*In the name of Allah,*
*The Compassionate, The Merciful*

# 2nd Tehran Hepatitis Congress

The 2nd Tehran Hepatitis Congress (THC-2)

October 7-9, 2009
Tehran, I.R. Iran

Baqiyatallah Research Center for
Gostroenterology and Liver Disease

# The 2nd Tehran Hepatitis Congress (THC-2)

Baqiyatallah University of Medical Sciences (BMSU),
Baqiyatallah Research Center for Gastroenterology and Liver Disease (BRCGL),
Iran Hepatitis Network

**THC-2 Secretariat**
Baqiyatallah Research Center for Gastroenterology and Liver Disease
Ground Floor of Baqiyatallah Hospital, Baqiyatallah University of Medical Sciences, Mollasdra Ave., Vanak Squ., Tehran, I.R. Iran
Tel/Fax: +98 21 8126 2072
Email: seminar@brcgl.ir
Website: www.thc2.ir

**Venue**
Razi Convention Center
Iran University of Medical Siences
Tehran, I.R. Iran

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# Welcome Message

Dear Colleagues,

On the behalf of Organizing Committee and as the president of the Baqiyatallah Research Center for Gastroenterology and Liver Disease (BRCGL) it is my great pleasure to invite you to participate in the 2nd Tehran Hepatitis Congress, which will be held in Tehran, I.R. Iran, from October 7-9, 2009. You will learn about the latest advances in all biomedical aspects, therapeutic and diagnostic modalities of HCV, HBV and concomitant hepatitis B or C virus infection, as well as current epidemiologic trends of viral hepatitis in the world and Middle East and will discuss them with a select group of scientists in the field.

Kind Regards,

**Seyed-Moayed Alavian, M.D.**

Professor of Gastroenterology and Hepatology.
President of Baqiyatallah Research Center for Gastroenterology and Liver Disease (www.BRCGL.ir)
Founder of Iran Hepatitis Network (NGO) ( www.hep.ir)
Editor-in-Chief of Hepatitis Monthly (www.hepmon.ir),
Tel/Fax: +98 21 8861 4523, +98 21 8126 2072
Email: Alavian@thc.ir, editor@hepmon.ir
P.O. Box 14155-3651, Tehran, I.R. Iran

# About Tehran

Tehran is the capital and largest city of I.R. Iran, and the administrative center of Tehran Province. Tehran is a sprawling city at the foot of the Tochal mountain range with an immense network of highways unparalleled in Western Asia. The city is famous for its numerous resorts on the Alborz slopes, large museums, art centers, and palace complexes.

Tehran is the largest city in the Middle East and is the 16th most populated city in the world with a population of around 7,800,000 people. Most Iranian industries are headquartered in Tehran, including the manufacturing of automobiles, electrical equipment, military weaponry, textiles, sugar, cement, and chemical products. Tehran is also a leading center for the sale of carpets and furniture. There is an oil refinery located south of the city.

In the 20th century, Tehran faced a large migration of people from all around I.R. Iran. Today, the city contains various religious minorities, and has many historic mosques, churches, synagogues and Zoroastrian fire temples. Contemporary Tehran is a modern and expensive city featuring many skyscrapers, of which the Azadi Tower and the Milad Tower have come to be symbols of Tehran itself.

## History

The origin of the name Tehran is unknown. Excavations place the existence of settlements in Tehran as far back as 6000 BC. Tehran was well known as a village in the 9th century, but was less well-known than the city of Rhages (Ray) which was flourishing nearby in the early era. In the 13th century, following the destruction of Ray by Mongols, many of its inhabitants escaped to Tehran. In some sources of the early era, the city is mentioned as “Rhages’s Tehran” . The city is later mentioned in Hamdollah Mostowfi’s Nuz’hat al-Qulub (written in 1340) as a famous village. Don Ruy Gonzáles de Clavijo, a Castilian ambassador, was probably the first European to visit Tehran, stopping in July 1404, while on a journey to Samarkand (now in Uzbekistan) and the Mongol capital at the time. At this time, the city of Tehran was unwalled. Tehran became a residence of the Safavid rulers in the 17th century. Tahmasp I built a bazaar and a wall around the city, but it somewhat fell out of favor after Abbas I turned sick when he was passing the city to go to a war with the Uzbeks.

In the early of 18th century, Karim Khan Zand ordered a palace, a harem, and a government office to be built in Tehran, possibly to declare the city his capital, but later moved his government to Shiraz. Tehran finally became the capital of I.R. Iran in 1795, when the Qajar king Agha Mohammad Khan was crowned in the city. It remains the capital to this day.

## Climate

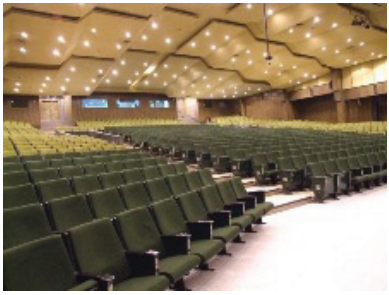
Tehran's climate is largely defined by its geographic location, with the towering Alborz Mountains to its North and the central desert to the South. It can be generally described as mild in the spring, hot and dry in the summer, pleasant in the autumn, and cold in the winter. As a large city with a significant differences in elevation among various districts, the weather is often cooler in the hilly north as compared to the flat southern part of Tehran. Summer is usually hot and dry with very little rain, but relative humidity is generally low and the nights are cool. The majority of the light annual precipitation occurs from late-autumn to mid-spring, but no one month is particularly wet. The hottest month is July (mean minimum temperature 23°C, mean maximum temperature 36°C) and the coldest is January (mean minimum temperature -1°C, mean maximum temperature 8°C).

Although compared with other parts of the country Tehran enjoys a moderate climate, weather conditions can sometimes be unpredictably harsh. The record high temperature is 48°C and the record low is -20°C.

# Razi Convention Center

The congress will be hold in Razi Convention Center located in Iran University of Medical Sciences, one of the main medical universities in I.R. Iran. The complex is next to Milad tower and off to Hemmat and Hakim highways and easily accessible by car, bus and subway.

This center, owned by Iran University of Medical Sciences, began its operations from May 1998. It consists of eight halls with a variety of seats as follows:



1. Main Hall: 1060 seats; located on ground floor
2. Halls 2 & 3: 300 seats (each); located on basement
3. Halls 4,5,6 & 7 (suitable for holding Instructional workshops): variable (each hall with 30-100 seats); located on first floor
4. A computer hall equipped with 12 Personal computers to instruct up to 20 people

Apart from the halls above, there are one language laboratory and some area for exhibition, reception, and serving.

Audio-visual facilities of the center includes sound, shooting films, and projection using slide projector, overhead, video imager, and computer equipment.

# Organizing Committee

## Chairman

*Prof. Kamran Bagheri Lankarani*
*Shiraz University of Medical Sciences*
*Shiraz, I.R. Iran*

## Scientific Manager

*Prof. Seyed Moayed Alavian*
*Baqiyatallah University of Medical Sciences*
*Tehran, I.R. Iran*

## Scientific Secretarial

*Prof. Mohammad Reza Zali*
*Shahid Beheshti University of Medical Sciences*
*Tehran, I.R. Iran*

## Manager

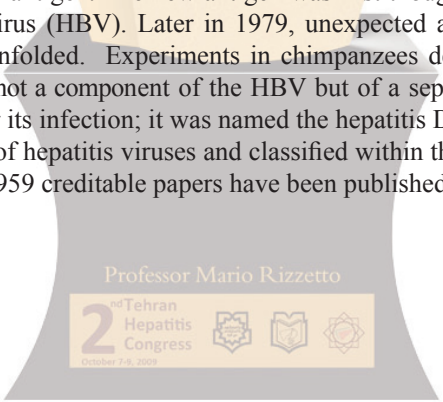
*Dr. Mehrdad Nooranipour*
*Baqiyatallah University of Medical Sciences*
*Tehran, I.R. Iran*

# International KOWSAR Award

**International Kowsar Award** for Hepatology as an international scientific award is going to be endowed for the first time to top researches who have lifelong experiencein the field of hepatology and have extended our knowledge and understanding of epidemiological aspects, pathobiological mechanisms, new therapeutics and molecular basis for diagnosis and treatment of liver diseases particularly viral hepatitis. This award is founded by Prof. Seyed Moayed Alavian, Professor of Gastroenterology and Liver Disease and Editor-in-Chief of Hepatitis Monthly journal, the only specialized journal pertaining to liver disease in the Middle East and Central Asia, in cooperation with Baqiyatallah Research Center for Gastroenterology and Liver Disease (BRCGL). By supporting this award we aim to:

- Promote sound and fruitful competition among the scientists especially the young persons achieving excellence
- Encourage and support the successful institutions in this competition
- Raise awareness among decision-makers and intellectuals about the present and potential abilities in our country

The first Kowsar award is going to be granted to **Prof. Mario Rizzetto**, Professor of Gastroenterology and liver diseases in University of Torino, Italy. Prof. Rizzetto in the mid 1970s discovered the delta antigen and antibody in carriers of the hepatitis B surface antigen. The new antigen was first thought to be a marker of the Hepatitis B Virus (HBV). Later in 1979, unexpected and amazing chapter in virology was unfolded. Experiments in chimpanzees demonstrated that the delta antigen was not a component of the HBV but of a separate defective virus requiring HBV for its infection; it was named the hepatitis D virus to conform to the nomenclature of hepatitis viruses and classified within the genus Delta virus. Since then, over 2959 creditable papers have been published about HDV.



*In the name of Allah, The Compassionate, The Merciful*

*Baqiyatallah University of Medical Sciences*

**Dear Professor Mario Rizzetto**

*It is my pleasure to declare that in recognition of your outstanding achievements in the scientific world, contribution to human health and prosperity and a life-time of efforts in medical sciences, Baqiyatallah University of Medical Sciences is delighted to offer you the*

## KOWSAR Award for Hepatology
(2009)

*Your discovery of the hepatitis Delta virus has changed forever our understanding of this family of malicious viruses and helped scientists all over the world to design effective means to combat hepatitis and alleviate patients' sufferings.*

*It is an honor for the Iranian scientific community to recognize your exceptional endeavors and accomplishments during your fruitful life.*

*We pray for more success in your service to humanity and wish you a prosperous and healthy life.*

*Professor Seyed Moayed Alavian*
*Scientific Manager*
*The Second Tehran Hepatitis Congress*

2nd Tehran Hepatitis Congress
Oct 7-9, 2009

# Scientific Committee

Adibi P., M.D.
Agah S., M.D.
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Amir Amini-Bavil-Olyaee
Hossein Irani
Ehsan Ameri
Farshid Alvandi

# International Invited Speakers (Alphabetical)

**Prof. Hubert E. Blum (Germany)**
Department of Medicine, University of Freiburg, Freiburg, Germany

**Prof. Rosa Cristina Coppola (Italy)**
Department of Public Health, University of Cagliari, Cagliari, Italy

**Prof. F. Blaine Hollinger (USA)**
Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, USA

**Prof. Peter Karayiannis (UK)**
Department of Medicine, Imperial College, London, UK

**Prof. Daniel Olivier Lavanchy (Switzerland)**
World Health Organization (WHO), Geneva, Switzerland

**Prof. Mario Rizzetto (Italy)**
Department of Gastroenterology, University of Torino, Torino, Italy

# Continuing Medical Education (CME) Credits

Gastroenterology 9.5
Gastroenterology - Pediatrics 9.5
Hematology 9.5
Hematology - Pediatrics 9.5
Nephrology 9.5
Nephrology - Pediatrics 9.5
Family Medicine (GP) 8
Infectious disease 8
Internal medicine 8
Anesthesia 6
Cardiology 6
Cardiovascular Surgery 6
Dentistry 6
Dermatology 6
Endocrinology 6
ENT 6
General Surgery 6
Laboratory Science 6
Obstetrics and gynecology 6
Ophthalmology 6
Orthopedics 6
Pathology 6
Pediatrics 6
Psychology 6
Radiology 6
Rheumatology 6
Nursing 5

# Exhibition and Sponsoring

A comprehensive exhibition will be run in conjunction with the congress. The exhibition will be held at the same venue. The exhibition package and floor plan has been designed to provide the best possible exposure for organizations in order to promote their products and services to key target audience.

Diagnostic and pharmaceutical companies sponsored our congress are listed below:

Roche Pharmaceuticals

The Schering-Plough Corporation

Dr. Abidi Pharmacceutical Laboratory
Ahran Tejarat
Bakhtar Bioshimi Pharmaceutical Co.
Pooyesh Darou Co.
Farpajouh Co.

# Scientific Program

## Main Hall (Hall 1-3)

Day 1- Oct 7

➢ *Inauguration Ceremony*, Oct 7, 8:00-8:30

| Date/Time | Lecturer | Tittle |
|---|---|---|
| 8:30-8:50 | Prof. Seyed Moayed Alvaian | Epidemiology of Hepatitis B in Iran, the Middle East, and the World |
| 8:50-9:10 | Prof. Hossein Forootan | Treatments and Follow up in Chronic HBV Infection |
| 9:10-9:30 | Prof. Mohammad Reza Zali | HBV Mutations after Therapy: What the Clinicians Need |
| 9:30-10:00 | Porf. Peter Karayiannis | Hepatitis B Virus and Antiviral Resistance to Nucleos(t)ide Analogues |
| 10:00-10:30 | - | ----------Break---------- |
| 10:30-11:00 | Prof. Kamran Bagheri Lankarani | Extrahepatic Manifestations of HCV |
| 11:00-11:30 | Prof. Hubert E. Blum | Non-Surgical Treatment of Hepatocellular Carcinoma |
| 11:30-12:00 | **Minister of Health, I.R. Iran** | CONFERRING KOWSAR AWARD |
| 12:00-12:30 | Prof. F. Blaine Hollinger | Lookback and Traceback for HBV: Balancing Benefits against Cost and Effort |
| 12:30-13:30 | - | --------Prayer-Lunch-------- |
| 13:30-14:00 | Prof. Daniel Olivier Lavanchy | Approach to Prevention of HAV and HBV |
| 14:00-14:30 | Prof. Rosa Cristina Coppola | Epidemiological Impact of HAV Control in a High HAV Endemicity Area |
| 14:30-14:45 | Dr. Mitra Mahdavi-Mazdeh | Hepatitis B and C in Dialysis Units in Iran & Hepatitis B Vaccination in Hemodialysis Patients |
| 14:45-15:00 | Prof. Behzad Einollahi | HBV Infection in Patients with End Stage Renal Disease |
| 15:00-15:15 | Prof. Fariborz Mansour-Ghanaei | Interferon in Treatment of Hepatitis B |
| 15:15-15:30 | Dr. Hossein Ghanaati | Hepato-biliary Intervention |

Day 2- Oct 8

| Date/Time | Lecturer | Tittle |
|---|---|---|
| 8:30-9:00 | Prof. Seyed Moayed Alvaian | Epidemiology of Hepatitis C in Iran, the Middle East, and the World |
| 9:00-9:30 | Prof. Mario Rizzetto | Hepatitis C: New Strategies of Therapy according to RVR, SVR etc. |
| 9:30-10:00 | Prof. Hubert E. Blum | Treatment of Chronic Hepatitis C |
| 10:00-10:30 | - | ----------Break---------- |
| 10:30-11:00 | Prof. Daniel Olivier Lavanchy | Treatment of chronic hepatitis B in Resource Constrained Public Health Settings |
| 11:00-11:30 | Prof. Peter Karayiannis | The Role of HBeAg in the Natural History of Chronic HBV Infection |
| 11:30-12:00 | Prof. Seyed Moayed Alvaian | Hepatitis B - Inactive Carrier Status |
| 12:00-12:15 | Prof. F. Blaine Hollinger | Hepatitis B and Transfusion Medicine: Unexpected Donor Screening Events |
| 12:15-12:30 | Dr. Seyed Mohammad Jazayeri | Occult Hepatitis B Infection, a Cause for Concern |
| 12:30-13:30 | - | --------Prayer-Lunch-------- |
| 13:30-14:00 | Prof. Mansour Ali Hezam Al-Amrany | HCV Infection, Insulin Resistance and Type 2 DM in Yemeni Patients |
| 14:00-14:15 | Dr. Siavash Mansouri | Applications of UES in Cirrhotic Patients |
| 14:15-14:30 | Dr. Farhad Zamani | Complications of HCV |
| 14:30-14:45 | Dr. Katayoun Samimi-Rad | Virology of Hepatitis C |
| 14:45-15:00 | Dr. Shahram Agah | Management of Hepatitis C in Cirrhotic Patients |

Day 3- Oct 9

| Date/Time | Lecturer | Tittle |
|---|---|---|
| 8:30-9:00 | Prof. Naser Ebrahimi Daryani | Hepatitis D |
| 9:00-9:30 | Prof. Mario Rizzetto | Virology & Biology of HDV |
| 9:30-9:50 | Dr. Seyed Mohammad Jazayeri | Application of Real Time PCR in Viral Hepatitis |
| 9:50-10:10 | Dr. Hossein Keivani | Serologic and Molcular Diagnosis of HBV |
| 10:10-10:30 | Dr. Mohsen Nasiri Toosi | Controversy in Management of HCV in Special Disease |
| 10:30-11:00 | - | ----------Break---------- |
| 11:00-11:30 | Prof. Rosa Cristina Coppola | Epidemiological Impact of HBV Vaccination in Young Adults: the Italian Experience |
| 11:30-12:00 | Dr. Peyman Adibi | Implementation Issues of Viral Hepatitis Prevention Programs |
| 12:00-12:30 | Prof. Mehdi Saberi-Firoozi | Long Term Immunity to Hepatitis B Virus Vaccine |
| 12:30-13:30 | - | --------Prayer-Lunch-------- |
| 13:30-13:45 | Dr. Mohmmad Javad Zahedi | Approach to Acute Viral Hepatitis |
| 13:45-14:00 | Prof. Mohammad Aghazadeh | Differenial Diagnosis: Acute Viral Hepatitis/Autoimmune Hepatitis/PSC |
| 14:00-14:15 | Dr. Maryam Keshvari | Epidemiology of Hepatitis A in Iran, the Middle East, and the World |
| 14:15-14:30 | Dr. Mohammad Ebrahim Ghamarchehreh | Clinical Manifestations and Diagnosis of Hepatitis A |
| 14:30-14:45 | Dr.Sedigheh Amini Kafi-abad | Blood Safety |
| 14:45-15:00 | Dr. Bita Behnava | Approach to Complications of Treatment of Hepatitis C |

## Hall 4

- **Day 1- Oct 7**
  ***Student Section, 8:30-15:30***

## Hall 5 - Workshop Room

- **Day 2- Oct 8**
  ***Real-time PCR Workshop, 9:00-13:00***

| Date/Time | Lecturer | Tittle |
|---|---|---|
| **9:00-13:00** | Kawsar Idea Exploration | Diagnosis and Quantitation of HBV - Iranian Kit |

**Kamran Bagheri Lankarani, M.D.**
Shiraz University of Medical Sciences
Shiraz, I.R. Iran

Professor Kamran Bagheri Lankarani was born in 1965 in Tehran. He got his M.D. from Shiraz University of Medical Sciences (SUMS) in 1989. He entered medical residency at the same year and graduated in 1992.He passed the national board exam of internal medicine in the same year and received award from the President of Islamic Republic of Iran at the time for attaining the best score in this national exam. He received his subspecialty board on Gastroenterology and Hepatology in 1996.He joined the department of internal medicine in SUMS in 1992 as an Assistant Professor .He served as director general of Namazi Hospital in Shiraz, Vice Chancellor of SUMS and Chairman of the Department of Internal Medicine and finally as the Minister of Health and Medical Education. He left office in September 2009. He is currently Full Professor of Internal Medicine at SUMS; a senior member of Gastroenterology and Hepatology Research Center at SUMS, Chairman of Health Policy Research Center at SUMS, senior staff member of liver transplant section at SUMS. He is also member of many national and international professional societies. He has published 60 papers in different fields of gastroenterology including viral hepatitis. He also has co-authored 5 books in this field. He is the Chief Editor of Shiraz Electronic Medical Journal, Chairman of Hepatitis Monthly, and a member of editorial board and reviewer of several national and international journals.

## Extrahepatic Manifestations of Chronic Hepatitis C

Kamran Bagheri Lankarani, M.D.

Chronic hepatitis C (CHC) is now considered a systemic disease. This virus not only infects hepatocytes but also by affecting lymphocytes can produce many systemic manifestations in susceptible hosts. There are many reports on these extra hepatic manifestations. The most documented extrahepatic manifestation of HCV infection is mixed cryoglobulinemia.The pathogenesis involves circulating immunocomplexes produced by a B-cell lymphoproliferative disorder. After the establishment of a strong epidemiological link between MC and HCV infection, the term 'essential' MC is currently outdated. Although up to 50% of CHC can have cryoglobulinemia usually in low titers clinically evident disease occurs at most in5-10% .The most common presentation are weakness, arthralgia and purpura; but the worst is renal involvement which can progress to end stage renal disease. Other manifestations include arthritis, neuropathy. MC and its complications can be cured by antiviral.

There are many reports on higher incidence of lymphoma especially non Hodgkin's lymphoma with B cell origin in CHC. Nearly 8-10% of patients with MC may progress to lymphoma in some reports. These patients usually benefit from combination of antiviral therapy and standard chemotherapy for lymphoma.

Renal disease in the absence of MC has also been reported in CHC. Both membranoproliferative glomerulonephritis and membranous nephropathy are reported to be associated with CHC although the increased incidence of these two conditions in CHC was debated by others.

Thyroid disease in CHC could be the result of antiviral therapy especially interferon (IFN), but there are evidence of increased incidence of sub-clinical hypothyroidism in CHC even before treatment. It has been shown that those patients with anti-thyroid peroxidase antibodies before treatment have an increased chance of developing Hashimoto's thyroiditis and Grave's disease while receiving

IFN and  for this need more close monitoring on IFN. So, most cases of clinical thyroid disease in CHC are related to combined detrimental effects of both the virus and IFN treatment. IFN is contraindicated at the presence of uncontrolled thyroid disease. A transient autoimmune thyropathy also has been associated with IFN alone which is usually relieved 6 months after discontinuation of IFN. A higher prevalence of papillary thyroid carcinoma is also reported in CHC.

Arthritis, idiopathic pulmonary fibrosis, porphyria cutanea tarda, lichen planus specially its oral form and neuropathy have been linked to CHC both at presence and absence of cryoglobulin. Increased incidence of fibromyalgia in CHC is controversial.

CHC has several metabolic effects of which the most important one is insulin resistance. The primary site of resistance in these patients seems to be peripheral tissue including muscle, adipose tissue and liver. There seems to be a viscous cycle between liver fibrosis and insulin resistance. Incidence of diabetes mellitus (DM) type2 but not type 1 is increased in CHC up to three times. These patients compared to usual cases of type 2 DM are thinner with lower LDL cholesterol and lower systolic and diastolic blood pressure. Risk factors for development of DM in CHC include older age, HCV genotype 3, liver fibrosis, family history of DM and liver/kidney transplantation. Interestingly in intravenous drug abusers (IVDA) with high incidence of CHC no increased incidence of DM were seen.

Accelerated atherosclerosis has also associated with CHC although the association is not confirmed in all studies. The same is true for cardiomyopathy. Several autoantibodies are positive in CHC but in most of instances they are non organ specific and in low titers and usually without any clinical significance. Some of the autoantibodies are more frequently expressed—especially RF, antinuclear antibodies, and anticardiolipin antibodies. Anti-LKM-1 has been detected in HCV-infected patients in Europe but not in the United States.

The presence of autoantibodies in the sera of HCV-infected patients may pose diagnostic dilemmas. Thus, a patient presenting with symmetric polyarthritis and positive RF may be misdiagnosed as having rheumatoid arthritis. Antibodies to cyclic citrullinated peptide (CCP) may be helpful to solve this diagnostic dilemma. In contrast to rheumatoid arthritis, CCP antibodies were not increased in HCV infection.

Sialadenitis and sicca symptoms are seen frequently in patients with HCV and HCV-associated Sjogren's syndrome is indistinguishable in most cases from the primary form.

Psychiatric disorders, especially major depression, are common in CHC. Although this disorder can be provoked by IFN therapy, there is a great deal of evidence indicating its presence in CHC even before treatment. Whether this is a co morbid condition related to underlying risky behaviors such as IVDA or it is induced by virus itself is a matter of debate. Selective serotonin reuptake inhibitors (SSRIs) are safe and efficacious in treating depressive symptoms secondary to IFN therapy. They can be used safely before starting IFN in susceptible patients with depression as pre-treatment measure.

Several other associations were suggested based on epidemiologic studies while there are anecdotal reports on other conditions. The nature of extrahepatic disorders calls for a multidisciplinary approach, leading to more accurate classification, diagnostic assessment, and therapeutic interventions.

## References

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3. Fallahi P, Ferri C, Ferrari S, et al. The Emerging Extrahepatic Manifestations of Hepatitis C Virus Infection in Chronic Hepatitis and Mixed Cryoglobulinemia. Hepat Mon. 2008;8: 207-11.
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9. Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB. Extrahepatic manifestations of

Hepatitis C Virus infection: a general overview and guidelines for a clinical approach. Dig Liver Dis. 2007;39: 2-17.

**Seyed Moayed Alavian, M.D.**
Baqiyatallah University of Medical Sciences
Tehran, I. R. Iran

Professor Alavian has graduated from Tehran University of Medical Sciences in MD and Internal specialty. He began his work as a fellow in the Digestive Diseases Research Center (DDRC) at Shariati Hospital from 1992 until 1994. He was ranked second in the country in the subspecialty board exam.

Professor Alavian established the first hepatitis clinic in Iranian Blood Transfusion Service in Tehran in 1995 and that center has registered 5000 cases of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection since then. He is the founder of Iranian Charity for Liver Support in 1995 in Tehran. He is also the founder of Hepatitis Monthly journal and editor-in chief of the journal. He is a member of editorial board of several creditable local and international journals. He has been the associate editor of Journal of Clinical Virology since 5 years ago.

He has been an advisor and consulted on national program projects for control of hepatitis in Iran. He is a member of the National Committee for Hepatitis in the Ministry of Health and Medical Education since 1995. He has been given several grants by national and international research centers for research on viral hepatitis.

He is currently professor of gastroenterology and hepatology in Baqiyatallah University of Medical Sciences, and director of Baqiyatallah Research Center for Gastroenterology and Liver Disease.

Professor Alavian is an experienced researcher and hepatologist who has been actively involved in various national, multicenter clinical trials and basic scientific projects related to viral hepatitis over the past 17 years. He has authored/co-authored over 200 articles in local and international journals, including 84 in ISI journals as well as 40 books and booklets for physicians and patients. He has been the principal investigator in numerous clinical trials related to the management and treatment

of hepatitis C and B patients. His main interests are health policy, epidemiological aspects of viral hepatitis and how to integrate new protocols for control of these infections. He is also interested in clinical trials of emerging medications for HBV and HCV, and treatment of viral hepatitis in special diseases including thalassemia and hemophilia.

## Epidemiology of Hepatitis C in Iran, the Middle East

Seyed Moayed Alavian, M.D.

Hepatitis C virus infection is a major global public health problem in both developed and developing countries. Epidemiologic evidence of HCV is one of the main evidences for strategic prevention of chronic liver diseases. Hepatitis C is a global health problem worldwide affecting over 170-200 million people and the virus is distributed worldwide with prevalence varying between different countries from 0.2 up to 40% (1, 2). Hepatitis C virus is spread parenterally, either through intravenous drug use or, in lesser-developed countries, through transfusion of blood products and contamination during medical procedures. Despite a declining incidence of new infections in hemophilia, thalassemia and hemodialysis patients, the burden of disease, both in terms of mortality and in terms of cost, is expected to increase over the next decade and HCV infection will be a potential cause of substantial morbidity and mortality in the future (2, 3). Control of HCV infection is an important public health concern because the majority of infections do not resolve but lead to chronic infection. Epidemiology and routes of transmission of hepatitis has changed since 18 years before. As the sensitivity of HCV screening tests had increased, new viral infection transmittable through blood products has been virtually eliminated in developed countries and had decreased in developing countries (4). The main risk factor for acquiring HCV infection before the routine anti-HCV screening of blood donors was blood transfusion (5). But now the relatively high proportion of non-transfused hepatitis C cases suggests that transfusion is not the predominant route of transmission of HCV in I.R. Iran. Today, intravenous drug abuse is the major risk factor for HCV infection (6). Injection drug use now is responsible for at least more than 60% of new cases of HCV infection worldwide. Because of sharing contaminated needles and other equipments used in injection, use of shooting galleries, cocaine use, unsafe sexual activities, and sharing the shaving equipments, IDUs constitute one of the most important groups at risk of being infected with HCV (5, 7) and it has been identified as the most common viral infection affecting IDUs (8). Therapeutic injections by health care providers, shaving by barbers, tattooing and ear-piercing, known to be associated

with HCV infection, are common in developing countries.

In a study on Iranian blood donors, transfusion, undergoing endoscopy, extramarital sexual activities, non-intravenous (n-IV) drug abuse, IV drug abuse, and receiving wounds at war were found to be independent risk factors of being HCV-positive (5). No apparent risk factors could be demonstrated in 24.5% of the positive cases (5). There are certain medical procedures, lifestyle patterns, and customs and cultural matters in I.R. Iran that predispose people to a number of HCV risk factors (5). In I.R. Iran, for clarifying the risk factors many studies have done in prisons and high-risk behaviors in drug abusers admitted to prisons. The high prevalence rate of HCV infection in prisoners in different parts of the country has confirmed (9, 10). In a study in 226 gypsies of Southwest of I.R. Iran, seven of them were positive for anti-HCV. Tattooing and phlebotomy are very common practices among gypsies (11).

Another study was conducted among HCV positive individuals referred to Ahwaz Jundi-Shapour University Hospitals from 1999 to 2003 (12). A total of 514 subjects were studied for HCV, of whom 254 were HCV-positive and 260 HCV-negative donors comprised the control group. Transfusion 132 (52%), no intravenous (n-IV) drug abuse and IV drug abuse 37 (14.5%), hemodialysis 25 (10%), receiving wounds at war and extramarital sexual activities (2.4%), tattooing (3.6%) were found to be independent risk factors of being HCV-positive. No apparent risk factors could be demonstrated in 29 (11.2%) of the positive cases (12). Non-sexual household contacts such as sharing tooth brushes nail clippers and razor blades are risk factors for HCV transmission in Pakistan (13, 14).

In developing countries including Pakistan, the risk of HCV transmission through blood transfusion is unknown but considered to be high due to lack of appropriate screening of blood and needs to be more investigated (15). Low educational level and/or low socio-economic status has also been associated with the prevalence of a number of infectious diseases. It seems that blood transfusion is still the major cause of HCV transmission in Pakistan. Community trends like reuse of disposable and/or glass syringes, repeated use of potentially contaminated razors by barbers, improper dental practices (6) and other risk factors seem to be unchanged. Widespread practices such as unsafe injections, improper disposal of hazardous waste, recycling of used syringes without proper sterilization, sharing of needles by injecting drug users and unsafe sex are believed to facilitate the transmission of

these infections, resulting in high prevalence rates in Pakistan (6, 16). I visited two cases with post-transfusion hepatitis C from south of Iraq last year in Tehran and I am sure that the screening of all blood products in Iraq is not valid and it seems that transfusion has an important role in transmission in Iraq too. There are both geographic and temporal differences in the patterns of HCV infection.

In I.R. Iran we had not overall estimation of HCV infection and studies that were done on HCV prevalence are restricted to specific geographic locations or provinces. Overall estimation of HCV infection can be used for health programming and promoting HCV infection programs in our country. Recently we did a meta-analysis for estimation of HCV prevalence in general population in I.R. Iran. Prevalence of HCV in general population in I.R. Iran with Survey Data analysis according to information of 6 provinces is %0.16 (Alavian et al 2009 In Press). In one Pakistani community, HCV seroprevalence was 6.5%, and individuals who received more therapeutic injections were found to be at a higher risk of infection (17). And in Iraq, HCV-antibody seroprevalence among pregnant women has been recorded as 3.2%, a figure that reflects the seroprevalence among the normal population (18).

Patients with hemophilia constitute a high-risk group for acquisition of HCV infection. Transmission of HCV via blood products has been a significant source of hepatitis C infection for patients with hemophilia. Extensive seroepidemiological studies have shown that 60%–91% of patients with hemophilia have antibodies to HCV have antibodies to HCV. Recently we did a meta-analysis and we found the prevalence rate of anti HCV Ab by Elisa in Iranian hemophilia is 40.836% (between 31.08 and 50.59) (Alavian et al 2009 In Press). Iranian thalassemia patients have the prevalence rate of HCV infection between 15.7 and 63.8 percent (19, 20). In our experience with thalassemia patients in Tehran, 24.2% of them were anti-HCV positive. HCV seropositivity was significantly associated with longer history of transfusion, but patients who had received their first blood transfusion after implementation of compulsory blood donors screening in I.R. Iran in 1995, had a significantly lower rate of HCV infection compared to those transfused thereafter 21. The prevalence rate in Iraq is 67.3% (22), in Saudi Arabia is 40% (23), and 14% in Turkey (24). Recently we did a meta-analysis and found that the prevalence rate in 14 provinces in I.R. Iran is 15.765% (between 12.60 and 18.92%) (Alavian et al 2009, to be published). HCV infection is an important issue in hemodialysis patients and the prevalence of anti-HCV Ab varies geographically, both inside and

between countries (25). The reported anti-HCV sero-positivity from 71% in Kuwait (26), 13.2% in I.R. Iran (27). Some investigators have suggested a decline in HCV prevalence among HD patients in recent years, mostly attributable to strict adherence to universal precautions 28. This decrease is more significant and has reported from I.R. Iran (28, 29).

## Conclusion

Clearly, the prevalence of HCV infection in general population in I.R. Iran is much less than our neighbours. The epidemiology and prevalence of HCV infection has changed in many countries in the world and in I.R. Iran too. Harm reduction as the core activity of triangular clinics works well for the infected while other supportive services help healthy but at risk population prevent the spread of HIV, HCV and other contagious diseases. We hope the already-in-place program of harm reduction gets national to cover all high-risk populations including IDUs in and out of prison (30). We need better strategies to control hepatitis C in IVDs in our community. Continued education of the public and healthcare professionals will play an important part in controlling this problem, for example through eliminating unsafe injections in the healthcare facilities that are reported as a risk factor for acquisition of hepatitis B and C in the community.

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## Epidemiology of Hepatitis B Virus Infection in I.R. Iran and Middle East Countries

Seyed Moayed Alavian, M.D

Hepatitis B is one of the most common infectious diseases globally. It has been estimated that there are 350-400 million chronic hepatitis B virus (HBV) carriers worldwide, of whom 75% are Asians (1). I.R. Iran is located in the Middle East and has an intermediate prevalence of hepatitis B chronic infection, according to CDC. The prevalence of chronic carrier state in I.R. Iran had been reported to be 3% in 1980s (2). It is estimated that over 35% of Iranians have been exposed to the HBV and about 3% are chronic carriers, ranging from 1.7% in Fars province to over 5% in Sistan-Balouchestan. In 1979, the prevalence of hepatitis B surface antigen in I.R. Iran ranged between 2.5% and 7.2% (3). It decreased to 1.7% in blood donors in 1987. In general population, this prevalence was 1.7% and 2.49% (4) in 1992 and 1993, respectively.

Another study showed that HBV prevalence is 1.07% in blood donors in Shiraz in 2000 (5). HBV prevalence has decreased dramatically in Iranian population during the last decade (6). Improvement of people's knowledge about HBV risk factors, national vaccination program since 1993 for all neonates, vaccination of high risk groups such as healthcare workers and introduction of disposable syringes for use in vaccinations, hospitals and clinics may explain this decrease (7).

The most common cause of acute viral hepatitis in adulthood, chronic hepatitis, cirrhosis, hepatocellular carcinoma and acute liver failure in I.R. Iran is hepatitis B (8-10). Fifty-one to 56% of Iranian cirrhotic patients were hepatitis B surface antigen (HBsAg) positive. In I.R. Iran, several studies have been performed to determine the prevalence of hepatitis B carrier state. The prevalence rate of HBsAg positivity is low now, with HBsAg carrier rate of less than 2.5% (1).

The overall seropositivity rate showed no significant decline between 1991 and 1999; however, in 2-14 year olds, the rates reduced significantly (1.3% versus 0.8%, $P<0.05$). Interestingly, we observed a significantly higher decline in hepatitis

B virus carrier rate in rural (1.5% versus 0.6%) than in urban areas (1.1% versus 0.9%). Universal vaccination significantly decreased the carrier rate among young children in this country (11). Universal vaccination of all neonates against hepatitis B virus has been implemented in the Islamic Republic of I.R. Iran since 1993 (Ministry of Health report). The impact of vaccination programs had been illustrated by 1999 and 1991 studies. The prevalence of HBsAg in children has decreased from 1.3 to 0.9% within 6 years of starting a Expanded Program on Immunization (EPI) (11). Similar results have been reported from other countries such as Saudi Arabia and Taiwan. Fortunately after 13 years of implementation, the coverage rate for infantile vaccination against HBV infection has reached an appropriate level from 62% in 1993 to 94% in 2005 (2).

The studies from Turkey and Saudi Arabia have showed the decrease in prevalence rate of HBV infection in general population too (12, 13). The prevalence of HBsAg in Yemen ranges from 8% to 20%. In a study of 178 randomly selected subjects, seroprevalence among mothers was 13.2% and 4% for infants aged between 6 and 12 months (14). The prevalence rate of HBsAg positivity in blood donors in Kuwait was 1.1% and 3.5% among Kuwaiti national and non-Kuwaiti, respectively (15). Of 301 families with a total of 903 Afghan refugees living in the camps of Baluchistan Province, Pakistan in 2003, 8.3% were positive for HBsAg (16). Seroprevalence of HBsAg in 1,694 pregnant women was 7.1% of the women in Oman, 1% in Qatar and 1.5% in the United Arab Emirates (UAE) in 2000 (17).

Evaluation of risk factors in HBV infected people is important for designing the strategies to control the disease. In a study in blood donors of Tehran (all blood donors of Tehran city from April 1997 to March 2000 were studied in a case control design), the most common risk factors were family history of positive HBsAg, history of blood transfusion, male gender, history of hospitalization, history of unsafe sex and living in city area. There was a significant difference between cases and controls regarding HBsAg status in donors' mother and spouse (18). Another study in blood donors in Qazvin revealed that close contact with an HBV infected person, extramarital sexual contact, history of sexually transmitted diseases and high risk jobs were independent risk factors for prediction of hepatitis B infection. Horizontal mode is more important than vertical transmission in this region of I.R. Iran (19). In Karaj, the risk factors in chronic hepatitis B were older age, male gender, marital status, history of contact with hepatitis, extramarital sexual activity, IV-drug use, major surgery, experimental dentist visit,

and some jobs (police, barber, and driver) (20). In a Cohort study (Nov 2001-Dec 2003) with historical controls, the prevalence of HBV infection increased after 16 years old (21).

The age at which HBV infection occurs influences the long-term outcome and determines the primary targets of a vaccination program. Thus, perinatal transmission from mother to child at or soon after birth results in about 90% chronic carriage, with its long-term complications of chronic hepatitis, cirrhosis and hepatocellular carcinoma, leading to death in middle age, particularly in men. This has serious economic consequences for the family and for the country as a whole (22). The contribution of each mode of transmission to morbidity and mortality must be known in order to develop the optimal vaccination program. Those countries that vaccinate only children will produce an impact in early life, but it will not be until those vaccinated children reach adolescence or early adult life that any impact on sexual transmission will be seen. Therefore, if sexual relation is the main mode of transmission in a country, adolescents should be vaccinated for an immediate impact on acute cases of hepatitis B, and on the development of chronic carrier state in this age group. Another important consideration before starting any intervention is the baseline disease situation. Fortunately in I.R. Iran, there is a good healthcare infrastructure for vaccination program.

The prevalence of HBV infection was higher in people who had a history of battlefield trauma, and relative risk in Wounded-In-Action was 1.6 times as much as in other people (23, 24). Screening of the military personnel and vaccination against HBV infection is mandatory in I.R. Iran now (25, 26).

Sexual transmission is the most important mode of spread of HBV in most developed countries. And the epidemiology of infection is also changing from vertical to horizontal route in I.R. Iran. In 2002, regarding the country's health needs and priorities, in order to extend the target groups for hepatitis B vaccination, the program was revised by the «National Committee of Hepatitis». That committee recommended also vaccinating people with high risk occupations like firefighters, workers of city hall, etc. The vaccination in young people (14-18 years old) started. Ministry of Health and Medical Education and undersecretary of Health Affairs, and CDC have been supported directly by His Excellency Minister of Health, Professor Lankarani to start this campaign. Hepatitis B vaccination takes years if not decades to show effectiveness in the community. We, epidemiologists,

gastroenterologists, infectious disease specialists and health care staff are responsible to capture this unique opportunity to elucidate the epidemiology of hepatitis B in Islamic Republic of Iran. Fortunately, the health infrastructure to expand the coverage for more vaccination is accessible in I.R. Iran. I believe that this approach will decrease the incidence rate in Iranian population, especially if followed by these considerations, educating the people, especially at risk group, implementing strategies to prevent the transmission to others and screening and finding the patients in early stages and asymptomatic phase (2).

## Conclusion

Hepatitis B virus infection is a problem of public health, and a major cause of mortality and morbidity, particularly in developing countries. Most countries in the Middle East region are still considered intermediate to high endemicity for HBV infection. Insufficient coverage of HBV vaccination, injection drug users sharing blood-contaminated equipment, unsafe blood transfusion, and inadequate health precautions are major risk factors for hepatitis B virus infection in this region. Screening HBV infection during pregnancy, and follow-up of infants with HBV infected mothers will reduce rates of perinatal HBV infection in these countries. Implementing local strategies for hepatitis B screening will reduce the infection rate. The socioeconomic and sanitary changes, expanded program on immunization of infants and of all high risk populations have changed the epidemiologic profile of hepatitis B virus infection in I.R. Iran. Universal vaccination has significantly decreased the carrier rate among young children. More studies on the impact of type of vaccines, environment, ethnicity and other contributing factors that can impede an adequate antibody response in our population are necessary. Education of people regarding infection prevention and transmission, especially of groups at risk of hepatitis exposure and limiting immigration from neighboring countries is the most cost-effective way of infection control.

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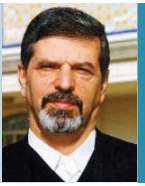
**Mohammad Reza Zali, M.D., FACG**
Shahid Beheshti University of Medical Sciences
Tehran, I.R. Iran



Professor Zali began his study of medicine in Tehran University of Medical Sciences in1963 and went to South Chicago Community Hospital, Chicago, USA, in 1973 for Internship and then to Tulane University, New Orleans, for Residency in Internal Medicine in 1974 and followed through Fellowship in Gastroenterology at the same university in 1977, where he graduted in 1978. He has held several official posts since his return to Iran (e.g. Deputy of Minister in the Ministry of Health and Medical Education; Director of Research, Iranian Academy of Medical Sciences, etc). He is a Permanent Member of the Iranian Academy of Medical Sciences. He is also a member of several professional societies and organizations (e.g. American College of Physicians, European Society of Gastroenterology, Iranian Gastroenterology Society, American Collage of Gastroenterology, American Gastroenterology Association, Iran National Science Foundation, and American Association for the Study of Liver Diseases …). He has been the ahuthor or co-author of 5 books, 106 international and 50 domestic articles and has had 87 international and 63 domestic paper presentations.

## HBV Mutants after Therapy: What the Clinicians Need

Mohammad Reza Zali, M.D.

Despite the availability of prophylactic vaccines, chronic hepatitis B remains a major global health concern, with more than 350 million chronically infected individuals worldwide, resulting in about 1 million deaths per year (1). Several studies suggest that suppression of viral replication is critical to reducing the risk of complications from chronic HBV infection (2, 3). There are two classes of approved agents for the treatment of chronic hepatitis B. The first class includes antiviral nucleoside/nucleotide analogs (Lamivudine, Adefovir, Entecavir, Telbivudine and Tenofovir) that directly inhibit HBV DNA replication and the other one is interferon based therapies (Standard IFN and Pegylated IFN) that may modulate host immune response as well as inhibit viral replication (4). Antiviral nucleot(s)ide analogs are well tolerated, very effective at suppressing viral replication, and appear to be completely safe. One negative point of nucleot(s)ide analogs therapy is the high rate of virological relapse when treatment is short and discontinued. Therefore, treatment must be administered long-term but long-term therapy is associated with the development of antiviral drug resistance which frequently negates the benefits of therapy and sometimes may be associated with hepatitis flares (5). Drug resistance is associated with the appearance of polymerase gene mutations, followed by an increase in viral load (virologic breakthrough) and a subsequent increase in alanine aminotransferase levels and worsening of liver disease. Lamivudine leads to resistance at a rate of approximately 20% of patients per year and can reach more than 70% after 4–5 years of therapy (6). The main mutations conferring resistance to lamivudine correspond to a methionine (M) to valine (V), isoleucine (I) or Serine (S) change at amino acid 204 within the YMDD catalytic domain of HBV reverse transcriptase. These mutations are frequently associated with compensatory mutations, rtV173L and/or rtL180M that partially restore the replicative capacity of the mutant strains (7, 8). Patients who develop mutations with lamivudine therapy were initially switched to adefovir or entecavir. However, recent data support the addition of a nucleotide agent such as adefovir, which avoids an increased rate of subsequent adefovir resistance (9). Adefovir

resistance has been demonstrated at 1, 2, 4 and 5 years at a rate of 0%, 3%, 18% and 29%, respectively. Furthermore, persistence of high level of HBV viraemia after 48 weeks of adefovir therapy predicts the emergence of resistance (10). Adefovir resistance is mainly associated with the selection of the rtN236T mutation within the D domain of the viral enzyme or with rtA181V amino acid change in the B domain of the RT. The rate of entecavir resistance is minimal (1.2%) in treatment-naive patient after 5 years of therapy. However, in lamivudine-refractory patients, the cumulative probability of entecavir resistance at years 1 through 5 is 6%, 15%, 36%, 46% and 51% respectively (11). Monitoring of the treatment response is one of the most important issues in treatment of HBV infected patients. Each of the surrogate markers, including serum aminotransferase levels, serum HBV DNA level, hepatitis B e antigen (HBeAg) or antibody to HBeAg (anti-HBe), hepatitis B surface antigen (HBsAg) or antibody to HBsAg (anti-HBs), and liver histology, has been used as a measure of the response to antiviral therapy. Periodic serum HBV DNA monitoring should now be viewed as the principal means of monitoring therapy and assessing response and will, therefore, play an increasing role in decision-making during antiviral therapy (12).

A critical assessment of the role of genotypic resistance testing in clinical practice needs to be performed to determine if inclusion of this test in clinical practice would improve outcomes. Management algorithms based on resistance testing need to be developed and validated.

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**Mario Rizzetto, M.D.**
University of Torino
Torino, Italy

Professor Mario Rizzetto got his degree in medicine and surgery in 1969 from the University of Padova, Italy, and went on to obtain specialty in Gastroenterology from the University of Torino in 1971 and then another specialty in Hepatology from the University of Milano in 1981.

Presently, he is a Professor of Gastroenterology at the University of Torino. He has received various awards for his scientific achievments (e.g. Premio Internazionale Chianciano 1984 for Research in Hepatology, International King Faisal Prize for Medicine 1985, Premio Internazionale «Fiuggi» for Medicine, Robert Koch Prize for Medicine, 1987, William Beaumont Prize for Gastroenterology, 1988, Gold Medal for Health Service, 1988, Premio Internazionale "Guido Lenghi e Flaviano Magrassi" for Virology, 1989, Hans Popper Prize for Hepatology, 1992, Premio Christopher Columbus Discovery for Biomedical Research, 1992, Premio Internazionale Ferdinando De Ritis, 1998, EASL Recognition Award, 2006, Ismar-Boas medal, Deutsche Gesellschaft fur Verdauungs und Stoffwechselkrankheiten, 2006), is a member of several organizations (e.g. Ordine dei Medici, Italy; Società Italiana di Immunologia ed Immunopatologia, Società Italiana di Gastroenterologia (SIGE), Associazione Italiana Gastroenterologi Ospedalieri, Associazione Italiana Studio Fegato (AISF), European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases, International Association for the Study of the Liver (IASL) and Medical Academy of Torino) and committees (e.g. World Health Organization Committee on hepatitis, National Research Council for Biological and Medical Sciences, National Advisory Committee on AIDS and infectious diseases, Scientific Committee of the Istituto Superiore di Sanità ). He also is or was a member of editorial board of various journals (e.g. La Ricerca in Clinica e Laboratorio, Italian Journal of Gastroenterology, Minerva Dietologica e Gastroenterologia, Journal of Hepatology, European Journal of Epidemiology, International Journal of Clinical and Laboratory Research, The Croatian Journal of Gastroenterology and Hepatology,

European Journal of Gastroenterology & Hepatology ...). His major publications and publications of the last 5 years include more than 100 articles and papers.

## Hepatitis C: New Strategies of Therapy according to RVR, SVR etc.

Mario Rizzetto, M.D.

The reduction of HCV-RNA during IFN therapy follows two phases. The viral RNA declines rapidly and steeply during the first few days of therapy, reflecting inhibition of HCV replication. Then the slope of HCV reduction becomes less steep, presumably reflecting the time needed to eliminate infected hepatocytes. The rapidity by which serum HCV-RNA is cleared from serum after the start of therapy appears at present the most important predictor of a sustained viral response (SVR).

HCV therapy guidelines have first focused on the 12th weeks interim treatment point (Early Viral Response = EVR). EVR is a valuable clinical milestone in disease sustained by HCV genotype 1; SVR is confined to patients who achieve an EVR (defined as $\geq 2$ – log10 reduction of HCV-RNA levels during the first 12 weeks of therapy). The positive predictor value of SVR is 70%. The negative predictive value is even higher; less than 5% of HCV1 patients not achieving an EVR, obtain a SVR.

A shorter and highly significant treatment interim has been identified at 4-6 weeks of therapy (Rapid Viral Response = RVR). It was shown that in patients with HCV genotype 2 achieving RVR, the rate of SVR after 12 weeks of therapy is similar to the rate obtained after the standard 24 weeks course, thus permitting the reduction to half of the treatment time.

New studies have correlated RVR in HCV genotype 1 patients with an over 80 % chance of SVR; most important, the same rate of response was achieved shortening treatment to 24 weeks instead of the standard 48 weeks course. Therefore, RVR appears to provide not only a strong prognostic indication of SVR but also a solid argument to shorten therapy also in HCV1 infections.

Data from Italy suggest that not less than one quarter of the Italian HCV genotype 1 patient can be expected to obtain a RVR and that about 85% of them

can be expected to achieve a SVR with a therapy course shortened to 6 months. Two prospective studies by Ferenci and Mangia considered the RVR interim both in patients with low and high baseline viremia; in each study the original HCV RNA did not influence SVR, once the patient had achieved a RVR.

Thus RVR-guided therapy may be used reduce therapy and optimise cost when therapeutic facilities are limited by economical restraints.

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## Virology & Biology of HDV

Mario Rizzetto, M.D.

The HD virion is made up of the HD-Antigen (HD-Ag) and a minute RNA species enclosed within a HBsAg coat derived from HBV. Currently this virus is divided into eight major genotypes differing as much as 40% in nucleotide sequence. Both the genomic and antigenomic strands contain a ribozyme, a RNA segment of less than 100 bases that retains the genetic information but is also able to self-cleave and self-ligate the circular HDV genome. HDV replication can proceed in host cells in the absence of HBV proteins. HDV needs HBV only to borrow the HBsAg capsid whereby it attaches to hepatocytes and propagates infection.

The HDV-RNA is replicated by host RNA polymerase II (Pol II), deceived by HDV to become redirected to read and copy its RNA. RNA Pol II carries out unchecked its transcriptional activity, elongating a multimeric linear transcript of either the genome or the antigenome over the viral RNA circular template; this elementary double-rolling circle mechanism of replication is unknown to animal viruses but operative in viroids.

Crucial are also the functions of the HD-Ag. Phosphorylation, acetylation, methylation, prenylation and several other post-translational modifications of the HD antigens have been shown to orchestrate the life cycle of the virus, demonstrating that the biological activities of the HD-Ag depend on a host of ordered protein-protein interactions regulated by its post-translational modifications.

Surveys in the 1980s showed that HDV is endemic worldwide, though with prevalences and patterns of infection varying in different areas. Medical scrutiny confirmed that chronic hepatitis D (CHD) usually runs a severe and progressive course, the prototype patient with CHD having the HBsAg in blood, elevated ALT, a liver biopsy exhibiting aggressive hepatitis but no markers of HBV replication.
Since the 1990s the circulation of HDV has declined significantly in Europe, following the control of HBV achieved in the last 15 years, which is depriving

the defective HDV of the HBV network necessary to propagate its infection. By contrast, HDV remains an important medical problem in many areas of the world where HBV remains unchecked.

However the reservoir of HDV is still consistent in Europe, sustained by two different pools of HDV-infected patients: the residual ageing domestic pool that survived the brunt of the hepatitis D epidemic in the 1970–1980s and the population of young patients with recent HDV infections migrating to Europe.
Therapy of hepatitis D remains an unsolved business. The therapy available today is not different from the limited IFN treatment attempted more than 20 years ago. The problem is formidable as HDV has no enzymatic protein to be targeted by conventional antiviral therapy. Potential targets to therapy are offered by the process of HD virion assembly. Critical to the interaction of Large HD-Ag with the HBV envelope protein and to propagation of infection is farnesylation (prenylation) of the last four aminoacids Large HD-Ag. By preventing the association of the HDV ribonucleoprotein with the HBsAg and, therefore, virion assembly, disruption of prenylation might form the basis of a new therapeutic strategy against HDV. In vivo the prenylation inhibitors FTI – 277 and FTI – 2153 were highly effective at clearing HD viremia in a mouse model of HDV infection.

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# Treatment and Follow up of Chronic Hepatitis B Virus Infection

Hossein Foroutan, M.D.

The aim is the establishment of national standards in the evaluation and antiviral treatment of patients with chronic hepatitis b virus (HBV) infection. This includes recommendations on the initial evaluation of patients, choice and duration of antiviral therapy, follow-up after antiviral therapy and monitoring of patients not currently requiring antiviral therapy.

The initial evaluation of chronic HBV-infected patients should include testing of liver biochemistry, virus serology and abdominal imaging. in patients without cirrhosis, antiviral treatment is recommended for those with a serum HBV DNA of at least 1.0 x 105 c/ml (≥2.0 x 104 iU/ml) in combination with: a) elevation of serum alanine aminotransferase (Alt) level above twice the upper limit of normal during at least three months, and/or b) histological evidence of porto-portal septa or interface hepatitis on liver histology.

In patients with cirrhosis, antiviral treatment is recommended if serum HBV DNA is 1.0 x 104 c/ml (≥2.0 x 103 iU/ ml) or higher, independent of Alt levels or histological findings. If the patient has decompensated cirrhosis, antiviral treatment is recommended if serum HBV DNA is 1000 c/ml (≥ 200 iU/ml or higher). Patients who do not have an indication for antiviral treatment should be monitored because there is a risk of (re)activation of disease activity. Monitoring every three to six months is recommended for HbeAg-positive and HbeAg-negative patients with high viraemia (HBV DNA ≥1.0 x 105 c/ml or ≥2.0 x 104 iU/ml) and normal Alt levels. for patients with serum HBV DNA below 1.0 x 105 c/ml (<2.0 x 104 iU/ml) the recommended frequency of monitoring is every three to six months for Hbe Ag-positive patients and every six to 12 months for Hbe Ag-negative patients.

Peg-interferon (PEG-IFN) therapy should be considered as initial therapy in both HbeAg-positive and HbeAg-negative patients without contraindications for treatment with this drug because of the higher chance of achieving sustained

response compared with nucleos(t)ide analogue therapy. In patients starting nucleos(t)ide analogue therapy, the use of lamivudine is not preferred if long-term antiviral treatment is expected due to the high risk of antiviral resistance against this drug. Of the currently licensed nucleos(t)ide analogues, entecavir has the lowest risk of antiviral resistance (compared with lamivudine, adefovir and telbivudine), while suppression of viral replication seems most profound with either entecavir or telbivudine.

The recommended duration of treatment with PEG-IFN is one year for both HbeAg-positive and HbeAg-negative patients. In HbeAg-positive patents, nucleos(t)ide analogue therapy should at least be continued until HbeAg seroconversion and a decline in HBV DNA to below 400 c/ ml (80 iU/ml) has been achieved and maintained for six months during therapy. Whether nucleos(t) ide analogue therapy can be safely discontinued in Hbe Ag-negative patients is unknown; usually prolonged or indefinite antiviral treatment is necessary Patients receiving PEG-inf should be monitored once a month, while three monthly monitoring suffices for those receiving nucleos(t)ide analogues. Genotypic analysis of the HBV polymerase is indicated if an increase in serum HBV DNA of at least 1 log10 c/ml (iU/ml) compared with the nadir value is observed during nucleos(t)ide analogue therapy. Antiviral therapy should be changed as soon as possible in case of confirmed genotypic resistance. Adding a second antiviral agent seems beneficial over switching to another agent. With the availability of multiple new antiviral drugs for the treatment of chronic hepatitis b, effective treatment is now possible for more patients and for longer periods. However, the complexity of HBV therapy has also increased. Nowadays, virtually all chronic HBV-infected patients can be effectively managed, either by inducing sustained off-treatment response or by maintaining an on-treatment response.

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**Peter Karayiannis, Ph.D., FRCPath**
Imperial College
London, UK

Professor Karayiannis got his BSc in Microbiology from Liverpool University in 1976 and his Ph.D. in Microbiology from the same university in 1980. He is a member of several organizations and societies (e.g. The Society for General Microbiology, The Institute of Biomedical Sciences, The Royal College of Pathologists, American Society for Microbiology, Member of the European and Hellenic Associations for the Study of the Liver) and also European Editor of the Journal of Viral Hepatitis, Member of the editorial board of the Journal of Hepatology, Member of the editorial board of the World Journal of Gastroenterology, Member of the Scientific Evaluation Committee of the Institute of Neurology in Cyprus, Patron of the Leukaemia Society, Ex-President of the Hellenic Medical Society and Ex-President of the Association of Cypriot Scientists and Professionals. He has published more than 200 original articles, reviews and chapters in books.

## Hepatitis B Virus and Antiviral Resistance to Nucleos(t)ide Analogues.

Peter Karayiannis, Ph.D., FRCPath.

Chronic carriers of the hepatitis B virus (HBV) have an increased risk of developing cirrhosis and hepatocellular carcinoma, 2-3 decades after exposure to the virus. Antiviral treatment offers the only means of preventing this progression. Immune modulators such as interferon have been in use for this purpose since the early 1980s. Treatment response rates however, measured in terms of HBV-DNA suppression to undetectable levels, have been low, ranging from 40% in HBeAg- down to 20% in anti-HBe-positive patients. Treatment duration is restricted to only one year. In recent years, nucleos(t)ide analogues, which mimic natural nucleosides have been introduced for the treatment of chronic HBV infection over periods longer than one year. They are incorporated into newly synthesised HBV-DNA causing premature chain termination. Their use over many years leads to persistent suppression of HBV-DNA replication and therefore protracted amelioration of the liver disease. There are currently five licensed drugs in use and they include lamivudine, adefovir, entecavir, telbivudine and tenofovir. Long-term usage of these drugs has resulted in the development of resistance through amino-acid substitutions that affect functional domains of the viral polymerase, which may precipitate virological and biochemical relapses. The frequency of these mutations is dependent on the genetic barrier of each drug which can be low as in the case of lamivudine to high with entecavir. The effect of these mutations on the replication efficiency of the virus, including compensatory mutations, cross resistance in determining switch-over to an alternative drug and future prospects, will be discussed and analysed during the presentation.

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## The Role of HBeAg in the Natural History of Chronic Hepatitis B Virus Infection

Peter Karayiannis, Ph.D., FRCPath.

The natural history of chronic hepatitis B virus (HBV) infection is characterised by four well defined phases which are known in turn as the immune tolerant, immune clearance, the non-replicative and the reactivation phases. In the immune tolerant phase, the virus replicates at high levels, liver histology shows minimal changes and as a result, transaminase levels are normal to slightly elevated. The patient is positive for HBeAg and as this protein exerts a tolerogenic effect, the virus is not recognised by the immune system. In the immune clearance phase, HBeAg levels begin to fall leading to a gradual awakening of the immune response. As a result, there is evidence of necroinflammation in the liver and transaminase levels rise, whilst HBV-DNA levels begin to fall. The fall in HBeAg levels is due to the appearance of the precore and core promoter variants, which during this period are responsible for the abrogation or the very much reduced levels of HBeAg, respectively. These variants may become selected at the ensuing seroconversion to anti-HBe, whilst the wild-type virus is cleared. This heralds the non-replicative phase of the disease with HBV-DNA detectable only by nested PCR. In the reactivation phase, the precore and core promoter variants become dominant and are responsible for the characteristic fluctuations in HBV-DNA and transaminase levels seen in this phase. In the absence of the tolerogenic effect of HBeAg, the core protein comes under immune pressure leading to the appearance of immune escape mutations. The significance of these and impact on subsequent liver disease outcome will be aired during the presentation.

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**Hubert E. Blum, M.D.**
Freiburg
Germany

Professor Blum began his study of medicine at the University of Freiburg in 1965 and attained the position of Full Professor (C4) at the same university in 1991. He is presently Chairman of the Department of Medicine at the University Hospital in Freiburg/ Germany and Clinical Director of the Division of Gastroenterology, Hepatology, Endocrinology and Infectious Diseases.

His main research interests are in the field of viral hepatitis B and C, including hepatocellular carcinoma (HCC). His major contributions are in the area of the molecular virology of hepatitis B virus (HBV) and hepatitis C virus (HCV), the molecular and immunological pathogenesis of hepatitis B, hepatitis C and HCC and the development of in vitro and in vivo models of HBV and HCV infection as well as HCC development. Further, his research unit is very active in developing novel therapeutic and preventive strategies, including molecular therapies for hepatitis B and C by antisense oligonucleotides, ribozymes and dominant negative mutants, HCC therapy or prevention by DNA immunization and the use of HCV pseudoparticles for vaccination against HCV infection. He has more than 250 peer-reviewed full papers, more than 250 basic science and clinical reviews, about 50 letters and editorials and more than 120 book chapters. He is a member of several academies (e.g. German Academy of Sciences Leopoldina, Academy of Sciences in Heidelberg, European Academy of Sciences and Brazilian Academy of Medicine) organizations and committees (e.g. WHO Consultant, Vice-President of the Federation of the European Academies of Medicine (FEAM), German-Chinese Society of Medicine...) and editorial board of national and international journals (e.g. Digestion, Hepatology, Deutsche Medizinische Wochenschrift, Viral Hepatitis Reviews, World Journal of Gastroenterology, Hepatobiliary & Pancreatic Diseases International and BMC Gastroenterology).

His research activities are documented in more than 400 scientific papers in leading international journals (Science, Mol Cell, J Clin. Invest, Proc Natl. Acad. Sci. USA,

New Engl. J Med, Lancet, Gastroenterology, Hepatology, J Virol. and others) and his scientific accomplishments have been recognized by numerous appointments, honours and awards.

# Non-surgical Treatment of Hepatocellular Carcinoma

Hubert E. Blum, M.D.

**Introduction:** Hepatocellular carcinoma (HCC) is one of the most common malignant tumors world-wide. The incidence ranges from <10 cases per 100,000 population in North America and Western Europe to 50-150 cases per 100,000 population in parts of Africa and Asia where HCC is responsible for a large proportion of cancer deaths. However, a rise in the incidence of and mortality from HCC has recently been observed in most industrialized countries. The major risk factors for HCC development are well defined and include among others chronic hepatitis B and C, alcohol use, hemochromatosis, overweight in males, diabetes mellitus. Some of the multiple steps involved in hepatocarcinogenesis have been elucidated in recent years. However, no clear picture of how and in what sequence these factors interact at the molecular level has emerged yet.

**Therapeutic options:** The appropriate choice of the therapeutic modality depends on the stage of the HCC, e.g., based on the Barcelona Clinic Liver Cancer (BCLC) staging, and comorbidities. In general, the therapeutic options fall into 2 main categories: surgical (resection, liver transplantation) and non-surgical interventions. The surgical options are resection and in selected cases liver transplantation. Since the majority of patients presents with advanced disease at the time of diagnosis and/ or with comorbidities that do not allow a surgical intervention, non-surgical strategies are of major importance in clinical practice and include: (1) percutaneous approaches, incl. percutaneous ethanol injection (PEI) and radiofrequency thermal ablation (RFA), (2) transarterial interventions, (3) radiation therapy and (4) drugs as well as experimental strategies, incl. gene and immune therapies.

**Percutaneous interventions:** Percutaneous interventions are the best options for small unresectable HCC. Apart from PEI and RFA, microwave-heat induced thermo therapy (HiTT), laser induced thermo therapy (LiTT), or cryoablation are less frequently used options. Interestingly, recent evidence suggests that RFA and resection are equally effective in patients with small HCC (> 2cm), RFA being

much less invasive and having a lower risk of a local recurrence. Recently, it has been shown that the combination of RFA with transarterial chemoembolization (TACE) ís more effective than either intervention alone (see below).

**Transarterial interventions:** These include transarterial embolization (TAE), transarterial chemoperfusion (TAC) and transarterial chemoembolization (TACE). In recent studies the combination of TACE and PEI/ RFA improved patient survival. Further, the transarterial application of doxorubicin drug-eluting beads enhanced the effect of RFA. For TACE patient selection is most important in order to be of benefit to the patients. In general, this intervention should be restricted to patients with liver cirrhosis Child A because in patients with more advanced cirrhosis survival is determined by the underlying liver cirrhosis rather than the HCC. In addition, in advanced cirrhosis TACE may cause liver failure.

**Radiation therapy:** While radiation therapy plays a minor role in the treatment of HCC to date, high dose proton beam radiotherapy, external beam radiation as intensity modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) as well as the selective intraarterial radiation therapy (SIRT) with 90Yttrium microspheres are being explored in clinical trials in patients with unresectable HCC, also with the intention to downstage the disease or to bridge to liver transplantation.

**Drugs:** To date sorafenib is the only drug approved for the treatment of HCC. It is a multikinase inhibitor which effectively blocks the raf pathway, resulting in a block of apoptosis resistance, angiogenesis, proliferation and invasion/ metastasis. In a clinical trial, sorafenib prolonged overall survival with acceptable toxicity. Nevertheless, it cannot be considered a routine therapy for advanced HCC, given the limited efficacy, the potentially severe side effects and high costs. Therefore, several small molecule tyrosine kinase inhibitors (nibs) as well as monoclonal antibodies (mabs) are being evaluated in clinical trials either alone or in combination with other drugs.

**Summary and perspectives:** Apart from surgical intervention, an increasing number of non-surgical therapeutic options are now available. Depending on the stage of the HCC, percutaneous and transarterial interventions, radiation therapy as well as drugs can result in an improved survival of many patients, in some patients even in a cure. New technologies, including gene expression profiling and proteomic

analyses, should allow to further elucidate the molecular events underlying HCC development and to identify novel diagnostic markers as well as therapeutic and preventive targets.

## Treatment of Chronic Hepatitis C

Hubert E. Blum, M.D.

**Introduction:** The hepatitis C virus (HCV) is a single-stranded RNA virus that belongs to the Flaviviridae family. Risk factors for HCV infection are transfusion of blood and blood products and transplantation of solid organs from infected donors, injecting drug use, unsafe therapeutic injections and occupational exposure to blood (primarily contaminated needle sticks). Transfusion associated HCV infection has been virtually eliminated in those countries that implemented routine HCV testing. Persistence of HCV infection occurs in the majority of HCV-infected individuals. Indeed, acute hepatitis C resolves spontaneously only in about 10-40% of cases. Chronic hepatitis C is characterized by the persistence of elevated AST/ ALT levels and the presence of anti-HCV antibodies and HCV RNA in serum. Most chronically HCV infected patients are asymptomatic, but some complain of nonspecific symptoms such as increased fatigue or abdominal discomfort. Severe complications and death usually occur only in persons with HCV-related cirrhosis, estimated to develop in 15-20% of patients. The natural course of HCV infection is highly variable. Factors that contribute to clinical progression include alcohol intake, coinfection with HIV or HBV, male sex and older age at infection.

**Clinical presentation and natural course:** Chronic hepatitis C is symptomatic also in only a minority of infected individuals. Most patients become symptomatic only after the development of complications of HCV-related liver cirrhosis such as hepatocellular carcinoma (HCC), ascites, jaundice, gastrointestinal hemorrhage or encephalopathy that are associated with significant morbidity and mortality. The aim of antiviral treatment of patients with chronic hepatitis C, therefore, is to prevent the development of liver cirrhosis and its complications. Since the natural course of chronic HCV infection is not always unfavorable and since current standard therapy is expensive and has numerous side effects, the decision to treat or not to treat must be made on an individual basis. In general, therapy may be deferred in patients with mild chronic hepatitis and low probability of response. By contrast, treatment is indicated in patients with progressive or more advanced

disease.

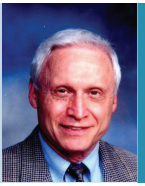
**Therapeutic options:** The current standard treatment of chronic hepatitis C is the combination of the subcutaneous injection of PEG-IFNα2 once per week and oral ribavirin daily. Recent evidence indicates that PEG-IFNα2a (Pegasys®) and PEG-IFNα2b (PegIntron®) have similar efficacies. Today, the treatment modalities for chronic hepatitis C are highly individualized and depend on the HCV genotype, the pretreatment HCV RNA level and the dynamics of HCV RNA loss during antiviral therapy. The duration of treatment is in general 24 weeks for genotypes 2 and 3 and 48 weeks for genotypes 1 and 4. The duration of treatment can be individualized on the basis of the baseline viral load and the dynamics of the virological response. In case of a very early or early virological response, the duration of treatment can be reduced to 12-16 weeks for genotypes 2 and 3 and to 24 weeks for genotype 1, respectively. In case of a delayed response, the treatment should be extended for patients infected with genotype 1 from 48 weeks to 72 weeks. On the other hand, in patients infected with genotype 1 antiviral treatment can be terminated if the loss of HCV RNA at week 12 of therapy is <2 logs. Overall, the SVR is 75-90% for patients infected with HCV genotypes 2 and 3 and 40-50% for genotypes 1 and 4. Therefore, novel antiviral strategies are needed to improve the SVR, especially for patients infected with HCV genotype 1, e.g., NS3-4A protease inhibitors, such as telaprevir, helicase or RNA polymerase inhibitors and different immune therapies. Two recently published randomized trials indeed showed that telaprevir significantly improves the SVR from 41% to 61% and 46% and 69%, respectively. In the near future, therefore, we can expect an improved SVR also for patients infected with the difficult-to-treat HCV genotypes 1 and 4.

**Prevention:** For the prevention of HCV infection there is no commercial vaccine available yet. Therefore, at present the strict observation of hygienic measures, abstention from intravenous drug use, tattooing, piercing or intranasal drug use as well as reduction of use of blood or blood products are the major possibilities to prevent HCV infection.

**Summary and perspectives:** HCV is a well characterized RNA virus that causes acute and chronic hepatitis C. The currently established therapy is highly individualized and results in a SVR in 95% of patients with acute HCV infection and in 75-90% of patients with chronic hepatitis C infected with genotypes 2 and 3. In patients infected with HCV genotypes 1 and 4, however, the SVR

is only 40-50%. Novel therapeutic options, such as HCV protease, helicase and polymerase inhibitors should result in improved SVR in these patients. Further, a T cell vaccine has been shown to protect chimpanzees from chronic HCV infection. This and other vaccines may be further developed to become commercially available for the prevention of HCV infection in individuals at risk.

**F. Blaine Hollinger, M.D.**
Baylor College of Medicine
Houston, Texas



Professor Hollinger has been actively involved in hepatitis research since joining the Department of Molecular Virology and Microbiology at Baylor College of Medicine in Houston, Texas in 1968 and the Department of Medicine (GI Section) in 1981. He is currently Professor of Medicine, Molecular Virology & Epidemiology and Director of the Eugene B. Casey Hepatitis Research Center. He has been an advisor and consultant on program projects, grants, and contracts related to viral hepatitis for the National Institutes of Health and the Food and Drug Administration (FDA) and a consultant to the Transfusion Transmitted Diseases Committee (TTD) of the American Association of Blood Banks (AABB). He served on the Blood Products Advisory Committee (BPAC) for the FDA from 1995-2000, becoming its Chairman in 1997, and in 2009 accepted a reappointment to BPAC.

Professor Hollinger is an experienced researcher and hepatologist who has engaged in number of national, multicenter clinical trials and basic scientific projects related to viral hepatitis over the past 35 years. He has published over 250 articles, books and chapters in this field that includes the characterization and diagnosis of viral hepatitis agents, development of sensitive immunological assays, prophylaxis of hepatitis A and B, vaccine development, therapy of hepatitis B and C, studies on the immunopathogenesis and natural history of viral hepatitis, and the epidemiology of blood-borne pathogens and posttransfusion hepatitis.

## Hepatitis B and Transfusion Medicine: Unexpected Donor Screening Events

F. Blaine Hollinger, M.D.

It is well recognized that the transfusion of blood containing hepatitis B surface antigen (HBsAg) is associated with the development of posttransfusion hepatitis B. This risk of acquiring an hepatitis B virus (HBV) infection underwent a dramatic reduction with the advent of HBsAg screening of blood donors in the 1970s in conjunction with the implementation of an all-volunteer donor population. Subsequent studies in the 1980s and 1990s implicated high-titered, anti-HBc positive blood that lacked HBsAg and anti-HBs, in the transmission of HBV. This prompted the addition of antibody to hepatitis B core antibody (anti-HBc) screening of blood donors in those countries where HBV is not endemic. Later, it was discovered that the units of blood from these anti-HBc reactive, HBsAg-negative donors sometimes contained HBV DNA. With improvements in HBV DNA amplification technology, we are now approaching single genome detection capabilities. When coupled with enhancements in the sensitivity and specificity of assays for anti-HBc and HBsAg, previous misinterpretations are being revised, and we now have a better understanding of risk.

Most experts would concur that blood collected during the early seronegative window period of HBV (when only HBV DNA is present) is highly infectious. This risk appears to be greater during the expansion phase of HBV DNA than that which is seen during the recovery phase of acute disease when anti-HBs may complex with the virus leading to modulation of the disease process and a reduction in the risk of transmission despite detection of HBV DNA.

Following the uneven implementation of ultrasensitive nucleic acid testing of blood donors in various regions of the world, the residual risk of HBV was found to be inconsistent with incidence/window period rates varying from 1:350,000 in the US based on data from the American Red Cross using PRISM HBsAg, to 1:50,000 in Japan and to 1:5000 or lower in Southeast Asia and Pakistan. As interest in evaluating the residual yield of HBV DNA positive donations in HBsAg

and anti-HBc negative donor samples (seronegative window period donations) has intensified, some unexpected findings have emerged. For example, from January 2008 to January 2009, the American Red Cross (ARC) tested 3,694,858 units of blood for HBV DNA either in minipools of 16 donations (84.4%) or as individual donations (16.6%) (Stramer et al, 2009). HBV DNA was detected in 9 donors (1:410,000) with only one of these (11%) requiring individual testing (ID-NAT) for detection (i.e., not detected by minipool testing). Enrollment and follow-up data were not available for 2 of the donors. Of the 7 remaining donors in whom data were available, 5 were in vaccinated individuals. Four of these were anti-HBs positive in the index donation (anti-HBs concentrations from 3-43 IU/L) whereas one became anti-HBs positive within 45 days. Viral loads in these index donations were low and ranged from 100-200 copies/mL (~16-33 IU/mL). Six of the 7 donors became IgM anti-HBc positive and only one was a first-time donor. Of interest was the fact that 5 of the donors were subsequently discovered to have sexual partners who were HBV chronic carriers with HBV DNA viral loads >108 copies/mL in the 4 samples that were available for testing. Among the 7 genotyped donor isolates, 4 represented genomes not typically found in the US (B2, C2, D3, F1; all from vaccinated donors) while 3 were primarily of US origin (A2). The infected partners associated with 4 of the donors had the same subgenotype, and full genome sequences verified the close relationship between these isolates.

Among the 5 vaccinated donors who were followed for 119-320 days, none developed ALT levels above 19 U/L or complained of symptoms and all became HBV DNA negative, thereby confirming the effectiveness of vaccination in preventing clinical disease. Only 3 of the 7 HBV DNA positive donors developed detectable HBsAg. A group in Taiwan (Wang et al, 2002) observed the development of HBV DNA in three vaccinated children within a week after receiving blood that resulted in an aborted subclinical infection similar to what was seen in the ARC donors. It is noteworthy that both unvaccinated ARC donors who were followed for at least 228 days developed significant ALT abnormalities (119 U/L and 640 U/L).

An important issue is whether anti-HBs in conjunction with a low viral load in a donor is sufficient to prevent transmission of HBV to a recipient. There are several studies which suggest that this is a rare event. Mosley et al (1995) found no HBV transmission associated with a donor whose anti-HBs values were at least comparable to a level of 15 IU/L regardless of anti-HBc status. Satake et al (2007) detected no infections in 22 HBV DNA positive components that contained

anti-HBs compared to 10 infections that occurred among 37 components devoid of anti-HBs (27%). Moreover, Aach et al (1974) were unable to detect any transmission from HBV immune donors. Dreier and coworkers (2004) and Gerlich (2006) failed to document transmission of HBV from donors who were HBV DNA positive at levels <260 IU/mL, but whose blood contained significant levels of anti-HBs (>1000 IU/L). Conversely, low levels of anti-HBs (<75 IU/L) in HBV DNA containing blood may carry a risk of transmission leading to acute hepatitis in a recipient (Levicnik-Stezinar et al, 2008). Fortunately, fulminant hepatitis is virtually unheard of following posttransfusion hepatitis B.

In summary, nucleic acid testing is capable of detecting HBV DNA in the absence of HBsAg and anti-HBc in a limited number of donors with a yield that approaches ~1:410,000 donations. The issue of transmissibility from window period donations exists at some finite level in unvaccinated donors in which the yield is ~1:690,000. The public health benefits of HBV NAT in blood banks remain unknown but are likely to be marginal at considerable cost in the US and Europe, but necessary in countries where the disease is endemic.

**Dr. Daniel Lavanchy, M.D.**
World Health Organization (WHO)
Geneva, Switzerland

He has obtained a Swiss federal diploma in medicine from University of Basel, Switzerland in 1975 and Doctorate in medicine from the same university in 1977. In 1987, he became a Specialist FMH in Internal Medicine and in Allergy and Clinical Immunology. From 2003 to 2005 he followed courses in École des Haute Études Commerciales (HEC) & Faculté de Biologie et de Médecine, Université de Lausanne, Switzerland, to obtain his Master degree in Health Economics and Management (MHEM). He has been in various positions such as Chef de secteur de recherche, Division d'Immunologie et Allergie (Prof. P.C. Frei) (1983-1995), Chief Viral Diseases, World Health Organization (WHO/OMS), (1995-2001) and Project Leader, World Health Organization (WHO/OMS) (2001-present).He is experienced in crisis management including supervision of epidemic investigations and implementation of emergency prevention and control activities, management of communications to the scientific community, public health officials and to the media, evaluation of laboratory bio-safety facilities (former head of the WHO Global Influenza Surveillance Program) and involved in the revision of the UN model regulations for the transport of infectious substances (UNCETDG), specifically on the transport of infectious substances including diagnostic specimens. He was in charge of the establishment of the first WHO recommendations for the use of the annual influenza vaccine, the first WHO global influenza pandemic plan, the first WHO annual recommendations for the influenza vaccine composition for the Southern Hemisphere, the global surveillance network for influenza (FluNet), and the global surveillance network for antiviral resistance monitoring of influenza viruses for the adamantanes and neuraminidase inhibitors.

His advocacy led to increased awareness among governments and health care personnel and to increased political and financial commitment by governments in the field of global surveillance for the management of communicable diseases, with special skills in bio-safety, laboratory diagnosis, influenza, smallpox and viral hepatitis.

He has been involved in the development of several national or international public health guidelines (e.g. hepatitis B immunization, hepatitis B & C treatment, influenza vaccine use, bio-safety standards); assistance to developing country institutions to improve their diagnostic, laboratory and epidemiological capacities, in charge of the publication of the worldwide prevalence of hepatitis C, and of the discovery of the role of anti-schistosomal mass injection treatment in the spread of hepatitis C virus infection in Egypt, as of today the largest iatrogenic incident reported.

He has more than twenty years of experience in clinical wards of different hospitals in Switzerland, in internal medicine, emergency medicine, surgery (mainly abdominal and traumatology), intensive care unit medicine, rheumatology (including physiotherapy and rehabilitation medicine), immunology and allergy, and medicine of the elderly, as well as supervision of routine clinical laboratory services and of clinical diagnostic and research projects and more than two years of experience in the pharmaceutical industry.

He has been a scientific reviewer for international journals and reviewer of projects and facilities in the field of viral hepatitis and influenza for WHO; governments and other scientific institutions. He has published more than 100 scientific articles and been author of chapters in reference books

## Approach to Prevention of HAV and HBV

Dr. Daniel Lavanchy, M.D.

In countries where hepatitis A is highly endemic, exposure to hepatitis A virus (HAV) is almost universal before the age of 10 years, and large-scale immunization efforts are not needed. In countries with high rates of disease in specific populations, vaccination of those populations against hepatitis A may be recommended. In areas of intermediate endemicity, where transmission occurs primarily from person to person in the general community (often with periodic outbreaks), control of hepatitis A may be achieved through widespread vaccination programmes.

Hepatitis B virus (HBV) is one of the world's most widespread infectious agents and the cause of millions of infections each year. Between 500 thousand and 1.2 million people die each year from chronic infection-related cirrhosis, hepatocellular carcinoma (HCC) or from acute hepatitis B. Hepatitis B vaccine provides protection against infection and its complications including liver cirrhosis and HCC. It is therefore, the first vaccine against a cancer, the first vaccine protecting from a sexually transmitted infection, and the first vaccine against a chronic disease ever licensed. The control and the eventual elimination of HBV infection are possible with the appropriate use of hepatitis B vaccines, and this will reduce significantly the disease burden and its associated costs.

# Treatment of chronic hepatitis B in Resource Constrained Public Health Settings

Daniel Lavanchy, M.D.

Worldwide, an estimated two billion people have been infected with the hepatitis B virus (HBV), and more than 350 million have chronic (long-term) HBV infections. An estimated 600 000 persons die each year due to the consequences of acute or most often chronic hepatitis B virus infection (WHO Fact Sheet No 204). HBV is estimated to account for 53% of all cases of hepatocellular carcinoma (HCC), the most frequent type of liver cancer. Therefore HBV infection is a major public health threat on a similar scale of magnitude as HIV, malaria and tuberculosis.

We discuss the feasibility of providing treatment for persons with chronic HBV infection in resource-constrained settings and outlines for a global strategy for increasing access to treatment to decrease hepatitis B-related mortality and morbidity.

The goal of HBV therapy is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC, and death, and that this goal can be achieved if HBV replication can be suppressed in a sustained manner, the accompanying reduction in histological activity of chronic hepatitis lessening the risk of cirrhosis and decreasing the risk of HCC. Two different types of drugs can be used for HBV treatment. 1) Interferon alpha and its pegylated form. 2) Reverse transcriptase inhibitors: in the past decade, several new oral nucleoside analogue antiviral agents, all chain terminators, have been developed for the treatment of hepatitis B virus infection. They include emtricitabine, telbivudine, entecavir, adefovir and tenofovir. However the cost of several agents and licensing or distribution agreements preclude their use or optimum use in many endemic regions.

## Lessons from HIV control

In the past few years, various organizations have developed comprehensive

programmes to reduce the substantial mortality rate from HIV especially in countries in Africa. In addition to measures to prevent HIV infection, four key strategies have been used to reduce the death rate from HIV: 1) identification of infected persons by screening, 2) determining candidates for antiviral therapy by ascertaining HIV RNA concentrations and CD4 cell counts, 3) Selecting appropriately effective combinations of antiretroviral agents based on antiviral resistance patterns, efficacy and cost, and 4) monitoring patients for antiviral resistance. These programmes have had dramatic effect in preventing death from chronic HIV infection in areas where they have been introduced and in returning persons previously ill with AIDS to a state of health where they can again care for their families, attend school, or resume working.

In recent years, many resource constrained countries, with international support, have provided considerable effort and resources to improve the infrastructure for HIV diagnosis and treatment programmes. The existing infrastructure for the HIV programmes could be adapted to accommodate both HBV and HIV screening and treatment programmes.

# Epidemiological Impact of HBV Vaccination in Young Adults: The Italian Experience

Rosa Cristina Coppola, M.D.

Hepatitis B virus (HBV) is one of the most widespread infectious agents of the world and the cause of millions of infections each year (1). Between 500 thousand and 1.2 million people die each year from chronic infection- related cirrhosis, hepatocellular carcinoma (HCC) or from acute hepatitis B (2).

The prevalence of chronic HBV infection is low (<2%) in the general population in Northern and Western Europe, North America, Australia, New Zealand, Mexico, and Southern South America, it is intermediate (2%–7%) in South Central and Southwest Asia, Israel, Japan, Eastern and Southern Europe, Russia, most areas surrounding the Amazon River basin, Honduras, and Guatemala. The prevalence of chronic HBV infection is high (>8%) in all Countries in Africa, Southeast Asia, the Middle East (except Israel), Southern and Western Pacific islands, the interior Amazon River basin and certain parts of the Caribbean (Haiti and the Dominican Republic) (3).

In areas of high endemicity, the most common route of transmission is perinatal or the infection is acquired during the pre-school years, whereas in areas of intermediate endemicity, transmission is either perinatal or horizontal. In areas of low endemicity, most HBV infections are acquired by horizontal transmission in early adult life, i.e. through intravenous drug use or unprotected sexual activities (4). The route of transmission has important clinical implications, because there is a very high probability (70–90%) of developing chronic hepatitis B (CHB) if the infection is acquired perinatally or in the pre-school years (5).

In 1991, WHO's Global Advisory Group of the Expanded Programme on Immunization recommended that hepatitis B vaccine be integrated into national immunization programs in all countries with a hepatitis B carrier prevalence of 8% or greater by 1995 and in all countries by 1997 (6).

Italy had an intermediate level of endemicity for Hepatitis B virus infection in the 1970s and 1980s when the average rate of HBsAg carriers in the italian population was 2,5% (up to 10% in some areas of Campania, Puglia and Lombardia). Among pregnant women, 2,4% were HBsAg carriers in 1984-86 (7).

Vaccination against hepatitis B became mandatory for all newborns and adolescents starting from 1991. At the end of 2003 or 12 years after the implementation of such policy of immunization, vaccination of adolescents was stopped, and that of infants was maintained (8).

Our study aimed to evaluate the prevalence of HBV infection in a group of 629 subjects, aged 0 – 27 years, which were supposed to have received the vaccine against hepatitis B according to the policy of immunization started from 1991. Anti-HBs, anti-HBc antibodies and HBsAg were detected, by commercially available assays, in samples of serum collected between 2005-2009. The overall prevalence of HBsAg was 2.1% (13/629). It was higher than the expected but in the last analysis, when we considered every single case, it emerged that 5 of them didn't receive the vaccine because they were born in the early '80 from HBsAg carrier mothers; one of them was adopted from Romania when he was 5 years old and only one of them, an HIV-HBV coinfected child born from HBsAg positive mother, was submitted too late to the vaccination and he didn't riceived HBIG at birth in addition to vaccine.

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## Epidemiology of Hepatitis A in Italy

Rossa Christina Coppola

The hepatitis A Virus (HAV) is a picornavirus, classified in the new gender of Hepatoviruses. HAV is one of the two viruses that cause hepatitis (together with the hepatitis E virus, HEV) which can be transmitted through water and food and direct person-to-person contact. Hepatitis A could also be transmitted via food contaminated by infected food-handlers, uncooked foods, or foods handled after cooking; hygiene is therefore important in their control. Hepatitis A has also caused outbreaks transmitted through injecting or non-injecting drug use.

Both hepatitis A and E are found worldwide. Hepatitis A is particularly frequent in countries with poor sanitary and hygienic conditions (in Africa, Asia, and Central and South America). Countries with economies in transition and some regions of industrialized countries where sanitary conditions are sub-standard are also highly affected, e.g. in southern and eastern Europe and some parts of the Middle East.

The disease may range from mild (lasting 1-2 weeks) to severe disabling disease (lasting several months). Nearly all patients recover completely with no long-term effects. Fatal cases due to fulminant acute hepatitis are rare. As the severity of hepatitis A is related to age (in children under the age of 6 only 50% exhibit clinical manifestations and less than 10% become jaundiced, a percentage that rises to 70-80% in adults) the changes in the epidemiology of HAV have brought about a new medical threat in the form of severe cases of hepatitis A in adulthood. In areas highly endemic for hepatitis A, most infections occur during early childhood and the majority of cases may not show any symptoms.

With improvement in economic and living conditions of the communities, the age of acquiring hepatitis A virus (HAV) infection is shifting from early childhood to adolescence and young adulthood. Such epidemiological shift leads to an increased incidence of symptomatic HAV infection, including heightened risk of liver failure. Moreover, the improvement of socio-hygienic standards in the developed world

has much decreased the circulation of HAV in the last 20 years. The reduction in the circulation of the HAV, with shifts from high-intermediate to intermediate-low HAV endemicity in many industrialized countries implies that a rising number of adults are more susceptible to the infection than in the past and epidemics may occur in previously "immune areas". (Del Re R, 2000; Pontrelli G, 2008). A large outbreak of hepatitis A occurred in the middle of the "90 in Apulia, a southern area of Italy at previous high HAV endemicity; the outbreak investigation showed a strong association between illness and consumption of raw seafood (Malfait P, 1996; Lopalco 1997).

Data from India indicate that the population is no longer homogeneous for its HAV exposure profile. Occasional outbreaks of HAV and higher proportions of symptomatic cases are reported amongst older children and adults from different regions of the country (Mathur P, 2008).

In Italy the incidence of hepatitis A follows an increasing North to South gradient. The steadily declining prevalence of immunity to HAV has reached 5% or less among the younger age groups in urban areas (Gentile C, 2009). The comparison of anti HAV sero-prevalence during three different periods in Cagliari showed a dramatic decrease in HAV immunity, particularly in younger classes. Recently, an outbreak of hepatitis A occurred as a consequence of contaminated seafood. The change of epidemiological pattern in many western and industrialized areas poses the question on the vaccine use in prevention strategy.

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**Mitra Mahdavi-Mazdeh, M.D.**
Tehran University of Medical Sciences
Tehran, I.R. Iran

Associate Professor of Nephrology in the Department of Internal Medicine, Tehran University of Medical Sciences, has been Head of the Center for Research & Development and Vice Chancellor of Research since 2007; she is also the Director of Research Center for Transplantation and the Iranian Tissue Bank Her major research interests include the epidemiologic features of ESRD, especially transplantation in developing countries and CKD. She has published 11 domestic and international papers.

## Hepatitis B and C in Dialysis Units in I.R. Iran and Hepatitis B Vaccination in HD Patients

Mitra Mahdavi-Mazdeh, M.D.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most important infections transmitted by the parenteral route in patients receiving maintenance dialysis. The prevalence varies markedly from country to country. The aim of this study is to review the efficacy of the strategies to reduce the incidence of these infections and the trend of results in I.R. Iran. As a routine, all hemodialysis patients in I.R. Iran give blood samples for assessment of serum HBSAg, HBS Abs, and HCV Abs at least biannually. The data are collected in the Ministry of Health.

There is an increasing prevalence/incidence of end-stage renal disease (ESRD) in I.R. Iran, from 238/ 49.9pmp in 2000 to 357/63.8pmp in 2006. The prevalence of positive HBSAg and HCV Abs decreased from 3.8% and 14.4% in 1999 to 2.6% and 4.5% in 2006, respectively. Regarding the genotype distribution in I.R. Iran, no one was found with genotype 2. As for decreasing HCV and HBV infection, the main successful strategy was implementation of compulsory thorough blood donor screening in I.R. Iran since 1995 and reduction of transfusion number due to common erythropoietin administration led to decreasing occurrence of HCV and HBV infection in hemodialysis and thalassemic patients.

In a study in Tehran Province on 2630 HD patients in 2005, 55% percent of patients were vaccinated for hepatitis B and 2.4, 8.4 and 0.1% were HBSAg, HCVAb and HIV Ab positive, respectively. Nearly 70.3% of the population was HBSAb positive. Although vaccination is freely available to all, 30% of patients refused this treatment.

As a routine, all HBSAg positive patients are dialyzed on separate machines. In recent years, an increasing role has been assigned to hospital-transmitted infections (nosocomial). Hepatitis C virus can be transmitted by infected hands of the medical staff, hemodialysis machines, other medical equipments, or objects circulating between patients, e.g., swabs, plaster rolls, disinfection fluid bottles, dish trays, etc. Our next

strategy should be mandatory vaccination in dialysis centers and in the pre-ESRD period. Concerning HCV infection prevention, 2 approaches may be recommended: the first is decrease of duration of the hemodialysis period by possible early transplantation of suitable patients.

The next is a strictly enforced isolation policy for HCV-positive patients that may play a role in limiting HCV transmission in HD units, and universal precautions in dialysis units should be maintained under constant and close surveillance.

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**Behzad Einollahi, M.D.**
Baqiyatallah University of Medical Sciences
Tehran, I.R. Iran

Professor Einollahi began his study of medicine in 1982 and graduated in 1989 from Tehran University of Medical Sciences. He continued his studies in the same university to attain specialty in Internal Medicine in 1993 and subspecialty in Nephrology in 1995. He was a member of ERA-EDTA and has been a member of Iranian Society of Nephrology, Iranian Society of Organ Transplantation, Middle East Society of Organ Transplantation (MESOT) and International Society of Nephrology. Currently, he is a Professor of Internal Medicine /Nephrology at Baqiyatallah University of Medical Sciences, Tehran. He has published 82 papers in international journals and 54 in Iranian journals, 94 of which are indexed in PubMed and has presented 157 papers in international conferences as well as 49 in local conferences.

## Hepatitis B Virus Infection in Patients with End Stage Renal Disease

Behzad Einollahi, M.D.

The frequency of hepatitis B virus (HBV) infection is now low among patients with end-stage renal disease (ESRD) requiring renal replacement therapy such as hemodialysis in industrialized countries, but its incidence remains much higher within dialysis units of developing countries. Moreover, individuals with chronic kidney disease may be more likely to develop chronic infection once exposed to HBV.

The natural history of hepatitis B in patients on maintenance dialysis is still poorly distinguished largely because chronic HBV characteristically progresses slowly. Patients undergoing hemodialysis with chronic HBsAg carriage typically have mild or absent elevation of serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) levels and infrequently develop symptoms of hepatitis. Thus, the recognition of liver disease by biochemical liver tests can be ignored in hemodialyzed cases. Therefore, a long follow-up is required to appraise the key complications of chronic HBV infection, especially cirrhosis and hepatocellular carcinoma (HCC). On the contrary, the life expectancy of individuals on dialysis is shorter than in the general population. Morbidity and mortality rates due to liver disease are three to four times greater in hemodialyzed patients.

Controlling the spread of HBV infection within dialysis units has been an important goal in the management of patients with ESRD. Vaccination to HBV is recommended in all individuals on dialysis, but renal insufficiency is associated with a lower response to HBV vaccine.

In this lecture, we are going to talk about the epidemiology of HBV infection in the dialysis setting, its clinical presentation, effective measures for its control and antiviral therapy.

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**Fariborz Mansour-Ghanaei, M.D.**
Gilan University of Medical Sciences
Rasht, I.R. Iran

Professor Mansour Ghanaei is director of Gastrointestinal and Liver Disease Research Center (GLDRC) since its foundation in 1997 by him. He Obtained National Board of Internal Medicine in 1993 from Shiraz University of Medical Sciences and became an Assistant Professor of Guilan University of Medical Sciences (GUMS) from then. He completed his sub specialty of Gastroenterology in 2001 and in 2006 was appointed to a full professor position in the same university.

Professor Ghanaei established Gastroenterology and Hepatology fellowship course at GUMS. He has served in several official positions including: Vice Director of Clinical Education at the School of Medicine, GUMS; Vice Chancellor of Research, GUMS; Vice Chancellor of Education, GUMS and Chancellor of GUMS (2002-2006).

Professor Ghanaei is an experienced researcher and actively involved in 21 completed and 21 ongoing local and national projects. He has published 8 books, 40 international (ISI) and 30 national papers in creditable journals and presented 22 papers in international gastroenterology congresses.

## Interferon for Chronic Hepatitis B Virus Infection

Fariborz Mansour-Ghanaei, M.D.

**Introduction:** Chronic hepatitis B virus (HBV) infection is a serious liver disorder which may result in cirrhosis and hepatocellular carcinoma. It is an immense health problem globally that affects 300 million individuals or 5 percent of the world's population.

Interferons (IFN) have antiviral, anti-proliferative, and immunomodulatory effects. IFN-alfa (IFNa) and IFN-beta have predominantly antiviral effects, while IFN-gamma has more marked immunoregulatory but less potent antiviral activity.

IFNa was the first treatment approved for chronic HBV infection in most countries. More recently, pegylated interferon (pegIFN alfa-2a only in the US and pegIFN alfa-2a as well as pegIFN alfa-2b in many countries outside the US) was approved for treatment of chronic HBV.

**Efficacy of Standard Interferon:** Multiple studies have evaluated the efficacy of standard interferon in HBeAg-positive chronic HBV. The following benefits were found in a meta-analysis of studies comparing treatment with standard interferon for three to six months with placebo:

- More frequent loss of viral replication markers (HBeAg): 33 versus 12 percent with placebo
- More frequent loss of HBV DNA (by hybridization assay): 37 versus 17 percent
- More frequent loss of hepatitis B surface antigen (HBsAg): 7.8 versus 1.8 percent

The treated patients were also much more likely to seroconvert to anti-HBe and to show normalization in ALT levels.Treatment with standard interferon in patients who are HBeAg-, HBV DNA+, with elevated serum ALT is usually associated

with a decrease in serum HBV DNA and ALT levels, but relapse is common after cessation of treatment. A longer course of therapy (24 months) may be more effective in inducing a sustained response. Interferon treatment may reduce disease progression, although the beneficial effect is seen mostly among responders.

**Efficacy of Pegylated Interferon:** Approval of pegylated interferon alfa-2a was based upon two studies in HBeAg-positive and HBeAg-negative chronic HBV in which pegylated interferon was compared with lamivudine or combination therapy with pegylated interferon plus lamivudine. The following observations were made:

- HBeAg seroconversion was observed significantly more often with pegylated interferon compared with lamivudine at the end of follow-up (32 versus 19 percent).
- Persistent suppression of HBV DNA and ALT normalization in HBeAg-negative patients occurred more often with pegylated interferon compared with lamivudine (43 versus 29 percent, and 59 versus 44 percent, respectively).
- Combination therapy with lamivudine did not increase the rate of sustained response compared with pegylated interferon monotherapy, although it was associated with the greatest degree of on-treatment virus suppression of the three arms.
- Serious adverse events occurred in 4, 6, and 2 percent of patients receiving pegylated interferon monotherapy, combination therapy, or lamivudine monotherapy, respectively. Two patients in the lamivudine monotherapy group developed irreversible liver failure (one received a transplant and the other died) after cessation of treatment.

**Selection of Patients:** IFNa (whether standard or pegylated) should be considered in patients with chronic HBV infection (HBsAg positive for more than six months) who have evidence of active virus replication (HBeAg and/or high serum HBV DNA levels >20,000 IU/mL for HBeAg-positive patients and >2000 IU/mL for HBeAg-negative patients) and active liver disease (elevated serum ALT concentration and chronic hepatitis on liver biopsy). IFNa treatment is safe and can be effective in patients who have cirrhosis on liver biopsy but no clinical or biochemical evidence of decompensation.

**Dose Regimen:** Standard IFNa is usually administered as subcutaneous injections in doses of 5 million units (MU) daily or 10 MU three times a week for 16 weeks

in patients with HBeAg-positive. Lower doses have been claimed to be effective in some Asian studies, but the efficacy of these doses needs to be confirmed. One controlled trial suggested that extending therapy for up to 32 weeks in patients who remained HBeAg-positive at 16 weeks improved rates of subsequent HBeAg seroconversion. A longer course of treatment (one to two years) has been suggested for HBeAg-negative chronic HBV, but the optimal duration of treatment is unknown.

The manufacturer recommends that pegylated interferon should be given at a dose of 180 microG/week for 48 weeks for HBeAg-negative or positive chronic HBV. However, it is possible that a shorter duration of therapy for HBeAg-positive chronic HBV would be sufficient while the optimal duration of therapy for HBeAg-negative chronic HBV is uncertain.

## Predictive Factors for Response

**HBeAg positive:** Several factors have been identified that are associated with a favorable response to standard IFNa treatment of HBeAg-positive patients. These include:

- High pretreatment serum ALT level
- Low pretreatment serum HBV DNA level
- Adult acquired HBV infection
- Active liver histology
- Female sex
- HIV antibody negative
- Delta virus antibody negative
- HBV genotype B versus C and genotype A versus D

The first two factors, elevated ALT and low serum HBV DNA levels, are generally considered to be the most accurate predictors of response to standard IFNa among HBeAg-positive patients.

A number of predictors for response with pegylated interferon have also been described:

- Genotype (genotype A is associated with higher rate of HBeAg seroconversion

and HBsAg clearance than genotypes B, C, or D)
• Low viral load
• High pretreatment serum ALT level
• Absence of previous interferon therapy
• More marked decrease in the titer of HBeAg during treatment

HBeAg negative: The most important predictive factors for sustained response among HBeAg-negative patients treated with standard IFNa are long duration of treatment and early (less than four months) biochemical response. One study (in HBeAg-negative hepatitis) found that younger age and higher IgM anti-HBc titer were also associated with a higher rate of sustained response.

Predictors of response with pegylated interferon are still being established. One study found that a marked elevation in serum ALT (>10 times the upper limit of normal or more than 300 IU) levels during therapy was predictive of a normal ALT and histologic improvement six months after stopping pegylated IFN therapy.

Contraindications of Interferon Therapy: IFNa should not be used in patients with a history of suicidal tendency, active psychiatric or autoimmune illness, severe leukopenia or thrombocytopenia, concurrent severe systemic disorders, or decompensated cirrhosis.

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## Hepato-biliary Intervention

Hossein Ghanaati, M.D.

Advanced in interventional radiology has been changed deeply diagnostic and therapeutic techniques in this lecture; briefly these techniques explain and new horizon in hepato biliary intervention will discuss.

### 1- Liver biopsy:

There are significant changes and improvement in liver mass biopsy, including new navigation systems such as CT fluoroscopy system, dual navigation and transjugular liver biopsy.

Percutaneous liver biopsies are quick, safe procedures commonly performed in outpatient settings. Suction, cutting, and spring-loaded cutting needles with triggering mechanisms have all been safely used for this purpose (1, 2). Thus, the role of ultrasonography to guide percutaneous liver biopsy remains controversial. Use of ultrasound is not mandatory (3).

A transjugular approach to liver biopsy is often used in patients with a contraindication to percutaneous biopsy, when concomitant Transjugular Intrahepatic Portosystemic Shunt (TIPS) is planned, or according to provider preference. Although the biopsy specimen is often smaller and more fragmented than that acquired from a percutaneous approach, it is usually diagnostic (4, 5).

### 2- Primary and metastatic liver tumors:

Liver cancer, namely hepatocellular carcinoma (HCC), is one of the most common cancers in the world and is the third most common cause of cancer-related death (6-11). If left untreated, liver cancer has a poor prognosis with more than 90% of patients dying of the disease within 5 years of diagnosis (7).

The liver is also a common site for metastatic disease from cancer arising in other organs. If possible, surgical removal of the tumor is standard treatment for liver cancer and gives the patient their best chance at long-term survival. Unfortunately, the majority of patients with liver cancer are not surgical candidates (11).

Traditional therapies, such as chemotherapy and radiation therapy have little if any long-term benefit for patients with both HCC and metastatic disease to the liver. As a result, minimally invasive therapies such as image-guided tumor ablation are being developed as alternative treatment options for these patients. Tumor ablation is the chemical or thermal destruction of cancerous masses using image guidance.

**A- Chemical Ablation**

Chemical ablation is the injection of a toxic chemical into a tumor through a thin needle. The chemical dehydrates the tumor, results in chemical injury to the organelles, causes vascular thrombosis, and osmotic shifts among other complex effects. The effect is destruction of the cells affected by the chemical. The most commonly used chemical is ethanol. The procedure is referred to as percutaneous (through the skin) ethanol injection (PEI).

PEI is most effective for small ($\leq$ 3 cm) primary liver tumors that frequently arise in a cirrhotic diseased liver. This is because the ethanol diffuses easily within the soft tumor, but not into the firm scarred liver surrounding it. As a result, the ethanol is able to diffuse evenly into the tumor and kill the cancerous cells

PEI is much less effective for liver metastases. These tumors are usually harder than HCCs, which can prohibit uniform diffusion of the chemical throughout the tumor. As a result, portions of the tumor are often incompletely treated, resulting in rapid re-growth of the tumor. Therefore, PEI is almost never utilized for the treatment of metastatic liver tumors, except in the setting of a neuro-endocrine tumor.

**B- Thermal Ablation**

Thermal tumor ablation modalities either freeze or heat tumors to lethal temperatures. These include cryo-ablation, radiofrequency (RF), microwave, laser and high-intensity focused ultrasound (HIFU).

**C- Cryo-ablation**

Cryo-ablation utilizes extremely cold temperatures to destroy cancerous cells. Ice crystals form as the tissues are frozen (12, 13).

**D- RF ablation**

RF ablation is the most commonly employed ablation modality for liver tumors and is often performed percutaneously. During RF ablation, an electric current is conducted into the body via a needle (electrode) placed into the tumor under imaging guidance (CT, US, or MRI) (15).

**E- Laser**

Laser ablation is used more frequently in Europe than in the United States. During laser ablation, fibers are inserted into the tumor and the tumor is irradiated with a laser beam.

**F- High-intensity focused ultrasound (HIFU)**

Thermal ablation with a HIFU beam is an exciting topic since, in contrast to the previously discussed modalities; it does not require the placement of an applicator into the tumor. Tissue heating results from absorption of the focused acoustic energy and does not require a skin puncture. HIFU is often combined with MRI, which can provide real-time temperature measurements and assist in treatment planning. While promising, small ablation zones and expensive, complex systems have limited its practical application. HIFU has yet to find a prominent role in the treatment of liver cancer, in part because respiratory motion makes accurate focusing of the ultrasound beam difficult. The main clinical utility to this point has been in the treatment of uterine fibroids, where it has shown promise.

## 3-Vascular intervention

Via endovascular route now it's possible to do dedicated and interventional procedures such as TIPS, reopening and stenting hepatic veins in Budd- Chiari syndrome and control of hematobilia.

Transhepatic embolization of esophageal and gastric varicose veins is other possible techniques for GI bleeding treatment.
Recently via hepatic artery or portal vein (percutaneous access) ; stem cells transplant is possible.

### 4-Biliary drainage

When there is difficulty or failure in ERCP base stenting, percutaneous techniques are modality of choice for percutaneous biliary drainage including: percutaneous transhepatic cholangiography (external drainage) and percutaneous stenting.

### 5-Percutaneous biliary duct stone removal.

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**Seyed Mohammad Jazayeri, M.D., Ph.D.**
Tehran University of Medical Sciences
Tehran, I.R. Iran

After graduation in medicine in 1990, he started a Ph.D. course in Glasgow University, UK, in the field of virology. His research subject was Hepatitis B virus core Ag (HBcAg) localization in two groups of patients who were either in active or remission phase of chronic disease. In the meantime, he was studying molecular epidemiology of HBV genotypes, mainly examining the core gene of samples from 14 countries. He discovered that there were some amino acid positions in the core region which specifies genotypes. He proposed hepatitis B virus genotyping based on core gene sequencing (as an alternative approach to either surface and/or complete genome sequencing). Furthermore, he tried to assign those amino acid residues to human population history, done on some samples from far Pacific Ocean including four countries. The results of this research have been published in several journals. Then, he moved to West of Scotland Specialist Virology Center to work on versatile viral subjects on picornaviruses, influenza, hepatitis C and other clinically-important viruses, mainly on molecular diagnostic aspects using real time PCR.

Dr. Jazayeri came back home in 2004. He is currently an assistant professor in the Department of Virology, School of Public Health, Tehran University of Medical Sciences (TUMS). He has established the Hepatitis B Molecular Research Laboratory in that department in 2007. Since then, 17 members including M.Sc. and Ph.D. students, infectious and gastroenterology specialists, research fellows and staff have been working full/part time in this laboratory. Dr. Jazayeri has been involved in different research projects including:

Distribution of HBV genotypes between different Iranian ethnic groups (funded by TUMS). HBV genomic variations among a closed community: Zoroastrians. Managing a national project on occult hepatitis B infection since 2008. Standardization and optimization of real time PCR on 24 different viral pathogens (funded by TUMS).

-…and different published and unpublished research projects based on molecular

epidemiology and molecular biology of HBV. He has published more than 15 articles, books and chapters in this field.

He is currently a member of Tehran University's Infectious Diseases Committee and the National Committee of Hepatitis.

## Occult Hepatitis B Infection: A Cause for Concern?

Seyed Mohammad Jazayeri, MD,

The detection of HBV-DNA without HBs-Ag with or without the presence of HBV antibodies outside the acute phase window period defines occult HBV infection. Two common findings and possible explanations for occult HBV are low levels of viral replication activity and /or mutation to the "a" epitope of the surface gene. Occult hepatitis B infection (OBI) is one of the most difficult diagnostic problems in most countries in the world, especially in terms of transfusion settings and in the general population with normal liver function tests. After decades of debate it is now accepted that occult HBV infection is a frequent event in a number of clinical situations such as chronic liver disease of unknown etiology, HCC and HCV and or HIV infections. Prevalence of such infection is far from negligible in the context of transplantation, hemodialysis settings and blood transfusion as in the general population. Evidence is accumulating that occult HBV infections are widespread in many geographic areas. Available data shows that the prevalence of OBI is widely divergent. Many issues are still open regarding OBI, starting with diagnostic criteria to clinical meaning; from a clinical point of view, OBI has been associated with HBV reactivation during immunosuppression, particularly during chemotherapy for malignancy, AIDS, in transplant recipients receiving organs from anti-HBc positive donors. We believe that the clinicians should take into account the presence of occult HBV infection in several categories of patients, such as immuno-suppressed subjects and cirrhotic individuals who, when they carry this peculiar infection, are at the highest risk of developing viral reactivation and liver cancer, respectively.

## Application of Real Time PCR in Viral Hepatitis

Seyed Mohammad Jazayeri, M.D., Ph.D.

Despite the increased sensitivity of serologic tests, a residual risk of HBV transmission still exists, and HBsAg may not be detected under some circumstances. Serology results can neither efficiently reflect serum viral load or hepatitis activity nor monitor the efficacy of antiviral treatment. Among several techniques for viral hepatitis quantification which are currently are employed (such as: Signal and Target amplifications), real time PCR (and especially the TaqMan option) is the most widely used in this regard. Novel hepatitis assays based on real-time PCR technology have a greater dynamic range, increased sensitivity and therefore they provide a better virological assessment of HBV and HCV replications. Its high degree of automation, rapid detection, mminimized hands-on time, genotype-independent detection, quantitation and multiplexing options has revolutionized the way clinical virology in terms of viral hepatitis. Real time PCR assays are significantly less variable than conventional PCR and RT-PCR protocols, which are subject to significant error.

Despite these, differences in assay precision, generating divergent results, lack of standardized reference material and the absence of international accrediting bodies, make it difficult to compare data from different laboratories, which emphasize the importance of standardization of quantitative assays to facilitate comparison of genome levels between patients.

Thus, after implementation of the real-time PCR test it is neces¬sary to continue to monitor performance of the assay, equip¬ment, reagents, and personnel. The ideal system needs automated extraction and detection technologies, combined with an extensive quality control program.

**Mansour Ali Al-Amrany**
Sana'a University
Republic of Yemen

Mansour Ali Al-Amrany has obtained his-MB, BCH in medicine and surgery - Excellent with honor (1999) from Cairo University, then his M.Sc. in Hepatology & Gastroenterology and Infectious Diseases - Excellent with honor (2002) – from Ain Shams University, followed by MD in Hepatology & Gastroenterology and Infectious Diseases (2006) from the same university. He is currently Assistant Professor of Internal Medicine and Hepatogastroenterology, and also Professor and the Head of Internal Medicine Department - Science and Technology University, Consultant of Gastrointestinal Endoscopy - Al-Kuwait University Hospital, Head of Hepatology and Endoscopy Units - Azal Specialized Hospital and Prof. of Internal Medicine at King Arwa University. He has published or going to publish the results of seven research projects carried out by him. He is a member of Yemeni Gastroenterology and Hepatology Association, Egyptian society of Endoscopy and Hepato-Gastroenterology, Egyptian society of Hepatology Gastroenterology and Infectious Diseases, African Association of the study of liver diseases and International Association of the study of liver diseases. He has also participated in 12 local and international conferences and workshops in various roles.

# The Association between HCV, Insulin Resistance, and Type II DM in Yemeni Patients Infected by HCV

Mansour Ali Hezam Al-Amrany, M.D.

**Introduction:** There is a direct experimental evidence for the contribution of HCV in the development of insulin resistance in human HCV infection, which finally leads to the development of type 2 diabetes (Kazuhiko, 2005). The risk factors for diabetes in HCV patients include: older age, HCV genotype 3, severe liver fibrosis, family history of diabetes, and liver/kidney transplantation (Noto and Raskin, 2006).

**Aims of the study:** Investigate the association of hepatitis C virus with development of insulin resistance and / or type 2 diabetes mellitus. Identify the risk factors that may contribute to the development of insulin resistance and / or type 2 diabetes mellitus among patients with hepatitis C virus infection.

**Patients and Methods:** This study was performed on 100 HCV infected Yemeni patients (based on 3rd generation ELISA). It was enrolled on Hepatobiliary Gastroenterology specialized center (HGSC) in Sana'a.

**Exclusion criteria:**
- HCV infected patients under antiviral treatment
- Patients with DM1

**Results:** Regarding sex of studied HCV patients, males (54%) are infected with HCV more than females (46%). Most of patients living in Sana'a (43%) and Amran (21%) governorates. 50% of the patients have family history of DM. 30% of patients have clinical evidence of obesity, chronic hepatitis (51%), liver cirrhosis(49%), active (60%), inactive (40%). Compensated (42%), decompansated (58%), among the 40 patients who do PCR high viral load in 37 patients and low viral load in 3 patients. HCV is associated with IR (30%) and DM2 (29%). There is no statistical significance in the relation between glycaemic status of the studied HCV patients regarding to their age, sex, residence, obesity, family history of DM, occupation.

DM2 was more in late HCV (58.6%) than early HCV (41.4%). DM 2 was more in active than inactive HCV (72.4%-27.6%).

**Conclusion:** HCV can be considered as important risk factor of IR and DM2, so careful monitoring of glycaemia in patients with chronic HCV infection is recommended.

# Applications of EUS in Liver Disease

Siavash Mansouri, M.D.

Although the entire liver cannot be seen by EUS, a large portion of the liver can be seen during a radial EUS examination, a significant part of the left lobe of the liver can be imaged from the gastroesophageal junction and from the body of the stomach. The inferior vena cava can be seen as an anechoic structure within the liver parenchyma.

The liver appears as a complex solid organ with many vascular and fluid-filled structures (bile ducts). Large parts of the right lobe of the liver can be imaged by trans-gastric imaging from the antrum and the duodenum, especially from the duodenal bulb.

## EUS for detection biliary lesions

In many reports, EUS is superior to ERCP and MRCP for diagnosing biliary lesions; for example stone or sludge and mass lesions.

EUS technique can be used as the first-line procedure in patients with biliopancreatic diseases in the evaluation of common bile duct (CBD) stones. The sensitivity of EUS ranges from 84% to 100%, with a diagnostic accuracy rate of 92–99%. In contrast, the sensitivity of endoscopic retrograde cholangiopancreatography (ERCP) was somewhat lower at 79–90%, because of the problem of false-negative results caused by small stones located within dilated bile ducts.

Thickening (greater than1.5 mm) of the common bile duct wall is seen in patients with PSC but not in those with apparently uncomplicated IBD or choledocholithiasis. The results of this study suggest that standard endosonography contributes to the imaging and potentially to the diagnosis of PSC.

## Liver lesions or metastases

Endoscopic ultrasound can be used to visualize the left lobe and part of the right lobe of the liver. Endoscopic ultrasound can be used to visualize the left lobe and will have a significant outcome in the management of gastrointestinal tumors. EUS-FNA plays an important role in assessing liver masses that are detected by EUS. Nguyen et al. reported finding 14 suspicious liver lesions among 574 patients undergoing EUS with a history or suspicion of gastrointestinal or pulmonary malignancy. All 14 patients underwent EUS-FNA and were proved to have malignancy. CT scans detected only three of the 14 lesions. The authors concluded that EUS can detect small focal liver lesions that are not detected on CT scan. However, certain parts of the liver are not accessible to EUS and newer equipment with wider scanning ranges may be required to fully image the liver.

Awad et al. hypothesized that EUS could detect small (<1.0 cm) hepatic lesions undetected by CT scans and could be used to biopsy deep-seated hepatic lesions. In their study, 14 patients underwent evaluation with CT scan and EUS. EUS successfully identified hepatic lesions in all 14 patients as well as new lesions in four of the 14 patients. Nine patients underwent EUS-FNA of whom eight proved to have malignant involvement and one patient had a benign lesion. This study concluded that EUS can detect small hepatic lesions previously undetected by CT scans and can be an important preoperative staging tool for liver involvement in malignancy.

## Esophageal varices

Endoscopic sclerotherapy (ES) and band ligation are standard treatments for esophageal varices. Unfortunately, recurrence is common and seems to be related to esophageal collateral vessels, easily identified by EUS. Eradication of these vessels might lead to a more durable therapeutic effect. EUS-ES is as safe and effective as ES in variceal eradication. Recurrence tends to be less frequent and occurs later. Persistence of esophageal collateral vessels after sclerotherapy is a risk factor for recurrence.

Endosonography usually allows detection of fundic varices even in their early stages. EUS is also able to demonstrate dilation of the azygos vein, which occurs in patients with more severe esophageal varices. The diameter of azygos vein ranges from 5+-1mm in normal individuals and patients with grade 1 esophageal varices

to 7.2+-1mm in patients with grade2 varices and 8.4+-1mm for grade 3 varices. For this reason, EUS is a rough orientational guide for assessing the severity of portal hypertension.

## Endosonography-Guided Cholangiopacreatography

Puncture and injection of contrast into the bile/pancreatic duct to visualize the ductal system was first described in the mid 1990's. Harada et al. first reported pancreatography following puncture of the pancreatic duct under ES guidance in 1995.

## Endosonography-Guided Biliary Drainage

As ESBD is a combination of techniques of ES-guided fine needle puncture and EBS, an echoendoscope, puncture needle, guide-wire, stent, and stent pusher are necessary. Stent placement is carried out during a fluoroscopy session. Puncture of the bile duct is achieved with 19 G needles for EUS-FNA. These needles allow passage of a 0.035-inch guide-wire through the lumen after removal of the core needle. As a stent is inserted and placed over the guide-wire, it is advantageous to use a thicker guide-wire. Use of a thinner needle such as 22 G, which only allows access of a 0.018-inch guide-wire, implies the risk of dislodgement of the guide-wire during the subsequent procedure.

After removal of the inner (core) needle and aspiration of bile followed by injection of contrast a slight amount of, a guide-wire is advanced deep into the intra-hepatic duct through the outer (sheath) needle.

Following removal of the outer needle while leaving the guide-wire, a dilator (tapered catheter or dilator balloon) is fed over the guide-wire and advanced to the puncture site, and dilation of the tract is performed.

Then, aspiration of bile is repeated, followed by removal of the dilator. Finally, a stent and a pusher are fed over the guide-wire and the stent is placed across the sinus tract. EUS is an important new tool for accessing the portal vein.

There are a large number of potential uses of EUS-guided portal vein catheterization, and many of them are dependent upon the safety profile of the procedure. EUS

was used to place a 19-gauge needle into a branch of an intrahepatic portal vein, performed a portogram by using contrast and/or carbon dioxide (CO2) injection, and, after confirmation of the location of the needle in the portal vein, a pressure transducer catheter was placed into the lumen of the portal vein. For 1 hour, continuously monitor the portal vein pressure, demonstrating minimal pressure variation over time. Hepatic venous pressure gradient (HVPG), an indirect measure of the portal vein pressure, is highly predictive of the patient's clinical course.
Cirrhotic patients with HVPG greater than 10 mm Hg have a 90% risk of decompensation within 1 year. Furthermore, cirrhotic patients with resistant HVPG are at risk of variceal hemorrhage.

The most obvious advantage is the fact that the EUS approach provides a direct measurement of the portal vein pressure.

Although interventional radiologists theoretically may gain access to the portal vein through the percutaneous route, a high rate of bleeding complications precludes the routine use of this approach. Furthermore, the determination of the HVPG cannot diagnose presinusoidal portal hypertension. The disadvantage of EUS-guided pressure measurements is the need to have endoscopic access to the upper GI tract.

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**Farhad Zamani, M.D.**
Iran University of Medical Sciences
Tehran, I.R. Iran

Dr. Zamani entered Iran University of Medical Sciences, Tehran, as a student of medicine, in 1986, and graduated in 1993. In 1996, he began his studies in Internal Medicine at the same university and following graduation in 2000, went to Tehran University of Medical Sciences to continue his studies as a Fellow of Gastroenterology & Hepatology and graduated in 2004. He returned to Iran University of Medical Sciences in 2004 and is currently serving there as an Assistant Professor. He has been a member of Iranian Internal Medicine Association, Iranian Gastroenterology and Hepatology Society and, American Gastroenterology Association (AGA). He has been the author or co-author of 13 published articles and 7 published abstracts.

# Complications of HCV

Farhad Zanmani, M.D.

The hepatitis C virus (HCV) is a cause of both acute and chronic hepatitis. Also, several extrahepatic diseases have been described with chronic HCV infection, including hematologic diseases, autoimmune disorders, renal disease and dermatologic conditions.

## Hematologic disease

Mixed essential cryoglobulinemia is a lymphoproliferative disorder that can lead to deposition of circulating immune complexes in small to medium sized blood vessels. It often presents with the clinical triad of palpable purpura, arthralgias, and weakness, but can also involve the kidneys, peripheral nerves, and brain. HCV infection appears to have an etiologic role in most patients with this condition. HCV can bind to B lymphocytes via CD81 and this binding lowers the activation threshold of these cells, thereby facilitating the production of autoantibodies. Also anti-HCV can be found in the vessel walls of skin biopsies obtained from patients with mixed cryoglobulinemia and cutaneous vasculitis. In addition, cryoglobulin levels decrease and skin lesions and symptoms improve with treatment of HCV. Hepatitis C may be a risk factor for the development of monoclonal gammopathies.

Multiple studies showed an association between HCV infection and B-cell non-Hodgkin's lymphoma (NHL). The risk was also increased for Waldenstrom macroglobulinemia and cryoglobulinemia but not other hematologic malignancies. Primary hepatic lymphoma has also been reported in association with HCV. In addition, HCV has been described in gastric mucosa in association with MALT lymphomas.

## Renal disease

Glomerular disease may occur in patients with chronic HCV infection. The most

common patterns are membranoproliferative glomerulonephritis and, less frequently, membranous nephropathy. Several series have reported that anti-HCV antibodies are nearly universal in patients with both membranoproliferative disease and cryoglobulinemia. Treatment of HCV has beneficial effect in these patients
Dermatologic disease

Porphyria cutanea tarda (PCT) is a skin disease caused by a reduction of hepatic uroporphyrinogen decarboxylase activity that is characterized by photosensitivity, skin fragility, bruising, and vesicles or bullae that can become hemorrhagic. There is a strong association between the sporadic form of PCT and HCV infection. All patients with PCT should be screened for HCV infection and treatment of HCV should be considered in HCV-infected patients. A leukocytoclastic vasculitis may occur in conjunction with essential mixed cryoglobulinemia, presenting clinically with palpable purpura and petechiae that usually involve the lower extremities.

Lichen planus (LP) is characterized by flat-topped, violaceous, pruritic papules with a generalized distribution. It can also involve mucus membranes, hair, and nails. LP can be seen in patients with a variety of liver diseases, particularly advanced liver disease; anti-HCV antibodies are present in 10 to 40 percent of these patients but a cause-and-effect relation is uncertain.

## Autoimmune disorders

A number of autoimmune disorders have been associated with HCV infection, including autoantibody formation, thyroid disease, sialadenitis, and autoimmune thrombocytopenic purpura. Autoantibodies are common in patients with chronic HCV infection; antinuclear antibodies, rheumatoid factor, anticardiolipin antibodies, smooth muscle antibodies, or antithyroid antibodies are detected in 40 to 65 percent of patients. Patients with HCV were more likely to have hypothyroidism, anti-thyroglobulin antibodies, and anti-thyroidperoxidase antibodies. Anti-HCV antibodies occur in 10 to 19 percent of patients with autoimmune thrombocytopenic purpura (ITP).

## Ocular disease

HCV infection has been associated with a variety ophthalmologic disorders including dry eyes, corneal ulcers (Mooren's ulcer), uveitis, and scleritis , and Sicca

syndrome.

## Diabetes mellitus

HCV infection has been linked to diabetes mellitus in several epidemiologic studies. HCV genotype 2a was overrepresented among the diabetic patients. Risk factors for the development of diabetes mellitus in HCV infected patients included older age, obesity, severe liver fibrosis, and a family history of diabetes mellitus. The cause of these associations is unknown, but their magnitude may be overestimated

## Distribution of Hepatitis C Virus Genotypes in Iran

Katayoun Samimi-Rad, Ph.D.

Hepatitis C virus (HCV) was determined in 317 Iranian patients by phylogenetic analysis. Subtypes 1a and 3a were dominant accounting for 50% and 34% whereas 1b, 2 (2b, 2k) and 4 accounted for 11, 4 and 1%. The dominant HCV subtypes (1a and 3a) in Iran were similar to those in England, Scotland and Australia (1, 2, 3). This subtype distribution differs from Turkey (4) and Central Asia countries, (5) where subtype 1b dominates, from Pakistan (6), where subtype 3a is prevalent and also from neighboring Arab countries, where subtype 4 dominates (7, 8, 9). Patients infected by blood products had more frequently subtype 1a (51.5%), while younger drug users had more frequently subtype 3a (54%). Genotype 4 with prevalence of (18%) in hemodialysis patients, was over –represented among this high risk group. The subtype distribution within Iran does not differ distinctly according to geographical origin. Study in some regions of southern Iran, where people with Arab origin live, shows the same distribution of HCV subtypes as other parts of Iran. There are few data regarding circulating HCV strains among Iranian blood donors and general population, further study of which will help us to better understand the molecular epidemiology of HCV in Iran.

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**Shahram Agah, M.D.**
Iran University of Medical Sciences
Tehran, Iran

In 1988, Shahram Agah, was a student of medicine in Shiraz University of Medical Sciences who later graduated in 1995, with a national first place in the comprehensive exam of basic medical sciences. He went on to graduate in Internal Medicine from the same university in 1998, with a national second place in the exam of the Iranian Board of Internal Medicine, which was repeated in the exam of the Iranian Board of Gastroenterology and Hepatology in 2000, when he graduated from Tehran University of Medical Sciences. He has experienced teaching in other institutes (e.g. Jahrom University of Medical Sciences). He is a Member of American Gastroenterological Association. He has published 11 international and 9 domestic papers , mostly on helicobacter pylori , functional GI disorders , hepatitis B and C. He is currently Associate Professor of Gastroenterology and Hepatology Dean of Gastrointestinal and Liver Diseases Research Center Chairman, Educational Development Center.

## Management of Hepatitis C in Cirrhotic Patients

Shahram Agah, M.D.

In long term follow up to 50% cirrhosis is reported in chronic HCV infected .patients (1-3). Chronic HCV infection and alcoholism are the two most common causes of cirrhosis in western countries (4). In Iran although HCV is not common as an etiology for cirrhosis but its importance as a cause has increased.

HCV patients with decompensated cirrhosis should be referred for liver transplantation. However, experienced hepatologists may consider treatment in those with mild degrees of decompensation, because the risk of death in patients in such condition is high (5). Use of growth factors (such as erythropoietin and granulocyte colony stimulating factor and granulocyte macrophage colony stimulating factor) may be helpful during treatment of these patients by limiting the need for reductions in the dose of antiviral therapy.

After transplantation, HCV recurs and may rapidly progress to cirrhosis and graft loss. Treatment is needed to prevent progression of disease and minimize recurrence after liver transplantation. In some studies the effectiveness, tolerability, and outcome of a low accelerating dose regimen (LADR) of antiviral therapy in the treatment of patients with advanced HCV were studied even in child C. (ascites, spontaneous bacterial peritonitis, varices, variceal hemorrhage, encephalopathy) In one study Sustained Virological Response (SVR) was 13% in patients infected with genotype 1 HCV and 50% in patients infected with non-1 genotypes ($P < .0001$) (6). Non-1 genotype, CTP class A (genotype 1 only), and ability to tolerate full dose and duration of treatment ($P < .0001$) were predictors of SVR. Twelve out of 15 patients, who were HCV RNA-negative before transplantation, had remained HCV RNA-negative 6 months or more after transplantation.

In conclusion, in a sizeable proportion of patients with advanced HCV, LADR may render blood free of HCV RNA, stabilize clinical course, and prevent post-transplantation recurrence.

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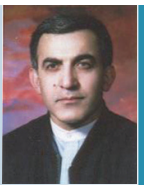
**Nasser Ebrahimi Daryani, M.D.**
Tehran University of Medical Sciences
Tehran, Iran



He began his study of medicine at Shahid Beheshti University of Medical Sciences in 1970 and then continued in Tehran University of Medical Sciences to obtain a specialty degree in Internal Medicine in 1983 and a subspecialty degree in Gastroenterology and Hepatology in 1996. He is a member of various professional bodies (e.g. the National High Council of Medicine, the National Committee of Hepatitis; Board of Governors of the Iranian Society of Internal Medicine and Board of Governors of the Iranian Society of GI Specialists) and editorial board of several journals (e.g. Iranian Journal of Gastroenterology and Hepatology, the Iranian Journal of Clinical Infectious Diseases, the Scientific Journal of Forensic Medicine, the Journal of Internal Medicine and the Journal of the School of Medicine, Tehran University of Medical Sciences).He has been the author or co-author of 17 Pub-Med indexed, 23 ISI indexed and 55 domestic papers. He has published 22 articles in the Iranian Journal of Digestion and given more than 120 lectures on various medical subjects.

# Hepatitis D

Nasser E. Daryani, M.D.

Hepatitis D (delta) virus was discovered by Rizzetto and associates in 1977 as a unique nuclear antigen in the hepatocytes of patients infected with HBV.
Epidemiology: At least 5% of HBV carriers worldwide are estimated to be infected with HDV, and therefore, the overall burden of HDV infection is between 15 and 20 million cases.

**HDV Infection:** Due to its dependence upon HBV, HDV infection always occurs in association with HBV infection. The clinical and laboratory findings vary with the type of infection:

**Co-infection:** Co-infection of HBV and HDV in an individual susceptible to HBV infection results in acute hepatitis B + D. This entity is clinically indistinguishable from classical acute hepatitis B and is usually transient and self-limited.

**Super-infection:** HDV super-infection of a chronic HBsAg carrier may present as a usually severe acute hepatitis in a previously unrecognized HBV carrier, or as an exacerbation of preexisting chronic hepatitis B.

**Helper-independent latent infection:** A third form of infection is a helper-independent latent infection which can be rescued by the helper virus at a later time. This form of infection was initially observed in the liver transplantation setting.
Modes of Transmission: a) Percutanous exposures (injecting drug use)
b) Permucosal exposures (sex contact)

**Diagnosis:** Due to the dependence of HDV on HBV, the diagnosis of hepatitis D cannot be made in the absence of markers of HBV infection. The diagnosis of HDV infection should be considered in the following clinical situations:

A) Acute hepatitis B virus infection — In patients with acute HBV infection, testing for HDV co-infection should be considered in those who have risk factors (intravenous drug users and patients from endemic countries) or who present with unusually severe or protracted hepatitis.

B) Acute hepatitis of undetermined origin in a chronic HBV carrier — Tests for HDV should be considered to rule out acute HDV super-infection in this setting. Since HDV super-infection may occur in previously unrecognized chronic HBV carriers, distinguishing between this condition and acute HBV/HDV co-infection can be difficult.

C) HBsAg-positive chronic liver disease — Tests for HDV should be considered in such patients to rule out coexistent chronic HDV infection. This is best achieved by screening for total anti-HDV antibody.

D) HDV super-infection in patients with chronic HBV infection is usually accompanied by suppression of HBV replication due to interference mechanisms that are not well understood

**Treatment:** The aim of treatment of hepatitis D is to eradicate or to achieve long-term suppression of both HDV and HBV. The primary endpoint of treatment is the suppression of HDV replication, which is accompanied by normalization of the ALT level and amelioration of necro-inflammatory activity on liver biopsy. A secondary endpoint is the eradication of HBV infection, with HBsAg to anti-HBs sero-conversion.

**Interferon Alpha:** The only drug approved at present for treatment of chronic hepatitis D is interferon alpha (IFNa).

**Pegylated interferon:** There is little published experience with pegylated interferon in the treatment of chronic hepatitis D. The largest published study included 38 patients who were treated with pegylated IFN alfa-2b (1.5 MU/kg per week) alone or in combination with ribavirin for 48 weeks.

Pegylated interferon plus adefovir dipivoxil — few studies have evaluated combination therapy for HDV using nucleoside analogues. In one of the largest controlled trials, patients receiving combination therapy had a significant decline

in HBsAg levels with two clearing HBsAg; further studies are needed to better characterize the clinical significance of this benefit.

## Alternative treatments

**Ribavirin** inhibits HDV replication in vitro, addition of ribavirin to pegylated IFNa did not improve response.
Foscarnet and acyclovir have a paradoxical stimulatory effect on HDV replication, at least in vitro.

**Suramin,** when administered in vivo, suramin was effective in preventing HDV infection in woodchucks only when they were inoculated with a low infecting dose.

**Lamivudine,** a potent inhibitor of HBV replication, had little or no effect on HDV replication in two series, and no synergistic effect with high dose IFNa in two other reports

**Mehdi Saberifiroozi, M.D.**
Tehran University of Medical Sciences
Tehran, I.R. Iran

Pofessor Saberifiroozi was born in 1959 in Fars province and after graduation from high school; He entered Shiraz University of Medical Sciences (SUMS) in Shiraz at 1978. He graduated as general physician in 1987 and due to his scientific grade level as the top 10 percent of the class, and his interest in continuing his studies he started a specialty course in internal medicine in SUMS.

After graduation in 1990 as the first in the national board exam of internal medicine, he started subspecialty training in SUMS, which ended in 1992. His postgraduate training was done under supervision of some of the best teachers in internal medicine department of Shiraz University of Medical Sciences. He is a member of the first liver transplant team in Shiraz University of Medical Sciences, and after 1993 he has been involved in the liver transplant group activities in Namazee Hospital in SUMS.

He started his academic activities in the department of internal medicine in SUMS at 1992. In addition to training undergraduate and postgraduate medical students, he has been involved in multiple research projects which resulted in publication of multiple articles in peer reviewed international journals. He has been active in administrative activities in the university also, such as the Head of department of Internal Medicine, chief of Gastroenterology section, director of Gastroenterology and Hepatology Research Center, Vice Chancellor for Educational Affairs. At the national level he has responsibilities such as member of the Board of Gastroenterology and Hepatology since 1996, member of residency curriculum design in the Ministry of Health, director of the National Center for Internal Medicine Strategic Planning.

He has participated in a fellowship program in hepatology and liver transplant in the King's College Hospital in London, UK from 2001-2002 and a course in management of health system held by WHO in UK in 2001 which was. Presently

he is working in the DDRC in Tehran University in Shariati Hospital. His interests in clinical practice include hepatobiliary disorders especially viral hepatitis, liver transplant, endosonography, diagnostic and therapeutic endoscopy. His interests in research are chronic liver disease, liver transplant, portal hypertension, and epidemiological studies.

## Long Term Immunity to Hepatitis B Virus Vaccine

Mehdi Saberifiroozi, M.D.

Hepatitis B virus infection is a significant health problem in the world. Around 2 billion individuals have evidence of past or current infection, and more than 350 million carriers of the virus are living around the world. Of these people many develop chronic liver disease such as cirrhosis and hepatocellular cancer and more than 1 million deaths occurs due to these complications yearly.

Prevention at an early age can control the chronic carriage of HBV and therefore disease states. It is the first vaccine against a major human cancer. The World Health Organization issued recommendations in 1991 that hepatitis B (HB) vaccine should be integrated into national infant and adolescent immunization programmes in all countries by 1997. Hepatitis B vaccine was included in the national infant immunization programs of 171 countries by December 2007, which in comparison to 31 countries in 1992 is a major progress for global prevention program.

World Health Organization recommends injection of three doses of vaccine at 0, 1, and 6 months. This type of vaccination is 95% effective in preventing HBV infection and its chronic consequences, such as cirrhosis and hepatocellular carcinoma. Due to long term immunity HBV vaccination is cost saving because it causes reduced morbidity, mortality, cost of treating disease and cost of booster vaccinations. Healthy individuals will develop protective immunity with the first two doses and the third dose has a booster effect in most cases. However after a few years the level of anti-HBs antibody will decrease to below 10 IU/l or to undetectable levels. As a significant question; is there a need for booster vaccination in individuals at a decade or more after primary vaccination? Who need booster dose or in what circumstances we should advise for re vaccination of vaccinees?

After exposure to HBs antigen or viral particles both humoral and cellular

immunity will activate. The cellular immunity indeed is a type of immune memory; such as memory B cells, memory T cells, memory cytotoxic T lymphocytes which act when natural or vaccine induced boosting will occur. In the primary infection or vaccination, these processes usually take place in a 1.5- 3 month's period. With development of T memory cell in the immune system, if the person exposes to viral antigens an anamnestic reaction to viral antigens will takes place, which is very rapid and usually during 3-4 days. This anamnestic reaction and defense mechanism against the virus prevents a breakthrough infection and HBs antigen positivity. However the anti-HBc antibody may become positive and transient viraemia without any symptom or disease can occur. However no breakthrough infection and HBs antigen positivity state has been reported in vaccinees. This anamnestic reaction can be started in vaccinees with low level anti HBs antibody or even cases with negative protective antibody.

For producing a good anamnestic response to viral antigen exposure, the primary vaccination response should have been effective and adequate post vaccination antibody level is critical for its occurrence.

The strength of the primary vaccination course and the anamnestic response are correlated and depends on the antigen dose and level of neutralizing antibody. Higher vaccine antigen dose is related to longer antigen persistence and, a more vigorous initial T-cell response. Antigen persistence, dose and nature determines the level of antibodies and the T-cell response, and consequently influences the strength of the anamnestic response, lymphoproliferation and the B- and T-cell-mediated immune memory.

According to guidelines in Western countries, it is now clearly evident that in healthy cases with history of complete HBV vaccination, no booster dose is indicated. In health care workers, chronic renal failure on regular hemodialysis, chronic liver failure, and immunodeficient patients there is suggestion for regular evaluation of antibody level and booster vaccination if the level of HBs antibody is less than 10 IU/L.

There is no consensus on need for routine booster vaccine 10- 15 years after vaccination. However some potential candidates for booster dose of HBV vaccine have been defined in different areas of the world. Most authorities agree for boosting in immunocompromised persons such as HIV disease and chronic renal failure on

regular hemodialysis or chronic liver failure especially HCV positive cases. In high endemicity areas, boosting after 10-15 years after vaccination can be suggested for communities that injecting booster dose is more feasible than HBs antibody monitoring, immunocompromised persons with non protective HBs antibody level (<10 mIU/mL), health care workers, persons with high risk behaviors and in some instances household contacts of HBV infected persons.

Certainly in the future with more effective preparations of vaccines such as DNA vaccines, vaccines with adjuvant, pre-S1 and pre S2 vaccines, and changing the number, dose, and route of administration, the efficacy and cost saving will be improved in the long term.

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## Acute Viral Hepatitis

Mohmmad Javad Zahedi, M.D.

Hepatitis is a syndrome of diverse etiology that has the final effect of hepatic inflammation and hepatic cell necrosis. The condition can be self limiting or progress to liver fibrosis and cirrhosis.

Hepatitis is acute when it lasts less then six months and chronic when it persists longer. A group of viruses known as hepatitis viruses (A TO E) cause most cases of acute hepatitis. These viruses have diverse modes of transmission and epidemiology. Other common causes of acute hepatitis include alcohol, drugs, toxins, metabolic disorders, ischemia and autoimmune process.

Clinically, the course of disease varies from asymptomatic or mild symptoms requiring no treatment to fulminant hepatic failure needing liver transplantation. A nonspecific viral prodrome is followed by anorexia, nausea, fever and right upper quadrant pain. Jaundice often develops typically as other symptoms begin to resolve. Must cases resolve spontaneously but HBV and HCV may progress to chronic hepatitis (1, 2, 3).

Diagnosis is made by Liver function tests and serologic test to identify the viruses. In Laboratory tests acute hepatitis characterized by elevation of ALT, AST with variable increase of Alk P or bilirubin. The degree of Aminotransferase elevation is more reflective of how abrupt the Liver damage than the true of Severity.

In approach to patients with acute hepatitis after taking a careful history and physical exam initial workup is investigate of viral causes and if these test are not diagnostic the next step is to order several markers of other etiologies.

Treatment of this patients including general support with good nutrition and antiemetic as well as relative bed rest (4, 5, 6). Liver transplant is needed for fulminant hepatitis.

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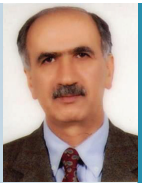
**Rahim Aghazadeh M.D.**
Shahid Beheshti University of Medical Sciences
Tehran, Iran



After graduation in medicine, Prof. Aghazadeh continued in Tehran University of Medical Sciences to obtain a specialty degree in Internal Medicine and Gastroenterology. He is currently Professor of Gastroenterology and hepatology in Shahid Beheshti University of Medical Sciences and he is also the Head of the gastroenterology and Hepatology Department of Taleghani Hospital.

Prof. Aghazadeh is a Member of Gastroenterology and Hepatology National Examination Board. He is acting as a member in Editorial Board of Iranian Journal of Gastroenterology (Govaresh), and in Executive Board of Iranian Gastroenterology and Hepatology Association. He has been author/co-author of 18 international and 17 domestic published articles.

**Maryam Keshvari, M.D.**
Iranian Blood Transfusion Organization
Tehran, Iran

Maryam Keshvari began her study of medicine in 1987 at Iran University of Medical Sciences and was graduated in 1995. She then went to Tehran University of Medical Sciences for a specialty course in infectious diseases in 1996, where she graduated in 2000. Since 2000, she has been actively working in the Iranian Blood Transfusion Organization. Presently, she is an Associate Professor of Infectious Diseases in the Iranian Blood Transfusion Organization, providing consultation to patients with Viral Hepatitis, HIV and other Sexually Transmitted Diseases, as well as patients with liver disease related complications. She is also active in Viral Hepatitis management.

# Hepatitis A Epidemiology in Iran, Middle East and the World

Maryam Keshvari, M.D.

## Introduction

Hepatitis A (formerly known as infectious hepatitis) is an acute infectious disease of the liver caused by the hepatitis A virus (HAV). Approximately 1.5 million symptomatic cases of hepatitis A happen annually in the world (1) Hepatitis A virus was first isolated in 1973 (2). It is a small, non- enveloped RNA virus that belongs to Picornaviridea family (3) and accounts for 75% of all cases of hepatitis in the world (4).

In countries that sanitary conditions are inadequate, the virus persists in the environment and almost 100% of the population acquires infection in childhood. At this age, infection has no or only minimal clinical symptoms. Patients, who recover, acquire an immunity which persists throughout life. In developed, industrialized countries that sanitary conditions are good, HAV has ceased to circulate in the environment and among the general population. Here, infections predominantly occur in adult persons travelling to endemic areas or exposed at home to the patients or those who work or live in special centers (i.e. day care centers) (5, 6). Prevalence of Hepatitis A Virus (HAV) infection differs greatly in various parts of the world, due to geographic area, sanitary conditions and socio-economic levels (7, 8).

However, there are several reports of shifting epidemiological pattern of HAV from high prevalence to lower endemicity as a result of improvements of living conditions from all over the world, even underdeveloped and developing countries (4, 6). Although this change seems desirable, it can lead to a higher risk of outbreaks among adult population who have not been exposed to HAV in their life and are not immune against it. 6 Superimposing of HAV in chronic liver disease patients during epidemics can end in many deaths (9-13). To protect these non immune people, or at least, to evaluate if it is necessary to protect them, estimating

the global prevalence of HAV, especially its epidemiology in areas like Middle East which are known as HAV endemic regions since long ago, seems necessary.

## Endemicity

Geographic areas can be characterized by high, intermediate or low levels of endemicity patterns of HAV infection. The levels of endemicity correlate with hygienic and sanitary conditions of each geographic area.

• **High:** In developing countries with very poor sanitary and hygienic conditions (parts of Africa, Asia and Central and South America), infection is usually acquired during early childhood as an asymptomatic or mild infection. Reported disease rates in these areas are therefore low and outbreaks of disease are rare. Reported disease incidence may reach 150 per 100 000 per year.

• **Intermediate:** In developing countries, countries with transitional economies and some regions of industrialized countries where sanitary conditions are variable (Southern and Eastern Europe, some regions in the Middle East), children escape infection in early childhood. Paradoxically, these improved economic and sanitary conditions may lead to a higher disease incidence, as infections occur in older age groups, and reported rates of clinically evident hepatitis A are higher.

• **Low**: In developed countries (Northern and Western Europe, Japan, Australia, New Zealand, USA, Canada) with good sanitary and hygienic conditions, infection rates are generally low. In countries with very low HAV infection rates, disease may occur among specific risk groups such as travelers (14).

## Routes of transmission

Hepatitis A virus is mainly transmitted via fecal-oral route. Person to person contact (15,16), and a wide range of contaminated food products have frequently been reported as causative factors of being infected by HAV. This kind of transmission also occurs when travelers from a HAV non-endemic area visit intermediate or high endemic places (17, 18). Contaminated water supplies, shellfish, oysters, fresh fruits and vegetables like green onions, tomatoes, strawberries, raspberries, and even their frozen products, have been mentioned as responsible factors of food transmission of HAV (15, 19, 20). As donated bloods are not screened for hepatitis

A, transfusion transmitted hepatitis A can also occur rarely (21). Transmission of this viral disease through blood products such as factor VIII or IX concentrates has been reported alternately (22-24). Sexually route of HAV transmission especially in homosexual populations was observed in some studies (25-28). Nosocomial, intrauterine, and vertical transmission of HAV are other possible ways of being infected by this virus (29-36).

In Iran, different studies have done and the range of HAV antibody positivity was between 22-97% (37 -44). A study by Termorshuizen and colleagues found a prevalence of 33.8% seropositive HAV in a Dutch population tested in a cross sectional study (45).

In Kuwait, the epidemiology of HAV in the 1980s was similar to developing countries with almost 100% of adults over the age of 20 years testing positive for anti-HAV. In the latest study the prevalence of HAV was 28% and one quarter of screened individuals below the age of 27 years had positive anti HAV (46). According to some studies, countries such as Qatar, United Arab Emirate and Saudi Arabia have a shifting endemicity from high to intermediate (47,48).

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**Mohammad Ebrahim Ghamarchehreh, M.D.**
Baqiyatallah University of Medical Sciences
Tehran, I.R. Iran

Dr. ghamarchehreh is a graduate in medicine from Iran University of Medical Sciences in 1995. He began his course in internal medicine at Shahid Beheshti University of Medical Sciences in 1997. He began his work as a fellow in the Research Center of Gastroenterology and Hepatology at Taleghani Hospital from 2005 and finished his fellowship of Gastroenterology in 2007.

His main interest in clinical setting is invasive pancreatobiliary diagnostic procedures. He is a consultant and researcher for nonalcoholic fatty liver disease and pancreatobiliary diseases.

# Clinical Manifestations, Diagnosis and Treatment of HAV

Mohammad Ebrahim Ghamarchehreh

**Clinical Manifestations:** HAV infection usually results in an acute, self-limited illness. The manifestations vary with age; it is usually silent or subclinical in children and in adults can vary in severity from a mild flu-like illness to fulminant hepatitis.

The incubation period averages 30 days, after which the illness begins in symptomatic patients with the abrupt onset of prodromal symptoms including, fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain. Within a few days to one week, these patients note dark urine, acholic stool, jaundice, and pruritus. The prodromal symptoms usually diminish when jaundice appears; jaundice typically peaks within two weeks.

HAV is rarely associated with a relapsing or cholestatic clinical illness, and may serve as a trigger for autoimmune hepatitis in genetically susceptible individuals. The two most common physical examination findings are jaundice and hepatomegaly, which occur in 70 and 80 percent of symptomatic patients, respectively. A variety of extra-hepatic manifestations have been associated with acute HAV infection including vasculitis, arthritis, optic neuritis, transverse myelitis, thrombocytopenia, aplastic anemia, and red cell aplasia.

Laboratory findings in symptomatic patients are notable for marked elevations of serum aminotransferases (usually >1000 IU/dL), serum total and direct bilirubin, and alkaline phosphatase.

**Diagnosis:** Serum IgM anti-HAV is the gold standard for the detection of acute illness. The presence of serum IgM anti-HAV antibodies in adults without clinical features of viral hepatitis does not necessarily indicate acute infection. Such patients may have previous HAV infection with prolonged presence of IgM anti-HAV, a false-positive result, or asymptomatic infection. The serologic detection

of antibodies is simpler, easier, and less expensive than other techniques. IgG anti-HAV appears early in the convalescent phase of the disease, and remains detectable for decades.

**Treatment:** Because the disease is usually self-limited, the treatment is supportive. Occasionally patients require hospitalization. Approximately 85 percent of individuals who are infected with hepatitis A virus have full clinical and biochemical recovery within three months, and nearly all have complete recovery by six months. Fatalities due to hepatitis A are more common with advancing age and, in patients with chronic hepatitis C. Reported case fatality rates are 0.1 percent in infants and children, 0.4 percent between the ages of 15 and 39, and 1.1 percent in those over age 40.

**Prevention:** Hepatitis A is transmitted predominantly by the fecal-oral route. Infected individuals are contagious during the incubation period and remain so for about a week after jaundice appears. Prevention can be aided by adherence to sanitary practices such as hand washing, heating foods appropriately, and avoidance of water and foods from endemic areas. Hand washing is highly effective in preventing the transmission of the virus since hepatitis A virus may survive for up to four hours on the fingertips.

Passive immunization with intramuscular polyclonal serum immune globulin prior to exposure can decrease the incidence of HAV infection by more than 90 percent. Passive immunity lasts for up to six months depending upon the dose of immunoglobulin used, but is effective only if administered within two weeks of exposure. Immunoglobulin pre-exposure prophylaxis should be reserved for non-immune individuals who are at risk for exposure hepatitis to A or who are allergic to the hepatitis A vaccine.

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**Sedigheh Amini Kafi-abad, M.D.**
Iran Blood Transfusion Organisation
Tehran, I.R. Iran

Dr. Sedigheh Amini Kafi-abad MD (1990), specialist in Anatomical and Clinical Pathology (1996) from Shahid Beheshti University of Medical Sciences. She has been working as an academic member of the Iranian Blood Transfusion Organization since 1998. She was the Director of the Technical Department in 1999, Quality Control in 2002 and worked as Deputy Managing Director for QC and Technical Affairs in 2008 at the HQ of IBTO. She has been an Assistant Professor of Immunohematology Department as from 2001. She also lectures in her field for postgraduate students.

Dr. Amini has conducted and participated in more than 28 research projects, some of which were national. She has presented more than 55 papers in national and international congresses; she has also published 32 papers in national and international indexed journals.

## Blood Safety in I.R. Iran

Amini-Kafiabad Sedigheh, MD

Introduction: Infections of blood-borne viruses, HIV, HBV, and HCV are a worldwide public health problem and particularly in developing countries represent significant causes of morbidity and mortality. Transfusion-associated infections have been drastically decreased in those countries where routine serologic screening of donors is implemented.

Since foundation of Iranian Blood Transfusion Organization (IBTO) in 1974, screening of blood donations for HBsAg became obligatory. However, in Iran screening of blood donations has became mandatory for HIV from 1989 and for HCV from 1996. Evaluation and monitoring the prevalence of these viruses in blood donations is a valuable index for assessing the quality of processes such as donor selection, public education, screening methods, and potential risk of transfusion-transmitted infections (TTIs). The safety of blood supply can be estimated by monitoring the prevalence of viral markers amongst the donor population.

Methods: Viral screening results of 8,284,097 allogenic donations from 2004 to 2008 were analyzed. All of donations were screened for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and syphilis. Prevalence of HBV and HCV infections per 100,000 donations and 95% confidence interval is calculated.

Results: The prevalence of HBV and HCV were decreased during 5 years study from 2004 to 2008. The overall prevalence was 0.52% for HBV and 0.12% for HCV. There was a significant and impressive drop in HBsAg prevalence from 0.73% in 2004 to 0.36% in 2008. HCV prevalence shows a slight decline in blood donations from 0.13% in 2004 to 0.11% in 2008. The prevalence of HIV appeared to have decreased from 0.005% in 2004 to 0.004 in 2008.

For HBsAg in all of repeat, lapsed and first time blood donations, prevalence rate

was decreased. The HBsAg frequency was slightly higher in male than female. It was increased by age in male and female.
Anti-HCV showed decreases in repeat and lapsed but slightly increased in first time blood donations. Anti-HCV prevalence in female was significantly lower than male donations, but the frequency of anti-HCV in age groups was similar.

Conclusion: Considering the fact that the screening tests in use during these years were of similar sensitivity, uniform confirmation procedure was used and the tests were performed in laboratories with similar proficiency and technical capabilities, it is reasonable to assume that the decline observed may have been due to additional safety measures in place. Some of the major factors that can be considered are as follows:

- A uniform and more efficient donor selection and deferral procedure is in place, which is carried out by trained medical doctors.
- Acquiring a computerized software and data registry of blood donors which allows the deferral of volunteers with a history of positive results.
- Self-deferral procedure which is implemented nationwide since 1997, during which donors are asked not to donate blood if they had AIDS- related symptoms, HIV-related risk behaviors and history of jaundice or viral hepatitis.
- Since 2002 the confidential unit exclusion (CUE) became mandatory and implemented in all blood centers across the country.
- Uniform donor deferral criteria, which is implemented and mandated nationwide since 1997.
- The steady decrease in number of replacement donations from 4% in 2004 to 0% in 2007 plays another significant role in the declined prevalence of blood borne pathogen.
- Increase in the number of repeat donors is another major factor since it has been reported that first time blood donors might pose a greater risk of infectious donation than repeat donors.
- Education efforts of IBTO and MOH to increase public's knowledge on blood-borne infections and routes of transmission.
- Vaccination against HBV among selected groups may also have contributed to the observed decline of HBsAg.

Finally, the lower prevalence of TTI in blood donations compared to the general population and trends of their prevalence suggest that most of the safety measures

employed at IBTO in the recent years have been effective.

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**Bita Behnava, M.D.**
Iranian Blood Transfusion Organization
Tehran, I.R. Iran

She was trained as a general practitioner and then infectious diseases specialist in Mashad university of Medical Sciences. She worked in Hepatitis Clinic of Tehran Blood Transfusion Center for 4 years and cooperated with Tehran Hepatitis Center. She has been actively involved in hepatitis research since joining the Liver and Gastrointestinal Research Center of Baqiyatallah Hospital.

She was a member of the program that treated several hundred hemophilic and thalassemic patients with chronic hepatitis C. She has published more than 10 articles in this field including: Management and diagnosis of viral hepatitis, viral hepatitis in hemophilic and thalassemic patients.

# Management of Side Effects of Interferon and Ribavirin Therapy

Bita Behnava, M.D.

Both IFN and ribavirin induce side effects that have to be considered in the management of patients with chronic hepatitis C. Overall, side effects occurred in almost 80 percent of the patients and resulted in 10–20% premature cessation of the therapy and an additional 20–30% of patients required dose modifications (1).

**Anemia:** Combination of IFN and RBV therapy is associated with mean maximal hemoglobin decreases of 2.9-3.1 g/dl within the first 12 weeks. The anemia is caused by RBV-induced hemolysis and IFN suppression of the bone marrow response. Careful monitoring of hemoglobin level is necessary in patients who are old, female and have low body weight (2).

Recent results have shown that treatment success is dependent upon cumulative ribavirin exposure, as patients who receive <60% of the planned dose have lower response rates (3). So, early diagnosis and treatment of ribavirin induced anemia, may allow patients to continue full-dose combination therapy with peginterferon and ribavirin, enhancing their probability of attaining a sustained virologic response (SVR) (3). For patients without cardiac disease, the standard recommendation during treatment with peginterferon and ribavirin is to reduce ribavirin dosage to 600 mg/d at hemoglobin levels less than 10 g/ dL, and to discontinue ribavirin at hemoglobin levels less than 8.5 g/dL (4). For patients with a history of stable cardiac disease, the standard care is to reduce ribavirin to 600 mg/d when hemoglobin decreases_2 g/dL during any 4-week period, and to discontinue ribavirin when hemoglobin is <12 g/dL (4). Erythropoietin can be used for treatment of anemia in these patients 5. The improvement in hemoglobin level was an independent predictor of improvement in health-related quality (5).

**Neutropenia:** IFN therapy can induce bone marrow suppression and result in neutropenia. Significant neutropenia occurs in 2o% of patients during PEG-IFN alpha-2a therapy. Despite the reduction in ANC, the rate of serious bacterial

infections is relatively low in HCV treated patients (6). Current recommendation is dose reduction when the absolute neutrophil count falls below 750 mm3 (7). G-CSF at a dose of 300 mcg one to three times a week can be used for correction of neutropenia induced interefron ,especially in those with higher risk of infections, such as cirrhotic patients and HIV/HCV co-infection (8).

**Thrombocytopenia:** Severe thrombocytopenia is usually seen only in those with established cirrhosis or in rare patients in whom IFN induces autoimmune thrombocytopenia. Dose reduction is advised when platelet counts fall below 50000/micL and discontinuation of therapy is recommended if platelet count drops below 30000mic/L (7).

**Interferon induced thyroiditis:** Up to 15% of patients with hepatitis C receiving IFN –alpha develop clinical thyroid disease, and up to 40% were reported to develop thyroid antibodies. The main risk factor for developing thyroid disease during antiviral therapy is the previous positivity for anti-thyroid antibodies (anti-thyroid peroxidase) especially in older women (9). Screening for auto-antibodies and serum thyroid-stimulating hormone is recommended before, during and after interferon-alpha treatment (9). Autoimmune interferon induced thyroiditis (IIT) is divided to three categories including Graves' disease (GD), Hashimoto's thyroiditis (HT) and the production of thyroid auto-antibodies (TAbs) without clinical disease, while non-autoimmune HT includes destructive thyroiditis and non-autoimmune hypothyroidism (10). The diagnosis of GD is made by the presence of clinical hyperthyroidism with positive TSHR antibodies and/or diffusely increased radioactive iodine intake on thyroid scan. The diagnosis of HT is based by the presence of TAbs and clinical hypothyroidism. Destructive thyroiditis is characterized by three phases, a sudden onset of hyperthyroidism, sometimes associated with neck tenderness and fever, followed by a hypothyroid phase, and eventually resolution and normalization of thyroid functions .The diagnosis of destructive thyroiditis is based on negative TSH-receptor antibodies (TRAb) and low thyroid radioactive iodine uptake (10).

In cases of symptomatic thyrotoxicosis, withholding IFNα therapy should be considered in consultation with an endocrinologist. However, if the workup is consistent with destructive thyroiditis treatment with a beta-blocker, in symptomatic hyperthyroidism phase is usually sufficient to enable continuation of the interferon regimen and also the patient should be monitored for the development

of hypothyroidism. If the workup is consistent with Graves' disease, treatment with radioactive iodine and/or surgery should be considered. Treatment of hypothyroidism usually consists of thyroid hormone replacement, with no need to stop IFNα therapy (10).

**Cutaneous complications:** The most common cutaneous side-effects of IFN-alpha and ribavirin are injection-site reactions (erythema ,pruritis, indurations and rarely abscess formation) which have been reported in approximately 60% of patients (7, 11). The rate of injection site reaction was higher with PEG-IFN-α-2b and ribavirin than with IFN-α-2b and ribavirin. Oral antihistamines and topical corticosteroid at the PEG-IFN-α injection site is suggested for skin reactions, in cases of abscess formation oral antibiotics and drainage should be considered (7, 11).

Other reported cutaneous complications are lichen planus, hyperpigmentation, photoallergic eczema, alopecia, herpes zoster, itching, exacerbation of psoriasis, xerosis, a transient generalized rash (12, 13). Some authors suggest small doses of oral prednisolone for generalized eruption during continuous combination therapy with PEG-IFN-α and ribavirin (11).

**Pulmonary complications:** Pulmonary disease is a rare but potentially fatal side effect occurring during interferon (IFN) α treatment for chronic hepatitis C, and rare cases of eosinophilic pneumonia, bronchiolitis obliterans, organizing pneumonia, interstitial pneumonias, sarcoidosis, pleural effusions, and asthma exacerbation during antiviral therapy for hepatitis C, have been reported (14, 15). The dry cough and shortness of breath are relatively common with IFN-RBV and most patients are able to tolerate it .If it becomes productive or acc0mpanied by fever or abnormal respiratory sounds,the patient should undergo chest X-ray (7).

**Autoimmune disease:** IFN has immunomodulatory properties, and treatment can induce autoimmune phenomena. Sarcoidosis has been described in association with the combination of Interferon and ribavirin therapy and also with HCV infection itself. Interferon- induced sarcoidosis may manifest as a systemic or cutaneous disease or a combination of both with pulmonary and skin involvement (16). Several autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus , autoimmune hepatitis ,antiphospholipid syndrome and type 1 diabetes mellitus have been reported to develop or exacerbate during IFN therapy in chronic hepatitis C patients (17-20). Stopping of IFN is necessary in such cases.

**Neuropsychiatric side effects:** Depression occurs in up to 37% of patients treated with PEG-IFN and RBV. Depression associated with IFN treatment is an important reason for decreasing the dose or discontinuing IFN treatment.

As a result, successful treatment of chronic hepatitis c often requires treatment or prevention of IFN-induced depression (21). It is critical to conduct pretherapy assessment of patients for underlying neuropsychiatric conditions including past history of depression,suicide attempts and substance or alchohol abuse which often predispose to depression in these patients (7). Depression-related symptoms include sadness, loss of interest, hopelessness, mood instability/fluctuations, dysphoria, impaired ability to think and/or remember, sleep disturbance, diminished appetite, suicidal thoughts, vague aches and pains, and fatigue (7, 21). It is suggested that pharmacologic therapy be given before beginning IFN in patients with risk factors for a mood disturbance, in other patients antidepressant treatment can be started after development of its initial features, generally after seven or more days of continuous depressive symptoms of mild or greater severity (22). Other psychiatric disorders that have been reported during IFN therapy are psychosis and mania.

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