develop chronic liver disease as frequently as do adults although only preliminary data exist on this particular issue. Details regarding testing of the newborn for HBV and HCV infection can be delayed to subsequent appointments when the carrier is either pregnant or planning a pregnancy. Finally, both HBV and HCV carriers should be told not to donate blood.

CHAPTER-10

HEPATITIS AND THE PHYSICIAN

Hepatitis is a subject that can provoke fear and uncertainty amongst physicians. The subject of occupational risk and exposure, treatment options, and the hepatitis risk to patients from physicians is addressed here.

Occupational Risk to Physicians

Perhaps of most immediate concern to physicians is their personal risk of contracting hepatitis from their patients. Even the presence of jaundice in a patient can induce peculiar aversive behaviour from health care personnel and the general public.

Hepatitis A is often not diagnosed specifically since many cases will be anicteric. Fortunately, by the time clinical symptoms appear, viral shedding in the stool will be at a low level. Proper hygiene, particularly in clinical practices will reduce but not eliminate the risk of contracting hepatitis A in the office. Physicians in this setting should consider vaccination for hepatitis A. Prior testing to determine previous exposure and immunity would be appropriate prior to vaccination. Fortunately we in Pakistan should rarely need it as most adults are immune. If doubtful get it tested.

Hepatitis B is a more serious and potentially sinister infection to obtain from a patient. Random testing at an American medical convention showed that 18.5% of 1192 physicians had been exposed to hepatitis B, and in surgeons, the prevalence was 28%. Despite widespread publicity about the safety of recombinant vaccinations for hepatitis B, many physicians have not been immunized.

In Pakistan the situation as usual is very unsatisfactory. In a short study from Karachi , it was found that out of 23 persons working in operation theatre , only one knew about his immune status. Only2 out of 15 doctors were vaccinated . There was only vague realization of the risks posed to health care personnel by HBV.The peril of ignoring the transmission of infectious agents through blood in the OT and other places has been often seen with tragic results sometimes.

Current recommendations following a needlestick injury involving an HbsAg positive patient in an unvaccinated physician include testing for anti-HBs and HbsAg and the administration of vaccination and hepatitis B immune globulin .These measures reduce, rather than eliminate, the risk of hepatitis B. For a physician considering hepatitis B vaccination, pre-vaccination testing with anti-HBs may be appropriate to assess pre-existing immunity but there is no reason to test for HbsAg.

Table 1

Risk and Management of Needlestick Injuries

Hepatitis Virus	Risk of Hepatitis	Treatment
Hepatitis B	30%	Vaccination + Hep B immune globulin
Hepatitis C	3%	HCV-RNA testing and interferon if positive

The risk of developing chronic hepatitis C is much less than for hepatitis B because of a lower concentration of virus in the blood. Guidelines for the treatment of needlestick injuries from hepatitis C patients are evolving. Measurement of HCV-RNA at two and four weeks, and a full course of interferon therapy if test results are positive, is one approach that has been suggested rather than validated. Another approach is to test anti-HCV immediately and at six months. There is little value in immunoglobulin administration since this product is prepared from patients pre-screened for hepatitis C and the antibody is not known to be neutralizing. A vaccine has yet to be developed for HCV.

Physicians that develop chronic viral hepatitis (B or C) with significant liver disease from this type of exposure face daunting prospects, including problems obtaining life and disability insurance, loss of income, long term disability and death. Most employed physicians qualify for worker's compensation programs but this may not be true for an independent practitioner.

Table 2

Strategies to Reduce the Risk of Transmission of Hepatitis From Physician to Patient

Vaccination of physicians

Universal precautions

Surgical gloves

Anti-viral therapy for infected physicians

Counselling about risk reduction of Transmission From Physician to Patient Risk

Two developments have led to the more widespread publication of cases of transmission from health care worker to patients; the concern about the lethal transmission of HIV, and the ability of molecular genotyping and sequencing to match viral strains between patient and physician. This 'fingerprinting' has led to the detailed descriptions of the transmission of both hepatitis B and C from surgeons to patientsPresently, surgeons in some countries like the United Kingdom are allowed to continue to operate if they are HbsAg positive but HbeAg negative. This may be reviewed in light of the recent report of transmission from surgeons that were HbeAg negative.

CHAPTER-11
VIRAL HEPATITIS IN PAKISTAN

Viral Hepatitis is a major health problem in Pakistan. It is also one of the comparatively better-studied diseases in our country. A number of research projects were undertaken in the last three decades to document the clinical and epidemiological aspects.

The present author (Gen Manzoor Ahmad) contributed about the clinical, biochemical and serological profile of acute viral hepatitis, cirrhosis, hepatitis B antigenemia ,the morphological profile and role of antigen negative and positive cases in the epidemiology of liver disease.and possible relationship of malaria and hepatitis. A significant series of studies focussed on anicteric and asymptomatic liver disease. It was shown that there was a large reservoir of asymptomatic liver disease in apparently healthy individuals that could play an important role in the epidemiology of acute and chronic hepatitis, cirrhosis and carcinoma. A large portion of this reservoir was attributed to HBV (and now also HCV).

It was also pointed out that Hepatitis NonA Non B as seen in our patients was different from that seen in the West. Later on sporadic NANB in our patients was shown to be due to HEV. A significant proportion had prior HBV exposure. A number of studies were about large out breaks due to HEV were also undertaken..

The PMRC center in Karachi extensively studied liver disease including viral Hepatitis. Another set of studies of significance emerged from uniformed University of USA in collaboration with AMC.

Some of the recent literature available from accredited journals about situation in Pakistan is summarized as under.

Hepatitis Viruses Exposure in Children

In a study on healthy children (1994), it was found that by age 5, 94% had antibodies against HVA while B and C were low, 2.97 and 0.44 respectively.

Prevalence of HBV

Pakistan lies in the medium range incidence countries. The prevalence rate of antigenemia was considered to be 10-14 percent. However currently it is thought to be about 7-8%. The antibodies against HBs and HBc are reported to be17 and upto 50% indicating widespread exposure and prevalence.

HCV

While population based studies are awaited, there is very high incidence reported in the high-risk groups such as haemodialysis patients (62% in a Lahore study) and Thalassaemics.

Delta Virus

Variable figures have been reported from different parts of Pakistan ranging from 3.1% in Rawalpindi 16% Lahore 27% Multan and as high as 50% in Fulminant Hepatitis cases from Karachi. More studies are needed to determine if they represent real differences. It will also be fruitful to find out if it plays any role in Fulminant cases.

Serology of AVH

In a 1994 report on acute hepatitis cases in a Lahore Hospital serodiagnosis was done in 93 patients admitted with acute viral hepatitis (AVH). Five (5.4%) had hepatitis A, 39 (41.9%) hepatitis B (2 of these were anti delta positive), 44 (47.3%) probable hepatitis E and 3(3.2%) had HAV/HBV co-infection. Antibody to hepatitis C (anti HCV) was detected in 6 patients (6.4%); 2 with HBV and 4 with probable HEV infection. Excluding 39 patients with hepatitis B and 3 with HBV as part of co-infection, there was evidence of previous HBV infection in 39 out of the remaining 51 patients. In the subset of 6 children, 3 had hepatitis A and 3 hepatitis E. Of these, 5 had evidence of previous exposure to HBV and one was also positive for anti HCV. The results were suggestive of a strong background of HBV infection raising concern about its chronic sequelae in the community

HEV Hepatitis

An outbreak due to HEV due to faulty water treatment plant in Islamabad was reported in 1997. It involved over 36000 people. The AR among the 162 recorded pregnant females was 21.6%, which was higher than that found among nonpregnant females of childbearing age (10.9%). All four reported adult deaths occurred among females in their third trimester of pregnancy with a case fatality rate of 11.4%, while the other four fatal cases were newborn infants of mothers with acute icteric hepatitis.

In another out break IgG was found in all. IgG anti-HEV appeared to be protective in contracts of patients. This study confirmed HEV as the cause of the outbreak, quantified IgM and IgG anti-HEV responses, provided evidence that IgG anti-HEV protects against hepatitis E, and demonstrated that IgG anti-HEV persists, but at diminished titer, after infection. Hepatitis E in young adults is the result of primary infection with HEV and, if reinfection occurs, it does not commonly cause serious illness.

In a yet another study it was reported that HEV was etiologically associated with the epidemic and was predominantly excreted at very low levels during the first week of jaundice.

Hepatitis Viruses in Blood Donors

The prevalence of blood borne viruses was reported in blood donors from Sindh and Karachi in 1996. The prevalence of HBsAg was found to be 2.28% (1,173/51,257), anti HCV was 1.18%(198/16,705) and that of anti HIV to be 0.02% (10/51,257). Higher rate of prevalence of HBsAg and anti HCV was observed in the younger age group of 21 to 30 years. Male to female ratio for HBsAg was 2.5:1 and for anti HCV 1:1. Seropositivity for HBsAg was significantly greater than anti HCV ($p < 0.0001$). No clear relationship was found

between high ALT (>55 U/l) and anti HCV positivity. Further examination of seropositive samples for HIV revealed only one donor to be positive by Western blot also.

Hepatitis Viruses in Chronic Liver Disease

The role of HBV and C in CLD and HCC is shown by a Karachi study (1997). Of 54 sera of Hepatocellular carcinoma(HCC) tested for HBV and HCV infections, 67% showed HBV infection, and 33% HCV infection. Among them 24% were positive for both HBV and HCV infections. No HBV and HCV infection was found in 24% cases of HCC. The findings suggested viral association for most of the HCC cases reported in the country.

The spread of HVC apparently due to therapeutic injections was reported from Hafizabad (1997). Twenty persons (6.5%) had anti-HCV antibody; 31% percent had hepatitis B core antibodies, and 4.3% had hepatitis B surface antigen. In the case-control study, persons who received more therapeutic injections (categorized as averaging 1, 2-4, 5-9 or > 10 injections per year in the previous 10 years) were more likely to be infected with HCV (odds ratio 0, 1.5, 2.5 and 6.9 respectively, P = 0.008) compared to persons averaging 0 injections per year. Efforts to limit therapeutic injections to only those that are medically indicated and that use sterile equipment are essential in order to prevent transmission of HCV.

The association of HCC with hepatitis viruses has been reported in a number of studies. HBV antigen was reported to be 60% when radio- immunoassay was used; 41% of cases were anti-delta positive (EIA).

105 sequential patients with biopsy-proven CLD (n = 82) and HCC (n = 23) were tested for HBV and HCV markers. Of the 105, 87 (83%) had evidence of hepatitis B exposure, 58 (55%) were positive for hepatitis B surface antigen (HBsAg), 23 (22%) had hepatitis C antibodies and 25 (24%) had detectable HCV RNA. Significantly more patients with HCC had evidence of HBV exposure in the absence of HCV markers (49/82 vs. 20/23, odds ratio 4.49, 95% CI 1.17-25.16). The proportion of patients positive for HBsAg with no HCV markers was also significantly higher in the HCC group (34/82 vs. 18/23, odds ratio 5.08, 95% CI 1.59-18.96). Another study found that; half of the patients with HCC have serological evidence of HCV infection.

HCV Genotype in Pakistan

Genotype HCV is important in evolution of the disease. Type 3 is the most common isolate in HCV-associated chronic liver disease. This was reported from University of Liverpool in 1996 on cases from Rawalpindi area. This was confirmed by another study reported from Karachi (1997). A Japanese study however reported that nucleotide sequences from these viruses showed significant homology with the Japanese HCV-TR isolate (91.7%-97.9%) and low homology with other Japanese, American, and UK isolates including HCV-1, HC-J4, HC-J6,

Other Data

A large body of unpublished or publication in non accredited journals is also availalble.4.78% of healthy donors were found to be C positive in an armed forces study.In

Karachi 6.6% positivity was found. It was also reported that household contacts, not necessarily spouses, were likely to be positive.

Those on hemodialysis have a very high risk.,46% (karachi) to 62.2 % (Lahore).

The risk factors for HCV infection in a number of studies in Pakistan have been as follows

Blood Transfusion
Parenteral Injections
Household contact
In a little less than one half, no cause could be found.

The comparative role of HBV and HCV in causing chronic liver disease and Hepatocellular carcinoma is not fully worked out. While in one study it appeared that HBV had a more pronounced role, another found HCV to be more responsible.

Summary of Hepatitis Profile in Pakistan

To summarise it has been established that Hepatitis A, mainly asymptomatic, was common during childhood. The adults usually developed immunity. HB virus was fairly common, about 10 percent. It causes considerable Chronic liver disease. HEV is mainly responsible for outbreaks as well as most sporadic cases in adults. It is especially of concern in pregnant females. Hepatitis C virus has come into prominence in recent years and is causing considerable anxiety. Blood transfusions and parenteral injections appear to be significant known factors.

CHAPTER-12

VIRAL HEPATITIS- EXPERIENCE AT HEALTHWAYS

Viral hepatitis is widespread in our country including the Rawalpindi Islamabad region. Unfortunately hard data, with few exceptions, is not available. An excellent study of outbreak of Hepatitis E in Islamabad was published recently. However there are not many attempts at documenting the problem systematically in recent years.

Although it is generally known that water borne types like A and E are the commonest, it is B and C which cause concern because of their potential to cause chronic liver disease. There are excellent institutions and interested and committed researchers in our area. It is hoped that they will restart the research in these serious problems. They will be reviving the tradition of contributing important knowledge about liver disease for which the institutions in this region are known.

Healthways being the largest referral center for lab investigations, a significant amount of data has emerged over the last two years. It would be useful to present it in order that the regional picture is highlighted. It is probable that many of our colleagues would have more extensive information. It will be important that it is published or otherwise brought to the attention of health professionals in our area.

Table I

Serological Markers in Viral Hepatitis Jan- Jun 1999

	Number Tested	Number Positive	Percentage
Hepatitis A Virus(HAV)			
AntiHAV(IgG)	4	3	–
Anti HAV(IgM)	1	1	–
Hepatitis B Virus (HBV)			
Anti HBs	730	74	10
AntiHBc	3		
Anti HBc IgM	2		
Hepatitis B e antigen			
Anti Hbe			
Hepatitis C Virus			
Anti HCV (Elisa)	435	174	40
Hcv Qualitative (PCR) 8			
HCV Quantitative(PCR)	12	9	–
Hepatitis D Virus			
AntiHDV IgG	2	0	–
AntiHDV Ig			
Hepatitis E Virus			
Anti HEV	2	1	–

Our data has obvious limitations because of selection bias. However inspite of this, it does convey some very useful local information.

There is marked increase in the utilization of different markers by physicians for better characterization of their hepatitis cases. This is evident if one compares our previous report (published in Hepatitis Update in 1997) with the present one. It is encouraging to make a note of this trend as it reflects better care of the patients.

It should however be noted that most still use Hepatitis B surface antigen for diagnosis of Hepatitis B . This could lead to erroneous results. There is high carrier rate in our country. These carriers ,though HBV+ ,

Table II

Liver Biopsy HCV cases Jan- Jun 1999	32
Chronic Hepatitis	12
Cirrhosis	8
Reactive Changes	8
Inconclusive Biopsy	4

could be suffering from more common HEV. On the other hand, a Hepatitis B case may have cleared the virus and become B negative. The presence of AntiHBc IgM would more accurately reflect the diagnosis.

Hepatitis B infection is very common as shown by the high positivity rate. The proportion is much less than reported earlier. The lower percentage may be due to greater number. However it is a general feeling amongst many people that the level of HBs positivity is declining and that of hepatitis C is increasing.There is need to further characterize these cases. One can not answer this question unless there is hard data available.

Most of these patients were suffering from acute hepatitis. Whether they cleared the virus or not is known. We also don't know how they acquired the virus.

The positivity rate for HCV is even higher. Most of these patients were tested because of vague abdominal complaints, weakness or their transaminases were raised The rise in trasaminases was only modest, many times only twice the normal level or even less. This underlines the fact that a simple test like transaminase may uncover serious underlying disease.

The increasing seriousness of HCV infection has also to be noted. The epidemiology of this virus needs to be worked out for our population without further loss of time.

The seriousness of HCV is further pointed out by the liver biopsy results. More than half of those who were discovered to be infected, showed chronic hepatitis. 25 % had developed Cirrhosis. For the vast majority of patients, these results were unexpected. In view of the extremely costly and uncertain treatment, it put their life and future in jeopardy.

About a quarter of cases showed only mild histological changes. The management of such cases also poses a dilemma. A pertinent discussion about this problem is given in an article in chapter on management

Summary

Hepatitis, both acute and chronic, is a serious problem in Rawalpindi Islamabad area. The waterborne types are extremely common as indicated by frequency of liver function tests performed. This is not surprising in view of abysmal water supply and sanitation situation.

Hepatitis B and more so C are a potent threat because of their propensity to develop chronic hepatitis and cirrhosis.

On slightly brighter side, there is increasing awareness amongst doctors in the area to investigate and rationally treat the hepatic disorders in general and hepatitis in particular.

There is urgent need for interested physicians to revive serious work in these problems without further delay.

CHAPTER-13
INVESTIGATION RESOURCES AVAILABLE AT HEALTHWAYS

The investigation resources available at Healthways for Hepatitis and liver disease cover a wide spectrum. The vast majority are carried out at inhouse faciiities. Arrangements, however, are available to utilize the expertise of referal institutions within the country and abroad for some of the more specialized tests.

It is obvious that the choice of tests will be dictated by clinical requirements. In that context it is important that careful history and a thorough clinical examination are of paramount importance. If this basic requirement is missed, the investigations, however elaborate, are unlikely to lead to correct answers. It is also important that only the appropriate tests are advised. The tests must always be interpreted in the light of clinical condition. If there is any question about the tests or their interpretation, our pathologists are always available for any assistance in this regard.

Some common tests for investigation of jaundice and other hepatic disorders cases are being listed here. The complete range is given in the directory of tests. If in addition any other procedure is required, please get in touch with the Pathologists. The tests have been divided into to various groups to facilitate selection.

Group1

General Tests

This group includes those which establish the diagnosis of jaundice or hepatic dysfunction and its possible type. It is well known that presence of jaundice does not necessarily mean hepatic disease(Haemolytic jaundice)nor its absence precludes lack of hepatic involvement(Anicteric Hepatitis).

Serum bilirubin –Direct / Indirect
Serum Alanine transaminase
Serum Aspartate transaminase
Serum Alkaline phosphatase
Urine Bile salts/pigment
Urine urobilinogen/urobilin
Blood complete picture
Reticulocyte count

Group2

These tests provide information about the extent of damage
Serum urea
Albumin/total proteins
Prothrombin time

Group 3

The type of Hepatitis/ recent/old infection/other information

Hepatitis A Virus Antibody IgM/IgG
Hepatitis B Core Antibody IgM
Hepatitis B Core Antibody (IgG)
Hepatitis Delta Antibody
Hepatitis B Surface Antibody
Hepatitis B Surface Antigen
Hepatitis Be Antibody (HBeAb)
Hepatitis Be Antigen (HBeAg)
Hep. B Profile (incl. HBsAg, HBsAb,
HbcAb, IgG, IgG, Igm, HbeAg & HbeAb)
Hep. Profile (HbsAg, HBsAb, HBcAb
(IgG, IgM), HbeAg, HBeAb, HAVAB-M).
HBDAB, HCV, HEV) Hepatitis A Virus Antibody
Hepatitis B Virus DNA
Hepatitis C Virus (Antibody)
Hepatitis C Virus RNA PCR Qualitative
Hepatitis C Virus RNA PCR Quantitative
Hepatitis E Virus

Group 4

Chronic Hepatitis/Cirrhosis
Transaminases
Gamma GT
Liver Biopsy

Group 5

Tests for Haemolytic jaundice

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The material for this monograph was collected from a number of resources. A few of Pakistani references are given below. In addition other papers and website material has also been extensively used. We are grateful to the authors.

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Division of Digestive and Liver Diseases
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cdc.gov/nicdd/diseases/hepatitis
hepatitis central.com
hepnet.com
American Liver Foundation
American Society of Gastroenterology

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The Cover: The cove shows histological changes seen in a case of chronic hepatitis C. There is extensive hepatic involvement with development of cirrhosis.

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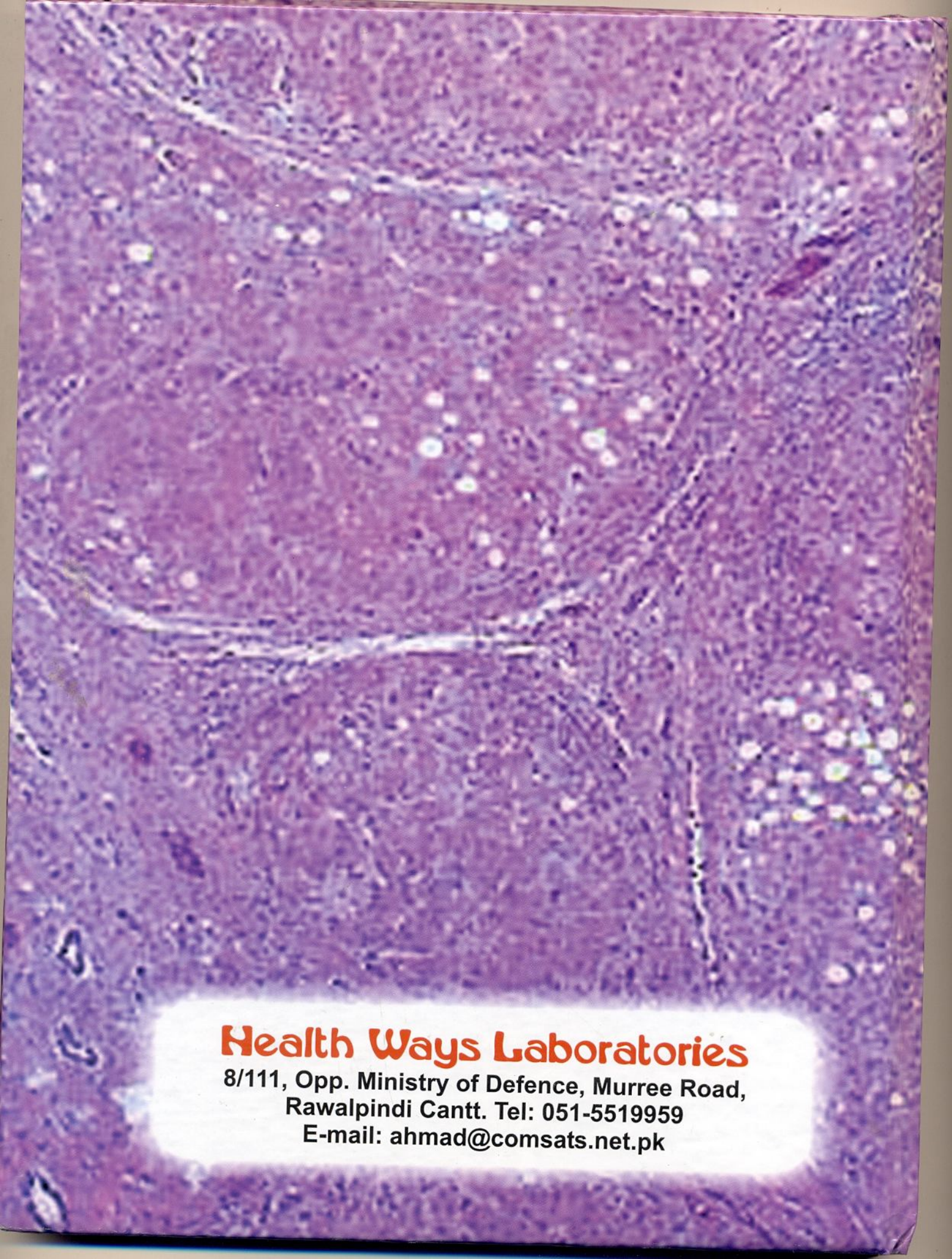

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