

Hepatitis B and C Public Policy Association NEWSLETTER



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Dear Friends,

It is a pleasure to introduce the summer issue of the Hepatitis B & C Public Policy Association's newsletter which features two articles from our new editorial board members Prof. Federico Villamil, Argentina and Prof. Seng Gee Lim, Singapore. In his contribution Prof. Villamil briefly discusses the clinical and socio-economical impact of the universal anti-hepatitis A virus vaccination program that was introduced in Argentina in 2005. Prof. Seng Gee Lim, Chairman of the recent APASL liver week 2013 Congress in Singapore, together with Dr. Guan-Huei Lee takes us through the most recent data presented in Singapore

last month on epidemiology of Hepatitis in Asia. Newly appointed EASL Secretary General, Prof. Markus Peck, illustrates the most recent EASL initiatives aimed at fostering scientific exchange, education and public awareness of liver diseases in Europe. Finally, Prof. Stefan Zeuzem introduces the 2nd edition of the Viral hepatitis Congress to be held in Frankfurt in September.

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EASL Current and future initiatives

Prof. Markus Peck-Radosavljevic, EASL Secretary General

Vienna, July 17, 2013

It is a pleasure for me to introduce myself to you as the new Secretary General of EASL, the European Association for the Study of the Liver. EASL's mission is to foster scientific exchange, education, and public awareness of liver disease and their management. EASL acts as an advisory to European Health Authorities in relation to issues dealing with liver disease and liver health.

As one of EASL's most important public policy activities, we launched the "EASL white paper on the burden of liver disease in Europe" this February, which is a literature review of the burden of liver disease in Europe. Even though there are serious gaps in the literature on a variety of liver diseases in different European countries, this is an important first step to emphasize the importance of liver disease to our European Authorities in Brussels as well as to local authorities in European countries. As expected, chronic viral hepatitis is the second most common cause of end stage liver disease and liver-related death in Europe,

highlighting the importance of introducing effective public policy measures in all of Europe to tackle chronic viral hepatitis in our region.

In the year to come we are focusing our EU public affairs agenda on developing a road map to liver disease research in Europe. And we will be reaching out more to our Eastern European colleagues to support them in their fight against liver diseases as well as integrate them more actively into our activities. EASL Schools of Hepatology will take place in Belgrade and Moscow and the Monothematic Conference will take place in Eastern Europe in 2015.

Viral hepatitis has always been big on the agenda of EASL but in these exciting times of rapid and very effective drug development to tackle not only chronic hepatitis B but also chronic hepatitis C, viral hepatitis takes center stage in many of our activities. During this year's International Liver Congress (ILC) in Amsterdam, a large number of

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exciting phase-III data dealing with treatment of chronic hepatitis C with new directly acting antivirals (DAA's) either in combination with interferon and ribavirin or without interferon have been presented and next year's ILC in London will feature viral hepatitis as the topic of the most important educational session during this meeting, the postgraduate course.

But EASL is not only dedicated to viral hepatitis: we are actively promoting research and development in all kinds of liver diseases, most notably alcoholic liver disease and non-alcoholic fatty liver disease. EASL is regularly publishing and updating clinical practice guidelines of a great variety of liver diseases to help guide clinical practice in the most up-to-date way possible. Next year we expect to release the updated clinical practice guidelines on the management of chronic hepatitis C as well as the clinical practice guidelines on the management of patients with hepatic encephalopathy. Several other clinical practice guidelines are currently in preparation.

EASL's official journal, The Journal of Hepatology, is the second highest ranking journal in liver disease and of great value for researchers in liver disease as well as practicing physicians with a focus on managing patients with liver disease. In the last years we invested considerable efforts on developing electronic tools for education clinic practice alike. Today we are happy to offer iLiver, a free smartphone app to be used as a quick reference guide at the bedside or the outpatient clinic. The newly launched liver tree is our

premiere electronic tool for online education as well as a rich resource of slides for presentations on liver diseases.

EASL will not only try to preserve the success of the last decade but try to evolve in new areas that have not been covered in the last several years. I invite you to actively participate by becoming a member to EASL, which will allow you to get access to the most interesting and up to date information relating to liver diseases in Europe and around the world and at the same time will become a part of our overgrowing family of liver doctors trying to improve in our fight against liver diseases.

Kind regards,

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The Viral Hepatitis Congress 2013

Frankfurt 26-28 September

by Prof S Zeuzem

The management of viral hepatitis has advanced steadily but slowly over the past several decades, with interferon-based regimens being the mainstay of treatment. However, as we enter an era that brings the promise of new therapies and wider treatment choices, increased understanding of the latest clinical research and new therapeutic landscape will allow patients to benefit from informed and individualised clinical decisions.

In September 2012, the inaugural Viral Hepatitis Congress was held in Frankfurt, Germany. Co-Chaired by Professors Ira Jacobson (WeillCornell Medical College, New York, USA) and Stefan Zeuzem (Johann Wolfgang Goethe University Hospital, Frankfurt, Germany), the Congress focused on the latest progress and innovations

in the management of viral hepatitis. More than 400 participants heard presentations from a broad international faculty.

This year The Viral Hepatitis Congress will return once again to the historic city of Frankfurt. The Congress will be held at the Frankfurt Messe Congress Centre, from 26–28 September 2013, and promises a relevant, meaningful and topical scientific programme. There will be a particular focus on the latest developments and innovations in the practical aspects of disease management, including:

- *A look at the strengths, weaknesses, opportunities and threats of the currently available anti-HCV therapies*

- *An in-depth review of the new era of HCV therapies, including the potential for IFN-free regimens*
- *Special considerations for patients with HCV comorbidities*
- *A case-based approach to clinical challenges in hepatitis C management*
- *The latest advances in screening and diagnostic technologies*
- *Dedicated sessions on Hepatitis B, D and E, and hepatocellular carcinoma*
- *Industry symposia*
- *Poster presentations.*

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The Congress scientific committee and faculty includes experts from across Europe, the USA, Canada and New Zealand, offering delegates the chance to discuss clinical experiences and key knowledge with the leading authorities in the viral hepatitis field.

In order to broaden the reach of the Congress and bridge the gap to the virtual audience, a core goal is to extend the learnings beyond the Congress itself. This will be accomplished in a number of ways:

- *Abstracts will be published as a supplement to the Journal of Viral Hepatitis*
- *Interviews with faculty will be available on a dedicated YouTube channel: ViralHepatitisTV*
- *Speakers' presentations will be*

recorded and webcast on www.viral-hep.org

- *Posters presented at the Congress will be brought together as online, interactive books.*

In this fast-moving and highly exciting era for hepatitis treatment, the opportunity to network and actively participate in the debate and discussion is a key component of the Congress, further enhancing the learning experience. Networking opportunities include the opening-night welcome reception and a lively poster and exhibition area directly outside the main auditorium, and immersive participation will be guaranteed by utilising a cutting-edge audience response system that allows audience voting, direct text questions, verbal discussion and 'real time' feedback.

For more information and the latest updates on The Viral Hepatitis Congress 2013, visit

www.viral-hep.org or contact the organising secretariat. Congress registration is open until 6 September 2013.

Enquiries to:

The Viral Hepatitis Congress,
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Results of the Universal Vaccination Program for Hepatitis A in Argentina

by Federico G. Villamil, MD

Background

Prior to 2005, when universal vaccination was introduced, Argentina was an area of intermediate endemicity for hepatitis A virus (HAV) infection. Gonzalez et al showed in 1997 that among 3,699 children from Argentina, anti-HAV was detected in 46% at 5 years of age and 68% at 10 years. Marked differences in the prevalence of HAV exposure was observed in different regions ranging from 29.4% in the city of Buenos Aires to 81.4% in the city of Tucuman, located in the Northwest of the country ⁽¹⁾. Not

surprisingly, HAV was by far the most frequent etiology of acute viral hepatitis in children, and represented 93% of 3,120 cases in the study reported in 2000 by Ciocca et al ⁽²⁾. However, the most striking feature of HAV infection in Argentina, and the one of greatest concern, was the high prevalence of acute liver failure (ALF) in the pediatric age. Ciocca et al showed that between 1982 and 2002 HAV was responsible for 61% of 210 ALF in children with a mean age of 5.3 years ⁽³⁾. At that time, hepatitis A was regarded as a benign

etiology of ALF with spontaneous recovery in most cases. This was not the case for Argentina. Among the 128 children with fulminant hepatitis A reported by Ciocca et al, only 40 (31%) survived with medical therapy, 33 (26%) died and 55 (43%) underwent liver transplantation. Similar results were observed in a survey carried out by the Argentina Society of Transplantation in 2001 (Villamil FG, unpublished observations) including 219 children with ALF referred to 5 transplant centers. Death or transplantation occurred

in 71% of patients. Munné et al showed that all HAV isolates from Argentina (n=82), obtained both from sporadic cases and epidemics, belonged to the IA subgenotype ⁽⁴⁾.

Rationale for Universal HAV Vaccination

In 2005, and following the recommendations of the Pediatric and Liver Societies, the Argentina Ministry of Health devised a plan for universal immunization for HAV using a single dose of formaldehyde-inactivated vaccine administered at 12 months of age.

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HAV vaccine was incorporated into the National Immunization Calendar and was given simultaneously with the triple (MMR) vaccine ⁽⁵⁾. The rationale for the single dose strategy at 12 months after birth was based on several facts. During the first year of life most children are protected by antibodies transferred from their mothers, living in a country where anti-HAV is detectable in >80% of adults. HAV-related disease usually manifests after 1 year of age and children aged 1-2 years are thought to be the main source of transmission. If this hypothesis was correct, then administration of a highly immunogenic vaccine at 12 months should be effective to prevent the spread of HAV infection. In addition, it was speculated that the high circulation of HAV in Argentina could act as a “natural booster” making a second dose of vaccine unnecessary.

Results of HAV Vaccination

Universal vaccination with HAV vaccine resulted in robust health and economic benefits. According to data reported by the Argentina Ministry of Health, reviewed by Gentile et al ⁽⁶⁾ and Vacchino MN ⁽⁷⁾, the number of cases

of acute hepatitis A decreased from 26,475 in 2005 to only 329 in 2010 and the corresponding rates of infection from 113.3/100,000 to 1.4/100,000 respectively, a reduction of 88.3%. Vaccine coverage throughout the country was 95% in 2006 ⁽⁷⁾ and 92.4% in 2011 ⁽⁶⁾. Importantly, ALF and need for transplantation due to hepatitis A substantially and rapidly declined after universal vaccination and has almost disappeared in recent years. Cervio et al ⁽⁸⁾ showed that the proportion of children with ALF due to HAV infection decreased from 54.6% in 2003-2008 (165/367) to 27.7% in 2006 (18/65) with no cases being reported after 2006 ⁽⁶⁾. A recent study from the Argentina Ministry of Health (Vizzotti et al, unpublished data) showed that 4 years after vaccination 93% of 1138 children had protective titers (>10 mIU/mL) of anti-HAV ⁽⁶⁾. Finally, universal vaccination for HAV in Argentina was found to be highly cost-effective. Lopez et al estimated that, with a 95% national vaccination coverage, 352,405 cases of hepatitis A would be prevented annually including 121,587 symptomatic cases and 428 deaths ⁽⁹⁾. The program would thus save

US\$ 23,989,963 annually which is equivalent to US\$ 3,429 per life-year gained.

Conclusions

Universal HAV vaccination in childhood was highly effective not only to decrease substantially the rate of infection in children but to eradicate also severe forms of acute hepatitis A leading to death or liver transplantation. Argentina was the first country to adopt the cost-effective strategy of single dose vaccination at 12 months of age. Four years after vaccination, more than 90% of immunized children developed protective anti-HAV serum concentrations.

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Epidemiology and Prevention of Hepatitis in Asia

by Prof. Seng Gee Lim, Chairman APASL Liver week 2013
and Prof. Guan-Huei Lee

The Asia Pacific region has long been known to have a high prevalence of viral hepatitis. Identification of biomarkers of hepatitis A, B, C, D and E has enabled us to estimate the burden of these diseases, and to implement subsequent control measures. Despite tremendous success, more effort is needed to control the problem of viral hepatitis in the Asia Pacific.

Hepatitis A

Hepatitis A infection has become less frequent in many places in the world, including the Asia Pacific region. The lower exposure rate renders many young people susceptible to HAV, which has become a public health issue [1].

Amongst Taiwan's school children, the prevalence of anti-HAV has fallen from 31% in 1979 to 2.5% in 2005, reflecting the continued improvement in the water supply, sewage system, personal hygiene, food handling and cooking [2]. Active immunization in high-risk population also contributes to the successful control of the virus. Hepatitis A vaccination in aboriginal towns in Taiwan successfully reduced the incidence rate of acute hepatitis A from a peak of 90.74 per 100,000 in 1995 to almost 0 incidence rate since 2008 [3].

Hepatitis B

Worldwide there are 350 million persons chronically infected with hepatitis B, 260 million (75%)

of these are in the Asia Pacific region. HBV-related cirrhosis or hepatocellular carcinoma accounts for 0.5~0.7 million deaths per year, of which at least 60% are in the Asia Pacific. Chronic hepatitis and cirrhosis of the liver further add to the morbidity of HBsAg carriers [1]. With an estimated 120-130 million chronic HBV patients, the disease burden remains high in China, followed by India (34 million) and Vietnam (7-14 million) [4].

The prevalence of hepatitis B-infected individuals has been falling dramatically in the younger age groups since the start of the universal vaccination program in Asia, along with the incidence of hepatocellular carcinoma (HCC). In Taiwan, the incidence of HCC under the age of 20 years fell from 0.6 per 100,000 person-years for those born before 1984, to about 0.2 per 100,000 person-years in those born after the start of mass HBV immunization (1984) [5]. The same has occurred in China, Thailand, and most dramatically amongst the Alaska native people where new HCC patients under 20 years old have almost been completely eradicated, from a high rate of 3 per 100,000 [6]. The percentage of HBV genotype A increased in CHB in Japan. Relatively high frequency of genotype A in younger patients may reflect recent infection in younger people by sexual transmission [7].

Viral transmission by contaminated blood products remains a

concern. Although most blood banks regularly screen the donor for HBsAg serology, occult HBV not detectable by serology is an increasing concern. In Indonesia, researchers analysed purified PCR product of 153 regular blood donor samples with HBsAg-negative, anti-HBc-positive and HBV DNA-positive profile. One-hundred (65.4%) isolates showed amino acid substitutions, with a total of 47 different mutational patterns distributed at 31 amino acid sites [8].

The safety of health care providers is still often overlooked. In a public general hospital in China, the rate of HBsAg carriers amongst health care workers is 6.13% (87/1420). The vaccination rate in the department of infectious disease was only 57.8% [9]. There is also a lack of standardized care in certain areas and patient compliance is a concern. In Western regions of China, half of HBV patients were not being treated and virological response rate is lower than expected [10]. To achieve better treatment targets, initial antiviral treatment should be optimized and patient's adherence should be improved.

Hepatitis C

Most of the chronic hepatitis C patients in the world reside in the Asia Pacific region (estimated 95-101 million). Of these, China (40 million) and Southeast Asia (30-35 million) carry the heaviest burden. In Asia, Mongolia has the highest population prevalence of >10% of

its population carrying the virus ^[1]. Genotype 1 is overall the most common, although some countries have predominance of other genotypes (e.g. Vietnam has high prevalence of genotype 6 HCV).

Even though the prevalence of the more favorable IL28B genotype CC is common in Asia, and better treatment is now available, many HCV-infected patients cannot have access to treatment due to economic reasons, and many cases remained undiagnosed. Prevalence of the favorable IL28B rs12979860 CC and rs8099917 TT genotypes in self-reported Caucasians, Asians, Aborigines and persons of Mediterranean origin were 27% and 48%, 79% and 78%, 35% and 58%, and 18% and 35% respectively in Australia, similar to earlier reports by ethnicity ^[11]. An association of favorable IL28B polymorphisms with spontaneous clearance in Iranian patients with hepatitis C was reported during this meeting ^[12].

As an effective vaccination for HCV is still not available, the important preventive measures for the transmission of HCV include the screening of blood donors, reduction in unnecessary parenteral treatment, Universal Infection Control Precautions, reduction in sexual promiscuity and needle exchange programs for intravenous drug users. In many Asian countries, the maintenance of safe blood transfusion remains a big challenge, and contaminated blood products and equipment continue to be an important source of new HCV infection as not all blood banks routinely test for HCV ^[1].

Progress is being made in a number of areas. Since 1995, there has been a statistically significant decrease in prevalence of HCV infection among hemodialysis patients from 65.3% to 24.5% over the past 3 decades ($P < 0.05$) in Saudi Arabia. This decrease in prevalence is partially due to strict adherence to Universal Infection Control Precautions guidelines and using dedicated dialysis machines for infected patients with hepatitis C ^[13].

Hepatitis D

Hepatitis D is transmitted along with HBV as co-infection or super-infection, resulting in more severe complications compared to infection with HBV alone. These complications include a greater likelihood of experiencing liver failure in acute infections and a rapid progression to liver cirrhosis, with an increased chance of developing liver cancer. It was estimated to have 15-20 million infected persons worldwide ^[1].

Prevention of HBV infection will also prevent hepatitis D, and immunizations against HBV will also prevent HDV infection. The prevalence of anti-HDV in HBsAg carriers in the Asia Pacific varies widely between different areas, from almost none in Malaysia and up to 23.5% in Miyako, Japan ^[14]. However most of the available population data was dated from the 1990s to early 2000, and the current prevalence would likely have reduced due to the impact of HBV vaccination in line with the success of HBV vaccination program.

In the APASL 2013 meeting HDV-RNA positive prevalence of 15.4% (41/266) in Vietnamese HBsAg-positive patients was reported ^[15]. In Mongolia, although 88.7% of the 655 children studied were immunized against hepatitis B, 64 (9.8%) tested positive for hepatitis B surface antigen (HBsAg) and/or HBV DNA and 13 (2.0%) for HDV RNA. Twenty-seven children (4.1%) also had detectable HCV RNA ^[16].

Hepatitis E

Hepatitis E virus is a non-enveloped RNA virus transmitted by fecal-oral route, mainly through contamination of drinking water. It is associated with fulminant hepatitis in 5-25% of pregnant women infected in the 3rd trimester, and an important cause of maternal mortality in endemic countries ^[1]. Chronic hepatitis E was also reported in immunosuppressed post-transplant patients.

In the Asia Pacific region, the prevalence of HEV seropositivity was approximately 25% in the general population, and 61% of the global cases and 65% of deaths from HEV occur here. It is also one of the most common causes of acute liver failure in East and Southeast Asia ^[17].

The most important preventive measures include the improvement of the sewage system, the water supply, and food handling. Active immunization is now available. Two recombinant vaccines were developed in the last 3 years, with one licensed in China in December 2011 and demonstrated excellent efficacy and safety that was presented during the symposium on hepatitis E ^[18].

Conclusions

There is still a heavy disease burden of viral hepatitis across the Asia Pacific but control measures have reduced the disease burden overall. This is best seen in hepatitis B, but without an effective vaccine for hepatitis C, reduction in disease burden and prevalence through control measures are hard to document. Hepatitis E remains a very promising field for disease prevention if the vaccine can be included in vaccination programs.

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