Background document

VHPB TECHNICAL MEETING

MULTI TOPIC meeting

The impact of viral hepatitis treatment and vaccination non-responders and occult hepatitis on public health

Vilnius, Lithuania

25-26 April 2019

Greet Hendrickx
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Content

This pre-meeting document contains a list of selected abstracts/ references from a Pubmed MEDLINE search on different topics of the meeting. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.
This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully it will give an overview of what has been published on the topics of the meeting

1. Treatment non responders – relapse – reinfection

1.1. In the area of DAA's are treatment non-responders/relapse an issue?

Session1.1: In the area of DAA's are treatment non-responders/relapse an issue?	
09:50-10:10	Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis ***Graham Cooke*** *(Imperial College London – UK).*
Related articles (proposed by speaker)	Simmons, B., Saleem, J., Hill, A., Riley, R. D. and Cooke, G. S. **"Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis**." Clin Infect Dis **2016** 62(6): 683-694.Division of Medicine, Imperial College London. BACKGROUND: Treatment for hepatitis C virus (HCV) can lead to sustained virological response (SVR) in over 90% of people. Subsequent recurrence of HCV, either from late relapse or reinfection, reverses the beneficial effects of SVR. METHODS: A search identified studies analysing HCV recurrence post-SVR. The recurrence rate for each study was calculated using events/person years of follow-up (PYFU). Results were pooled using a random-effects model and used to calculate 5-year recurrence risk. Three patient groups were analysed: (1) Mono-HCV infected "low-risk" patients; (2) Mono-HCV infected "high-risk" patients (injecting drug users or prisoners); (3) human immunodeficiency virus (HIV)/HCV coinfected patients. Recurrence was defined as confirmed HCV RNA detectability post-SVR. RESULTS: In the 43 studies of HCV mono-infected "low-risk" patients (n = 7969) the pooled recurrence rate was 1.85/1000 PYFU (95% confidence interval [CI], .71-3.35; I(2) = 73%) leading to a summary 5-year recurrence risk of 0.95% (95% CI, .35%-1.69%). For the 14 studies of HCV monoinfected "high-risk" patients (n = 771) the pooled recurrence rate was 22.32/1000 PYFU (95% CI, 13.07-33.46; I(2) = 27%) leading to a summary 5-year risk of 10.67% (95% CI, 6.38%-15.66%). For the 4 studies of HIV/HCV coinfected patients the pooled recurrence rate was 32.02/1000 PYFU (95% CI, .00-123.49; I(2) = 96%) leading to a summary 5-year risk of 15.02% (95% CI, .00%-48.26%). The higher pooled estimates of recurrence in the high-risk and coinfected cohorts were driven by an increase in reinfection rather than late relapse. CONCLUSIONS: SVR appears durable in the majority of patients at 5 years post-treatment. The large difference in 5 year event rate by risk group is driven mainly by an increased reinfection risk. Martin NK, et al, 2016, Can Hepatitis C Virus (HCV) **Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights,** CLINICAL INFECTIOUS DISEASES, Vol: 62, Pages: 1072-1080 Abstract BACKGROUND: We report on the hepatitis C virus (HCV) epidemic among human

immunodeficiency virus (HIV)-positive men who have sex with men (MSM) in the United Kingdom and model its trajectory with or without scaled-up HCV direct-acting antivirals (DAAs). METHODS: A dynamic HCV transmission model among HIV-diagnosed MSM in the United Kingdom was calibrated to HCV prevalence (antibody [Ab] or RNA positive), incidence, and treatment from 2004 to 2011 among HIV-diagnosed MSM in the UK Collaborative HIV Cohort (UK CHIC). The epidemic was projected with current or scaled-up HCV treatment, with or without a 20% behavioral risk reduction. RESULTS: HCV prevalence among HIV-positive MSM in UK CHIC increased from 7.3% in 2004 to 9.9% in 2011, whereas primary incidence was flat (1.02-1.38 per 100 person-years). Over the next decade, modeling suggests 94% of infections are attributable to high-risk individuals, comprising 7% of the population. Without treatment, HCV chronic prevalence could have been 38% higher in 2015 (11.9% vs 8.6%). With current treatment and sustained virological response rates (status quo), chronic prevalence is likely to increase to 11% by 2025, but stabilize with DAA introduction in 2015. With DAA scale-up to 80% within 1 year of diagnosis (regardless of disease stage), and 20% per year thereafter, chronic prevalence could decline by 71% (to 3.2%) compared to status quo in 2025. With additional behavioral interventions, chronic prevalence could decline further to <2.5% by 2025. CONCLUSIONS: Epidemiological data and modeling suggest a continuing HCV epidemic among HIV-diagnosed MSM in the United Kingdom driven by high-risk individuals, despite high treatment rates. Substantial reductions in HCV transmission could be achieved through scale-up of DAAs and moderately effective behavioral interventions

Garvey et al **Fall in HCV incidence in HIV+ve MSM in London following wider access to DAA therapy** CROI Abstract 85 March 4-7th Washington

Abstract Body: Modelling of the London HCV epidemic in HIV+ MSM suggested early access to DAA treatment plus risk-behaviour modification may reduce incidence. With high rates of linkage to care and treatment access, micro-elimination of HCV within HIV+ MSM may be realistic, ahead of 2030 WHO targets. Data from European cohorts have shown a reduction in HCV incidence amongst HIV+ MSM. We examine the effect of HCV treatment access (in the pre- and post-DAA era) and risk-behaviour modification upon incidence of HCV first and re-infections in HIV+ MSM in three large London clinics. A retrospective cohort study was conducted at 3 London HIV clinics (Royal Free and St Mary's Hospitals, Mortimer Market) between July 2013 and June 2018. During each 6-month period the following data were collected [1] number of first acute HCV diagnoses [2] number of subsequent acute HCV diagnoses (re-infections) [3] denominator of HIV+MSM under active follow up [4] number of PEG IFN/RBV or DAA-based HCV treatments for acute/early HCV (<12m since diagnosis) [5] number of PEG IFN/RBV or DAA-based HCV therapies for chronic HCV (>12m since diagnosis). Incidence rates (acute HCV diagnoses/ HIV+ MSM 1000 PYFU) and re-infection rates (re-infections/all incident infections x 100) were calculated for each time-period. 293 acute HCV infections were identified (246 first infections and 47 re-infections). DAA treatment became widely available in late 2015. All centres adopted risk-reduction behaviour intervention with counselling/psychology. Incidence of first HCV episode peaked at 17.72/1000 HIV+MSM PYFU [95%CI 12.81–22.64] in 2015. Rates fell to 4.64 [95%CI 2.53–7.78] by 2018. Re-infection rates increased from 9% to 16% during the study period. Supervised early HCV treatments (<12m of diagnosis) increased from 22% to 61% between 2013 and 2018. Supervised chronic HCV/HIV treatment rates increased from 2.8/month in pre-DAA era to 15.6/month in post-DAA era. Time from diagnosis to starting any HCV treatment reduced from average of 40.9 months (2013) to 3.1 months (2018). There has been a 74% reduction in incidence of first HCV infection and 62% reduction of overall HCV incidence in HIV+MSM since the epidemic peak of 2015 which coincides with wider access to

DAA-based therapy across London. However re-infection rates remain high and maybe increasing. Further interventions to reduce ongoing transmission including access to treatment for reinfection are likely needed if micro-elimination is to be achieved

Related articles (PubMed search)

van der Meer, A. J. and Berenguer, M. "**Reversion of disease manifestations after HCV eradication**." J Hepatol **2016** 65(1 Suppl): S95-S108.Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands. Electronic address: a.vandermeer@erasmusmc.nl.

Pisaturo M, Minichini C, Starace M, Caroprese M, Macera M, Brancaccio G, . . . Coppola N. **Hepatitis C late relapse in patients with directly acting antiviral-related sustained virological response at week 12**. Liver international : official journal of the International Association for the Study of the Liver. 2018.

Alternative: Wirth, T. C. and Manns, M. P. "**The impact of the revolution in hepatitis C treatment on hepatocellular carcinoma**." Ann Oncol **2016** 27(8): 1467-1474.Department of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Hannover.

1.2. Predictive factors for treatment non-responders or relapse and possible solutions

Session 1.2: Predictive factors for treatment non-responders or relapse and possible solutions

Genetic

Predictive Genetic Factors

10:50–11:10 Treatment of hepatitis C: the use of the new pangenotypic direct-acting antivirals in "special populations"

Stanislas Pol *(Universite Paris Descartes, Paris, France).*

Pol, S. and Parlati, L. "**Treatment of hepatitis C: the use of the new pangenotypic direct-acting antivirals in "special populations"**." Liver Int **2018** 38 Suppl 1: 28-33.Hepatology Department, Universite Paris Descartes, Cochin hospital, APHP, Paris, France.

The treatment of hepatitis C virus (HCV) infection markedly progressed these two last decades. Since 15 years, the combination of pegylated interferon alpha and ribavirin led to a sustained virologic response (SVR) which corresponds to a complete recovery in around 45 % of patients with HCV genotype 1, 65 % with HCV genotype 4, 70 % with HCV genotype 3 and around 85 % with HCV genotype 2. A better understanding of the HCV life-cycle recently resulted in the development of several potential direct-acting antiviral drugs (DAA) targeting viral proteins (NS3/4A protease

inhibitors, NS5B nucleosidic and non nucleosidic polymerase inhibitors, NS5A replication complex inhibitors). A lot of data has been reported with the combinations of pegylated interferon alpha/ribavirin and the first generation oral DAA, Telaprevir and Boceprevir. These regimens have demonstrated a high level of antiviral efficacy (75 % of SVR) and an acceptable safety profile. After this first major step, the combination of the second generation DAA with pegylated interferon alpha/ribavirin will impact antiviral potency (75 to 90 % of SVR) and tolerance and will reduce the duration of therapies and the pill burden. The next step, which is an actual revolution, will be the oral combination of new DAA which is likely to become the standard of care for chronic HCV after 2015. Most studies have been conducted in small numbers of "easy-to-treat" patients with short post-treatment period with outstanding results but we are now waiting for confirming these results in more difficult-to-treat patients (experienced genotype 3-infected or genotype 1-infected patients who failed to first generation protease inhibitors, cirrhotic, HIV co-infected patients, allograft recipients or candidates to transplantation).

Related articles (proposed by speaker)

1. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. 2017; http://www.hcvguidelines.org. Accessed 16 July 2017.
2. Colombo M, Aghemo A, Liu H, et al. Treatment With Ledipasvir-Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic Hepatitis C Virus Genotype 1 or 4 Infection: A Randomized Trial. Ann Intern Med. 2017 Jan 17;166(2):109-117.
3. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic HCV genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015;163(1):1-13.
4. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for previously Treated HCV Infection. N Engl J Med. 2017;376(22):2134-2146.

Alternative Zanaga, L. P., Miotto, N., Mendes, L. C., Stucchi, R. S. and Vigani, A. G. "**Treatment of hepatitis C virus genotype 3 infection with direct-acting antiviral agents**." Braz J Med Biol Res **2016** 49(11): e5504.Divisao de Molestias Infecciosas Departamento de Clinica Medica, Universidade Estadual de Campinas, Campinas, SP, Brasil.

Related articles (pubmed search)

Zanaga, L. P., Miotto, N., Mendes, L. C., Stucchi, R. S. and Vigani, A. G. "**Treatment of hepatitis C virus genotype 3 infection with direct-acting antiviral agents**." Braz J Med Biol Res **2016** 49(11): e5504.

11:10–11:30 *Risk factors for re-infection*

Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study.

Naveed Janjua *(University of British Columbia, Canada)*

Islam, N., Krajden, M., Shoveller, J., Gustafson, P., Gilbert, M., Buxton, J. A., Wong, J., Tyndall, M. W., Janjua, N. Z. and British Columbia Hepatitis Testers Cohort, t. "**Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study**." Lancet Gastroenterol Hepatol **2017** 2(3): 200-210

BACKGROUND: People remain at risk of reinfection with hepatitis C virus (HCV), even after clearance of the primary infection. We identified factors associated with HCV reinfection risk in a large population-based cohort study in British Columbia, Canada, and examined the association of opioid substitution therapy and mental health counselling with reinfection. METHODS: We obtained data from the British Columbia Hepatitis Testers Cohort, which includes all individuals tested for HCV or HIV at the British Columbia Centre for Disease Control Public Health Laboratory during 1990-2013 (when data were available). We defined cases of HCV reinfection as individuals with a positive HCV PCR test after either spontaneous clearance (two consecutive negative HCV PCR tests spaced >/=28 days apart without treatment) or a sustained virological response (SVR; two consecutive negative HCV PCR tests spaced >/=28 days apart 12 weeks after completing interferon-based treatment). We calculated incidence rates of HCV reinfection (per 100 person-years of follow-up) and corresponding 95% CIs assuming a Poisson distribution, and used a multivariable Cox proportional hazards model to examine reinfection risk factors (age, birth cohort, sex, year of HCV diagnosis, HCV clearance type, HIV co-infection, number of mental health counselling visits, levels of material and social deprivation, and alcohol and injection drug use), and the association of opioid substitution therapy and mental health counselling with HCV reinfection among people who inject drugs (PWID). FINDINGS: 5915 individuals with HCV were included in this study after clearance (3690 after spontaneous clearance and 2225 after SVR). 452 (8%) patients developed reinfection; 402 (11%) after spontaneous clearance and 50 (2%) who had achieved SVR. Individuals were followed up for a median of 5.4 years (IQR 2.9-8.7), and the median time to reinfection was 3.0 years (1.5-5.4). The overall incidence rate of reinfection was 1.27 (95% CI 1.15-1.39) per 100 person-years of follow-up over a total of 35 672 person-years, with significantly higher rates in the spontaneous clearance group (1.59, 1.44-1.76) than in the SVR group (0.48, 0.36-0.63). With the adjusted Cox proportional hazards model, we noted higher reinfection risks in the spontaneous clearance group (adjusted hazard ratio [HR] 2.71, 95% CI 2.00-3.68), individuals co-infected with HIV (2.25, 1.78-2.85), and PWID (1.53, 1.21-1.92) than with other reinfection risk factors. Among the 1604 PWID with a current history of injection drug use, opioid substitution therapy was significantly associated with a lower risk of reinfection (adjusted HR 0.73, 95% CI 0.54-0.98), as was engagement with mental health counselling services (0.71, 0.54-0.92). INTERPRETATION: The incidence of HCV reinfection was higher among HIV co-infected individuals, those who spontaneously cleared HCV infection, and PWID. HCV treatment complemented with opioid substitution therapy and mental health counselling could reduce HCV reinfection risk among PWID. These findings support policies of post-clearance follow-up of PWID, and provision of harm-reduction services to minimise HCV reinfection and transmission. FUNDING: The British Columbia Centre for Disease Control and the Canadian Institutes of Health Research.

Related articles (proposed by speaker)

Rossi C, Butt ZA, Wong S, Buxton J, Islam N, Yu A, Darvishian D, Chapinal N, Alvarez M, Binka M, Gilbert M, Wong J, Tyndall M, Krajden M, Janjua NZ. The BC Hepatitis Testers Cohort Team. Hepatitis C Virus Reinfection after Successful Treatment with Direct-Acting Antiviral Therapy in a Large Population-Based

Cohort. J Hepatology 2018 pii: S0168-8278(18)32288-8. https://doi.org/10.1016/j.jhep.2018.07.025

Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis. Clin Infect Dis. 2016 Mar 15;62(6):683-694. doi: 10.1093/cid/civ948. (see above)

Related articles (pubmed search)

Jhaveri, M. A., Manne, V. and Kowdley, K. V. "**Chronic Hepatitis C in Elderly Patients: Current Evidence with Direct-Acting Antivirals**." Drugs Aging **2018** 35(2): 117-122.Liver Care Network and Organ Care Research, Swedish Medical Center, 1124 Columbia Street, Suite 600, Seattle, WA, 98104, USA.

11:30–11:50 *Is Re-infection after DAA treatment an issue*

Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era.

Oluwaseun Falade-Nwulia *(Johns Hopkins University, Baltimore, MD, USA)*

Falade-Nwulia, O. Sulkowski, M. S., Merkow, A., Latkin, C. and Mehta, S. H. "**Understanding and addressing hepatitis C reinfection in the oral direct-acting antiviral era**." J Viral Hepat **2018** 25(3): 220-227.Johns Hopkins University School of Medicine, Baltimore, MD, USA.

The availability of effective, simple, well-tolerated oral direct-acting antiviral (DAA) hepatitis C regimens has raised optimism for hepatitis C virus (HCV) elimination at the population level. HCV reinfection in key populations such as people who inject drugs (PWID) and HIV-infected men who have sex with men (MSM) however threatens the achievement of this goal from a patient, provider and population perspective. The goal of this review was to synthesize our current understanding of estimated rates and factors associated with HCV reinfection. This review also proposes interventions to aid understanding of and reduce hepatitis C reinfection among PWID and HIV-infected MSM in the oral direct-acting antiviral era.

Related articles (proposed by speaker)

Rossi C, Butt Z, Swong S et al Hepatitis C virus reinfection after successful treatment with direct-acting antiviral therapy in a large population-based cohort J Hepatol. 2018 Nov;69(5):1007-1014. doi: 10.1016/j.jhep.2018.07.025. Epub 2018 Aug 22

Berenguer J, Gil-Martin Á, Jarrin I. Reinfection by hepatitis C virus following effective all-oral direct-acting antiviral drug therapy in HIV/hepatitis C virus coinfected individuals. AIDS. 2019 Mar 15;33(4):685-689. doi: 10.1097/QAD.0000000000002103.

Related articles (pubmed search

Falade-Nwulia O, Sulkowski MS, Merkow A, Latkin C, Mehta SH. Understanding and addressing hepatitis C reinfection in the oral direct acting antiviral era. J Viral Hepat. 2018 Mar;25(3):220-227. doi: 10.1111/jvh.12859

Martinello, M., Hajarizadeh, B., Grebely, J., Dore, G. J. and Matthews, G. V. "**HCV Cure and Reinfection Among People With HIV/HCV Coinfection and People Who Inject Drugs**." Curr HIV/AIDS Rep **2017** 14(3): 110-121.

1.3. The impact of treatment hurdles on Public health

Session 1.3: Panel discussion: The impact of treatment hurdles on Public health

12:05–12:25 Hepatitis C: Is eradication possible

Mario Mondelli *(University of Pavia, Italy).*

Lombardi, A. and Mondelli, M. U. "**Hepatitis C: Is eradication possible?**" Liver Int **2018**. Hepatitis C has a relevant global impact in terms of morbidity, mortality and economic costs, with more than 70 million people infected worldwide. In the resolution, "Transforming our world: the 2030 Agenda for Sustainable Development" was included as a focus area in the health-related goal with world leaders pledging to "combat" it by 2030. In response, WHO drafted the Global Viral Hepatitis Strategy carrying the ambitious targets to reduce the number of deaths by two-thirds and to increase treatment rates up to 80%. Despite the availability of highly effective therapeutic regimens based on direct-acting antivirals many barriers to HCV eradication still remain. They are related to awareness of the infection, linkage to care, availability of the therapeutic drug regimens and reinfection. Overall, if an effective prophylactic vaccine will not be available, HCV eradication appears difficult to achieve in the future.

Related articles (proposed by speaker)

Lombardi A, Mondelli MU and ESCMID Study Group for Viral Hepatitis. Hepatitis C: is eradication possible? *Liver Int* 2019;39:416–426.

Salmon-Ceron D, Mondelli MU, Matičič M, Arends JE and ESCMID Study Group for Viral Hepatitis. The success of HCV cure: every rose has thorns. *J Viral Hepat* 2018;25:320-328.

Mondelli MU. Natural History of HCV Infection - What Is the Public Health Impact of Untreated Disease? *Future Virol* 2017;12:13-8.

Walker CM. Designing an HCV vaccine: a unique convergence of prevention and therapy? *Curr Opin Virol* 2017;23:113-119.

Swadling L, Capone S, Antrobus RD, Brown A, Richardson R, Newell EW, Halliday J, Kelly C, Bowen D, Fergusson J, Kurioka A, Ammendola V, Del Sorbo M, Grazioli F, Esposito ML, Siani L, Traboni C, Hill A, Colloca S, Davis M, Nicosia A, Cortese R, Folgori A, Klenerman P, Barnes E. A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory. *Sci Transl Med* 2014;6:261ra153.

Related articles (pubmed search

Bartenschlager, R., Baumert, T. F., Bukh, J., Houghton, M., Lemon, S. M., Lindenbach, B. D., Lohmann, V., Moradpour, D., Pietschmann, T., Rice, C. M., et al. "**Critical challenges and emerging opportunities in hepatitis C virus research in an era of potent antiviral therapy: Considerations for scientists and funding agencies**." Virus Res **2018** 248: 53-62.

Alter, H. J. and Chisari, F. V. "**Is Elimination of Hepatitis B and C a Pipe Dream or Reality?**" Gastroenterology **2019** 156(2): 294-296.

1.4 extra Pubmed information: Hepatitis/treatment/non-respond*/ relapse

2. Hepatitis B Vaccination Non responders

2.1. Definitions and impact of non-responding on hepatitis vaccination

Session 2.1: Definitions and impact of non-responding on hepatitis vaccination

Chairs: XXX – XXX

14:15-14:35 Review on definitions and impact of non-responders on hepatitis vaccination

Do we need better hepatitis B vaccines?

Dieter Glebe *(Justus Liebig University Giessen, Institute of Medical Virology, National Reference Centre for Hepatitis B and D Viruses, Giessen, Germany)*

Gerlich, W. H. "**Do we need better hepatitis B vaccines?**" Indian J Med Res **2017** 145(4): 414-419.Institute for Medical Virology, Biomedical Research Center Seltersberg, Justus Liebig University Giessen, D35292 Giessen, Germany.

Gerlich, W. H. "**Prophylactic vaccination against hepatitis B: achievements, challenges and perspectives**." Med Microbiol Immunol **2015** 204(1): 39-55.Institute for Medical Virology, National Reference Center for Hepatitis B and D, Justus-Liebig-University Giessen, Schubert Str. 81, 35392, Giessen, Germany, wolfram.h.gerlich@viro.med.uni-giessen.de.

Large-scale vaccination against hepatitis B virus (HBV) infection started in 1984 with first-generation vaccines made from plasma of chronic carriers containing HBV surface antigen (HBsAg). Thereafter, it was replaced in most countries by second-generation vaccines manufactured in yeast cells transformed with gene S encoding HBsAg. Both generations of vaccines have been applied for universal neonate and early childhood vaccination worldwide and have led to a 70-90 % decrease in chronic HBV carrier rates. However, 10-30% of newborns from HBsAg/HBeAg-positive mothers cannot be protected by passive/active vaccination alone and become chronic HBV carriers themselves. Asymptomatic

occult HBV infections are frequent even in those who have protective levels of anti-HBs. Suboptimal protection may be due to heterologous HBsAg subtypes that are present in 99% of HBV carriers worldwide. Second-generation vaccines contain partially misfolded HBsAg and lack preS1 antigen that carries the major HBV attachment site and neutralizing epitopes. Third-generation vaccines produced in mammalian cells contain correctly folded HBsAg and neutralizing epitopes of the preS antigens, induce more rapid protection, overcome nonresponse to second-generation vaccines and, most importantly, may provide better protection for newborns of HBV-positive mothers. PreS/S vaccines expressed in mammalian cells are more expensive to manufacture, but introduction of more potent HBV vaccines should be considered in regions with a high rate of vertical transmission pending assessment of health economics and healthcare priorities. With optimal vaccines and vaccination coverage, eradication of HBV would be possible.

Related articles (pubmed search

Tajiri K, Shimizu Y. **Unsolved problems and future perspectives of hepatitis B virus vaccination**. World journal of gastroenterology. 2015;21(23):7074-83.

Saco TV, Strauss AT, Ledford DK. **Hepatitis B vaccine nonresponders: Possible mechanisms and solutions**. Ann Allergy Asthma Immunol. 2018;121(3):320-7

2.2. Reasons or risk factors for non-responding

Session 2.2: Reasons or risk factors for non-responding

Risk factors

14:35-14:55

How response and non-response can immunologically be explained:

Transcriptome profiling in blood before and after hepatitis B vaccination shows significant differences in gene expression between responders and non-responders.

Pieter Meysman *(University of Antwerp/Antwerp University Hospital, Belgium)*

Bartholomeus E, De Neuter N, Meysman P, Suls A, Keersmaekers N, Elias G, Jansens H, Hens N, Smits E, Van Tendeloo V, Beutels P, Van Damme P, Ogunjimi B, Laukens K, Mortier G. **Transcriptome profiling in blood before and after hepatitis B vaccination shows significant differences in gene expression between responders and non-responders**. Vaccine. 2018;36(42):6282-9

INTRODUCTION: As the hepatitis B virus is widely spread and responsible for considerable morbidity and mortality, WHO recommends vaccination from infancy to reduce acute infection and chronic carriers. However, current subunit vaccines are not 100% efficacious and leave 5-10% of recipients unprotected. METHODS: To evaluate immune responses after Engerix-B vaccination, we determined, using mRNA-sequencing, whole blood early gene expression signatures before, at day 3 and day 7 after the first dose and correlated this with the resulting antibody titer after two vaccine doses. RESULTS: Our results

indicate that immune related genes are differentially expressed in responders mostly at day 3 and in non-responders mostly at day 7. The most remarkable difference between responders and non-responders were the differentially expressed genes before vaccination. The granulin precursor gene (GRN) was significantly downregulated in responders while upregulated in non-responders at day 0. Furthermore, absolute granulocytes numbers were significantly higher in non-responders at day 0. CONCLUSION: The non-responders already showed an activated state of the immune system before vaccination. Furthermore, after vaccination, they exhibited a delayed and partial immune response in comparison to the responders. Our data may indicate that the baseline and untriggered immune system can influence the response upon hepatitis B vaccination.

Related articles (proposed by speaker)

Leuridan E, Van damme P**. Hepatitis b and the need for a booster dose.** Clinical infectious diseases. 2011 jul 1;53(1):68-75.

Bartholomeus E, De Neuter N, Meysman P, Suls A, Keersmaekers N, Elias G, Jansens H, Hens N, Smits E, Van Tendeloo V, Beutels P. **Transcriptome profiling in blood before and after hepatitis b vaccination shows significant differences in gene expression between responders and non-responders**. Vaccine. 2018 oct 8;36(42):6282-9.

Fourati S, Cristescu R, Loboda A, Talla A, Filali A, Railkar R, Schaeffer Ak, Favre D, Gagnon D, Peretz Y, Wang Im. **Pre-vaccination inflammation and b-cell signalling predict age-related hyporesponse to hepatitis b vaccination**. Nature communications. 2016 jan 8;7:10369.

Meysman P, Saeys Y, Sabaghian E, Bittremieux W, Van De Peer Y, Goethals B, Laukens K. **Mining the enriched subgraphs for specific vertices in a biological graph. Ieee/acm transactions on computational biology and bioinformatics**. 2016 jun 7.

Related articles (pubmed search

Wooden, S. L. and Koff, W. C. "**The Human Vaccines Project: Towards a comprehensive understanding of the human immune response to immunization**." Hum Vaccin Immunother **2018** 14(9): 2214-2216.a Human Vaccines Project , NY , NY , USA.

Qiu, S., He, P., Fang, X., Tong, H., Lv, J., Liu, J., Zhang, L., Zhai, X., Wang, L., Hu, Z., et al. "**Significant transcriptome and cytokine changes in hepatitis B vaccine non-responders revealed by genome-wide comparative analysis**." Hum Vaccin Immunother **2018** 14(7): 1763-1772.a

Newport MJ. **The genetic regulation of infant immune responses to vaccination**. Frontiers in immunology. 2015;6:18.

Bolther, M., Andersen, K. L. D., Tolstrup, M., Visvanathan, K., Woolley, I., Skinner, N., Millen, R., Warner, N., Ostergaard, L. and Jensen-Fangel, S. "**Levels of regulatory B cells do not predict serological responses to hepatitis B vaccine**." Hum Vaccin Immunother **2018** 14(6): 1483-1488.a

Roh, E. Y., Song, E. Y., Yoon, J. H., Oh, S., Chang, J. Y., Park, H., Seo, S. H. and Shin, S. "**Effects of interleukin-4 and interleukin-12B gene polymorphisms on hepatitis B virus vaccination**." Ann Hepatol **2017** 16(1): 63-70.Department of Laboratory Medicine, Seoul National University Boramae Medical Center, Seoul, Korea.

Jafarzadeh, A., Bagheri-Jamebozorgi, M., Nemati, M., Golsaz-Shirazi, F. and Shokri, F. "**Human Leukocyte Antigens Influence the Antibody Response to Hepatitis B Vaccine**." Iran J Allergy Asthma Immunol **2015** 14(3): 233-245.Molecular Medicine Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

14:55-15:15

Host risk factors (genetics, age, sex, BMI, Vit D...)

Primary vaccine failure to routine vaccines: Why and what to do?

Erika Garner-Spitzer *(Medical University Vienna Austria)*

Wiedermann, U., Garner-Spitzer, E. and Wagner, A. "**Primary vaccine failure to routine vaccines: Why and what to do?**" Hum Vaccin Immunother **2016** 12(1): 239-243

Abstract: There are 2 major factors responsible for vaccine failures, the first is vaccine-related such as failures in vaccine attenuation, vaccination regimes or administration. The other is host-related, of which host genetics, immune status, age, health or nutritional status can be associated with primary or secondary vaccine failures. The first describes the inability to respond to primary vaccination, the latter is characterized by a loss of protection after initial effectiveness. Our studies concentrate on the evaluation of immunological characteristics responsible for primary vaccine failures in different (risk) populations for which the underlying mechanisms are currently unknown. Here we summarise current knowledge and findings from our studies. About 2-10% of healthy individuals fail to mount antibody levels to routine vaccines. Comparing the immune responses to different vaccines in non-responder and high-responder vaccinees revealed that hypo-responsiveness is antigen/vaccine-specific at the humoral but not at the cellular level. We found that T-regulatory as well as B-regulatory cells and the production of IL-10 are involved in non/hypo-responsiveness. Non-responsiveness increases with age and in particular vaccination to a novel vaccine in persons > 65 years is associated with a high low/non-responder rate, indicating that vaccine schedules and doses (at least for primary vaccination) should be adapted according to age. In light of the growing number of allergic but also obese people, our current studies concentrate on these risk groups to reveal whether different vaccination approaches are necessary for optimal protection compared to healthy individuals. These studies are in line with the significant paradigm shift taking place in many fields of medical research and care, and will extend the concept of personalised medicine into the field of vaccinology.

Related articles (proposed by speaker)

Yang, S., G. Tian, Y. Cui, C. Ding, M. Deng, C. Yu, K. Xu, J. Ren, J. Yao, Y. Li, Q. Cao, P. Chen, T. Xie, C. Wang, B. Wang, C. Mao, B. Ruan, T. Jiang, and L. Li. 2016. Factors influencing immunologic response to hepatitis B vaccine in adults. Scientific reports 6: 27251.

Painter, S. D., I. G. Ovsyannikova, and G. A. Poland. 2015. The weight of obesity on the human immune response to vaccination. Vaccine 33: 4422-4429.

McDermott, A. B., J. N. Zuckerman, C. A. Sabin, S. G. Marsh, and J. A. Madrigal. 1997. Contribution of human leukocyte antigens to the antibody response to hepatitis B vaccination. Tissue antigens 50: 8-14.

Klein, S. L., A. Jedlicka, and A. Pekosz. 2010. The Xs and Y of immune responses to viral vaccines. The Lancet. Infectious diseases 10: 338-349

Giefing-Kroll, C., P. Berger, G. Lepperdinger, and B. Grubeck-Loebenstein. 2015. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. Aging cell 14: 309-321

Related articles (pubmed search)

Apiung, T., Ndanu, T. A., Mingle, J. A. and Sagoe, K. W. "**Hepatitis B virus surface antigen and antibody markers in children at a major paediatric hospital after the pentavalent DTP-HBV-Hib vaccination**." Ghana Med J **2017** 51(1): 13-19

Thomas, R. J., Fletcher, G. J., Kirupakaran, H., Chacko, M. P., Thenmozhi, S., Eapen, C. E., Chandy, G. and Abraham, P. "**Prevalence of non-responsiveness to an indigenous recombinant hepatitis B vaccine: a study among South Indian health care workers in a tertiary hospital**." Indian J Med Microbiol **2015** 33 Suppl: 32-36.Department of Clinical Virology, Christian Medical College Hospital, Vellore, Tamil Nadu, India

Age

Rezaee, R., Aghcheli, B., Poortahmasebi, V., Qorbani, M., Alavian, S. M. and Jazayeri, S. M. "**Prevalence of National Responsiveness to HBV Vaccine After 22 Years of Iranian Expanded Program on Immunization (EPI): A Systematic Review and Meta-Analysis Study**." Hepat Mon **2015** 15(5): e23618

Van Der Meeren, O., Crasta, P., Cheuvart, B. and De Ridder, M. "**Characterization of an age-response relationship to GSK's recombinant hepatitis B vaccine in healthy adults: An integrated analysis**." Hum Vaccin Immunother **2015** 11(7): 1726-1729.

Salama, II, Sami, S. M., Salama, S. I., Foud, W. A., Abdel Hamid, A. T. and Said, Z. N. "**Persistence of protection to hepatitis B vaccine and response to booster dose among children and adolescents in Dakahleya- Egypt**." Egypt J Immunol **2014** 21(1): 13-26

BMI

Liu, F., Guo, Z. and Dong, C. "**Influences of obesity on the immunogenicity of Hepatitis B vaccine**." Hum Vaccin Immunother **2017** 13(5): 1014-1017.

Fan, W., Chen, X. F., Shen, C., Guo, Z. R. and Dong, C. "**Hepatitis B vaccine response in obesity: A meta-analysis**." Vaccine **2016** 34(40): 4835-4841

Young, K. M., Gray, C. M. and Bekker, L. G. "**Is obesity a risk factor for vaccine non-responsiveness?**" PLoS One **2013** 8(12): e82779

Sex

Thomas, R. J., Fletcher, G. J., Kirupakaran, H., Chacko, M. P., Thenmozhi, S., Eapen, C. E., Chandy, G. and Abraham, P. "**Prevalence of non-responsiveness to an indigenous recombinant hepatitis B vaccine: a study among South Indian health care workers in a tertiary hospital**." Indian J Med Microbiol **2015** 33 Suppl: 32-36

Voysey, M., Pollard, A. J., Perera, R. and Fanshawe, T. R. "**Assessing sex-differences and the effect of timing of vaccination on immunogenicity, reactogenicity and efficacy of vaccines in young children: study protocol**

for an individual participant data meta-analysis of randomised controlled trials." BMJ Open **2016** 6(7): e011680

VitD

Grzegorzewska, A. E., Jodlowska, E., Mostowska, A., Sowinska, A. and Jagodzinski, P. P. "**Single nucleotide polymorphisms of vitamin D binding protein, vitamin D receptor and retinoid X receptor alpha genes and response to hepatitis B vaccination in renal replacement therapy patients**." Expert Rev Vaccines **2014** 13(11): 1395-1403

Jhorawat, R., Jain, S., Pal, A., Nijhawan, S., Beniwal, P., Agarwal, D. and Malhotra, V. "**Effect of vitamin D level on the immunogenicity to hepatitis B vaccination in dialysis patients**." Indian J Gastroenterol **2016** 35(1): 67-71

2.3. Possible Solutions for non- responders

Session 2.3: Possible Solutions for non- responders

16:00-16:20

Review: Alternative vaccination strategies for primary non-responders on hepatitis B vaccination

Stijn Raven (Radboud universitair medisch centrum, Nijmegen, The Netherlands)

Related articles (proposed by speaker)

Heininger U, Gambon M, Gruber V, Margelli D**. Successful hepatitis B immunization in non- and low responding health care workers**. Hum Vaccin 2010;6: 725-728

David MC, Ha SH, Paynter S, Lau C. **A systematic review and meta-analysis of management options for adults who respond poorly to hepatitis B vaccination**. Vaccine 2015;33:6564–656

Hoebe CJ, Vermeiren AP, Dukers-Muijrers NH. **Revaccination with Fendrix(R) or HBVaxPro(R) results in better response rates than does revaccination with three doses of Engerix-B(R) in previous non-responders**. Vaccine 2012;30:6734–6737

Hadler SC, Francis DP, Maynard JE, et al. **Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men.** NEnglJMed 1986;315:209–214

Cardell K, Akerlind B, Sallberg M, Fryden A. **Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine.** JInfectDis 2008;198:299–304

16:20-16:50

Overview of the development of new vaccines, able to have non-responders, responding?

Daniel Shouval (Liver Unit, Hadassah University Hospital, Jerusalem, Israel)

Shouval D, Roggendorf H, Roggendorf M.**Enhanced immune response to hepatitis B vaccination through immunization with a Pre-S1/Pre-S2/S vaccine.** Med Microbiol Immunol. 2015 ;204:57-68

Abstract
Efficacy and safety of recombinant yeast-derived hepatitis B vaccines for prevention of hepatitis B have been demonstrated unequivocally worldwide as reflected in reduction in HBsAg carrier rates and hepatocellular carcinoma. A new generation of recombinant HBV vaccines expressed in mammalian cells containing Pre-S/S epitopes has been developed in several countries. Such vaccines are useful in special risk groups, i.e., in non-responders to conventional HBV vaccines including older adults, obese people, health care workers, patients with renal failure and on dialysis, transplant patients, patients with HIV as well as travelers on short notice to HBV endemic regions. The future of such vaccines depends on their enhanced immunogenicity and cost profile. Sci-B-Vac™ is a mammalian cell-derived recombinant Pre-S1/Pre-S2/S hepatitis B vaccinewhich has been shown to be highly immunogenic, inducing faster and higher seroprotection rates against HBV with higher anti-HBs levels at lower HBsAg doses as compared to conventional yeast-derived vaccines. Recently, it has been suggested that such Pre-S/S vaccines against HBV might be efficacious not only for prevention but also for intervention in persistent HBV infection. Data obtained in a recent clinical trial conducted in Vietnam in patients with chronic hepatitis B suggest that repeated monthly i.m. injections of the Sci-B-Vac™ co-administered with daily oral lamivudine treatment can suppress HBV replication and lead to anti-HBs seroconversion in ~50 % of treated patients. Optimization of protocols and efficacy of such an intervention, intended to bypass T cell exhaustion and immune tolerance to HBV remains to be explored

Related articles (proposed by speaker)

Yang S, Tian G, Cui Y, Ding C, Deng M, Yu C, Xu K, Ren J, Yao J, Li Y, Cao Q, Chen P, Xie T, Wang C, Wang B, Mao C, Ruan B, Jiang T, Li L. **Factors influencing immunologic response to hepatitis B vaccine in adults.** Sci Rep. 2016 Jun 21;6:27251

Leroux-Roels G.**Old and new adjuvants for hepatitis B vaccines**. Med Microbiol Immunol. 2015 Feb;204(1):69-78
Cooper C, Mackie D.**Hepatitis B surface antigen-1018 ISS adjuvant-containing vaccine: a review of HEPLISAV™ safety and efficacy.** Expert Rev Vaccines. 2011 ;10(4):417-27

JN, Zuckerman AJ, et al. **Evaluation of a new hepatitis B triple-antigen vaccine in inadequate responders to current vaccines**. Zuckerman UK Hepacare Study Group.Hepatology. 2001 ;34:798-802

Jungers P1, Chauveau P, Couroucé AM, Devillier P, Excler JL, Bailleux F, Saliou P **Immunogenicity of the recombinant GenHevac B Pasteur vaccine against hepatitis B in chronic uremic patients** J Infect Dis.1994 Feb;169(2):399-402.

Related articles

Solutions for non-responders

(pubmed search)

General

Walayat, S., Ahmed, Z., Martin, D., Puli, S., Cashman, M. and Dhillon, S. "**Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine**." World J Hepatol **2015** 7(24): 2503-2509

David, M. C., Ha, S. H., Paynter, S. and Lau, C. "**A systematic review and meta-analysis of management options for adults who respond poorly to hepatitis B vaccination**." Vaccine **2015** 33(48): 6564-6569.

Adjuvants

Minz, S. and Pandey, R. S. "**Lipid A adjuvanted Chylomicron Mimicking Solid Fat Nanoemulsions for Immunization Against Hepatitis B**." AAPS PharmSciTech **2018** 19(3): 1168-1181

Koc, O. M., Savelkoul, P. H. M., van Loo, I. H. M., Peeters, A. and Oude Lashof, A. M. L. "**Safety and immunogenicity of HBAI20 Hepatitis B vaccine in healthy naive and nonresponding adults**." J Viral Hepat **2018** 25(9): 1048-1056

Del Giudice, G., Rappuoli, R. and Didierlaurent, A. M. "**Correlates of adjuvanticity: A review on adjuvants in licensed vaccines**." Semin Immunol **2018** 39: 14-21

Vilajeliu, A., Sequera, V. G., Garcia-Basteiro, A. L., Sicuri, E., Aldea, M., Velasco, C. and Bayas, J. M. "**Immunogenicity and immunization costs of adjuvanted versus non-adjuvanted hepatitis B vaccine in chronic kidney disease patients**." Hum Vaccin Immunother **2016** 12(9): 2317-2321

Fabrizi, F., Tarantino, A., Castelnovo, C., Martin, P. and Messa, P. "**Recombinant Hepatitis B Vaccine Adjuvanted With AS04 in Dialysis Patients: A Prospective Cohort Study**." Kidney Blood Press Res **2015** 40(6): 584-592

Mohsen, M. O., Zha, L., Cabral-Miranda, G. and Bachmann, M. F. "**Major findings and recent advances in virus-like particle (VLP)-based vaccines**." Semin Immunol **2017** 34: 123-132

Other shedules and concentrations

Yang, L., Yao, J., Li, J., Chen, Y., Jiang, Z. G., Ren, J. J., Xu, K. J., Ruan, B., Yang, S. G., Wang, B., et al. "**Suitable hepatitis B vaccine for adult immunization in China**." Immunol Res **2016** 64(1): 242-250

Chatkittikunwong, G. and Khawcharoenporn, T. "**Hepatitis B revaccination in HIV-infected vaccine non-responders: is double dosing always necessary?**" Int J STD AIDS **2016** 27(10): 850-855

Zhang, L., Liu, J., Lu, J., Yan, B., Song, L., Li, L., Cui, F., Zhang, G., Wang, F., Liang, X., et al. "**Antibody response to revaccination among adult non-responders to primary Hepatitis B vaccination in China**." Hum Vaccin Immunother **2015** 11(11): 2716-2722.a

Administration

Yousaf, F., Gandham, S., Galler, M., Spinowitz, B. and Charytan, C. "**Systematic review of the efficacy and safety of intradermal versus intramuscular hepatitis B vaccination in end-stage renal disease population unresponsive to primary vaccination series**." Ren Fail **2015** 37(7): 1080-1088.

2.4. Impact of non-responders on public health, is it a threat to eliminate hepatitis. Are new recommendations for the management of non-reponders needed

Related articles (Pubmed search)	Pan, H. X., Zeng, Y., Song, X. F., Zhang, Y. J., Xu, K., Liang, Z. L. and Zhu, F. C. "**Immune response to hepatitis B vaccine with high antigen content in non-responders after standard primary vaccination in Chinese adults**." Vaccine **2014** 32(29): 3706-3712 Zhang, L., Liu, J., Lu, J., Yan, B., Song, L., Li, L., Cui, F., Zhang, G., Wang, F., Liang, X., et al. "**Antibody response to revaccination among adult non-responders to primary Hepatitis B vaccination in China**." Hum Vaccin Immunother **2015** 11(11): 2716-2722. Apiung, T., Ndanu, T. A., Mingle, J. A. and Sagoe, K. W. "**Hepatitis B virus surface antigen and antibody markers in children at a major paediatric hospital after the pentavalent DTP-HBV-Hib vaccination**." Ghana Med J **2017** 51(1): 13-19. Zitt, E., Hafner-Giessauf, H., Wimmer, B., Herr, A., Horn, S., Friedl, C., Sprenger-Mahr, H., Kramar, R., Rosenkranz, A. R. and Lhotta, K. "**Response to active hepatitis B vaccination and mortality in incident dialysis patients**." Vaccine **2017** 35(5): 814-820.

3. Occult hepatitis B

3.1. Introduction and Definitions

Session 3.1 : Definition Occult hepatitis B

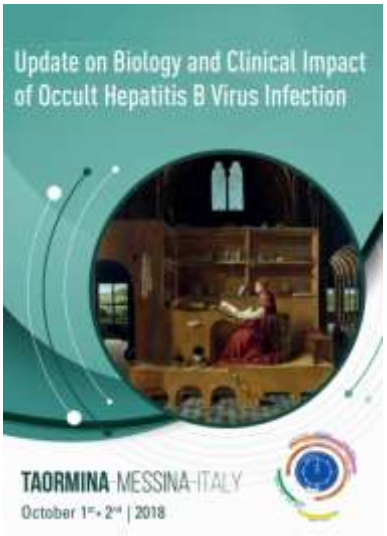
08:30 - 08:50 Review on definitions based on EASL meeting in Taormina-Messina, Italy, Oct 18

Update on Biology and Clinical impact of Occult hepatitis B virus infection

Giovanni Raimondo (University Hospital of Messina, Italy)

EASL/AISF Meeting Taormina-Messina Italy Occult hepatitis

Agenda and participants :
https://www.unime.it/sites/default/files/Programma%20OBI_2018.final_.pdf



Raimondo G., Locarnini S., Pollicno T., Levrero M., Zoulim F., Lok A. and the *Taormina Workshop on Occult HBV Infection Faculty Members*. **Update of the statements on biology and clinical impact of occult hepatitis B virus infection**. Journal of Hepatology 2019, in press

In October 2018 a large number of international experts with complementary expertise came together in Taormina to participate in a workshop on occult hepatitis B virus infection (OBI). The objectives of the workshop were to review the existing knowledge on OBI, to identify issues that require further investigation, to highlight both the existing controversial and newly emerging aspects, and ultimately to update the statements previously agreed in 2008. This paper represents the output from the workshop

Related articles

(Pubmed search)

Locarnini S, Raimondo G. **How infectious is the hepatitis B virus? Readings from the occult**. Gut. 2019;68(2):182-3.

Aghasadeghi, M. R., Banifazl, M., Aghakhani, A., Eslamifar, A., Vahabpour, R. and Ramezani, A. "**No evidence for occult HBV infection in hepatitis B vaccine non-responders**." Iran J Microbiol **2014** 6(5): 350-353.

Makvandi, M. "**Update on occult hepatitis B virus infection**." World J Gastroenterol **2016** 22(39): 8720-8734.Manoochehr Makvandi, Health Research Institute, Infectious and Tropical Disease Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz 15794-61357, Iran.

The event of mutations in the surface antigen gene of hepatitis B virus (HBV) results in undetectable hepatitis B surface antigen with positive/negative anti-hepatitis B core (anti-HBc) antibody status in serum and this phenomenon is named occult hepatitis B infection (OBI). The presence of anti-HBc antibody in serum is an important key for OBI tracking, although about 20% of OBI cases are negative for anti-HBc antibody. The diagnosis of OBI is mainly based on polymerase chain reaction (PCR) and real-time PCR assays. However, real-time PCR is a more reliable method than PCR. OBI is a great issue for the public health problem and a challenge for the clinical entity worldwide. The persistence of OBI may lead to the development of cirrhosis and hepatocellular carcinoma. With regard to OBI complications, the screening of HBV DNA by the highly sensitive molecular means should be implemented for: (1) patients with a previous history of chronic or acute HBV infection; (2) patients co-infected with hepatitis C virus/human immunodeficiency virus; (3) patients undergoing chemotherapy or anti-CD20 therapy; (4) recipients of organ transplant; (5) blood donors; (6) organ transplant donors; (7) thalassemia and hemophilia patients; (8) health care workers; (9) patients with liver related disease (cryptogenic); (10) hemodialysis patients; (11) patients undergoing lamivudine or interferon therapy; and (12) children in time of HBV vaccination especially in highly endemic areas of HBV. Active HBV vaccination should be implemented for the close relatives of patients who are negative for OBI markers. Thus, the goal of this review is to evaluate the rate of OBI with a focus on status of high risk groups in different regions of the world.

08:50 - 09:10

Molecular definition/ Immunological aspects

Molecular and immunological mechanisms of occult hepatitis B virus infection and pathogenesis

Mengji Lu *(University Hospital of Essen, Germany)*

Zhang, Z. H., Wu, C. C., Chen, X. W., Li, X., Li, J. and Lu, M. J. "**Genetic variation of hepatitis B virus and its significance for pathogenesis**." World J Gastroenterol **2016** 22(1): 126-144.

Hepatitis B virus (HBV) has a worldwide distribution and is endemic in many populations. Due to its unique life cycle which requires an error-prone reverse transcriptase for replication, it constantly evolves, resulting in tremendous genetic variation in the form of genotypes, sub-genotypes, and

mutations. In recent years, there has been considerable research on the relationship between HBV genetic variation and HBV-related pathogenesis, which has profound implications in the natural history of HBV infection, viral detection, immune prevention, drug treatment and prognosis. In this review, we attempted to provide a brief account of the influence of HBV genotype on the pathogenesis of HBV infection and summarize our current knowledge on the effects of HBV mutations in different regions on HBV-associated pathogenesis, with an emphasis on mutations in the preS/S proteins in immune evasion, occult HBV infection and hepatocellular carcinoma (HCC), mutations in polymerase in relation to drug resistance, mutations in HBV core and e antigen in immune evasion, chronicalization of infection and hepatitis B-related acute-on-chronic liver failure, and finally mutations in HBV x proteins in HCC.

Related articles (proposed by speaker)

Cao, L., Wu, C., Shi, H., Gong, Z., Zhang, E., Wang, H., Zhao, K., Liu, S., Li, S., Gao, X., Wang Y, Lu, M., Chen, X**.** (2014) **Coexistence of hepatitis B virus quasispecies changes the replication activity and the ability to induce host antibody and celluar immune responses.** J Virol. **88(15):**8656-8666.

Zhang Z., Wu, C., Chen, X., Li, X., and Lu, M. (2016) **Genetic variation of hepatitis B virus and its significance for pathogenesis.** World J Gastro, 22(1):126-144. (see above)

Liu, H., Li, F., Zhang, X., Yu, J., Wang, J., Jia, J., Yu, X., Shen, Z., Yuan, Z., Zhang, X., Zhang, Z., Zhang, X., Lu, L., Li, H., Lu, M., Zhang, J. (2018) **Differentially Expressed Intrahepatic Genes Contribute to Control of Hepatitis B Virus Replication in the Inactive Carrier Phase**. J Infect Dis. 217(7):1044-1054. (Corresponding author).

Wu, C.-C., Chen, Y.-S., Cao, L., Chen, X.-W., Lu, M.-J**.** (2018) **Hepatitis B virus infection: defective surface antigen expression and pathogenesis.** World J Gastro 24:3488-3499.

Abstract: Hepatitis B virus (HBV) infection is a global public health concern. HBV causes chronic infection in patients and can lead to liver cirrhosis, hepatocellular carcinoma, and other severe liver diseases. Thus, understanding HBV-related pathogenesis is of particular importance for prevention and clinical intervention. HBV surface antigens are indispensable for HBV virion formation and are useful viral markers for diagnosis and clinical assessment. During chronic HBV infection, HBV genomes may acquire and accumulate mutations and deletions, leading to the expression of defective HBV surface antigens. These defective HBV surface antigens have been found to play important roles in the progression of HBV-associated liver diseases. In this review, we focus our discussion on the nature of defective HBV surface antigen mutations and their contribution to the pathogenesis of fulminant hepatitis B. The relationship between defective surface antigens and occult HBV infection are also discussed.

Lin, Y., Wu, C., Wang, X., Liu, S., Kemper, T., Li, F., Squire, A., Zhu, Y., Zhang, J., Chen, X., Lu, M**.** (2019) **Synaptosomal-associated protein 29 is required for the autophagic degradation of hepatitis B virus**. FASEB J. online**.**

Azarkar Z, Ziaee M, Ebrahimzadeh A, Sharifzadeh G, Javanmard D. **Epidemiology, risk factors, and molecular characterization of occult hepatitis B infection among anti-hepatitis B core antigen alone subjects**.

Related articles **(Pubmed search)**	Journal of medical virology. 2019;91(4):615-22.OBJECTIVES: Features of occult hepatitis B virus (HBV) infection among the anti-hepatitis B core antigen (anti-HBc) positives have yet to be described in more details. This study aimed to determine the molecular prevalence of occult HBV infection (OBI), and association to risk factors among seropositives for anti-HBc. METHODS: This was part of a community-based screening project that included 5234 cases. All participants completed a questionnaire on demographic and socio-epidemiological information. Then, the blood samples were collected and tested for anti-HBc and HBsAg using ELISA method. To identify OBI, nested-polymerase chain reaction (PCR) assays were performed for HBV-S and X genes, and viral load was determined using an in-house real-time PCR. Sequencing and phylogenetic analysis have been implemented for genotyping. RESULTS: Overall, 596 cases, positive only for anti-HBc were included in the study. OBI was detected among 61 cases (10.2%). The genotype and subgenotype of HBV among all of them was D1, except one that was D4. Most of them had low viral loads ranged from 1.2 x 10(2) to 1.34 x 10 (3) copies/mL; 19.6% had undetectable viral loads. Important mutations in surface protein and reverse transcriptase were sI92T, sQ129H, rtL80I, rtS85F, rtL91I. The prevalence of OBI was related to some risk factors, such as tattooing (P = 0.02), sexual activities (P = 0.009), and diabetes (P = 0.031). CONCLUSION: Our study suggests that OBI should be considered among anti-HBc seropositive subjects. This form of HBV infection was accompanied with some mutations, risk factors, and diseases. However, further investigations are needed to determine virological importance of documented mutations Almeida, R. W., Mello, F., Menegoy, I. V., Santo, M., Ginuino, C. F., Sousa, P. S. F., Villar, L. M., Lampe, E. and Lewis-Ximenez, L. L. "**Detection and molecular characterisation of a diagnosis escape variant associated with occult hepatitis B virus in Brazil**." Mem Inst Oswaldo Cruz **2017** 112(7): 485-491. BACKGROUND: Many studies have identified mutations in the hepatitis B surface antigen (HBsAg) as important factors limiting the ability of commercial serological assays to detect this viral antigen. However, an association between mutations in the HBsAg gene and the occurrence of occult HBV infection (OBI) in patients has not been established. OBJECTIVES: To detect hepatitis B virus (HBV) DNA in patients with anti-HBc as a unique serological marker, a previously published, cost-effective TaqMan-based real-time polymerase chain reaction (PCR) test with minor groove binding probes was adapted for use in this study. The current study also aimed to investigate HBsAg mutations and genotypes of HBV in OBI at the Viral Hepatitis Ambulatory Clinic in Rio de Janeiro to determine any possible association. METHODS: Intra-assay and inter-assay reproducibility were determined, and the mean coefficient of variation values obtained were 2.07 and 3.5, respectively. Probit analysis indicated that the 95% detection level was 25 IU/mL. The prevalence of OBI was investigated in 35 serum samples with an 'anti-HBc alone' profile from individuals who attended our clinic between 2011 and 2013. FINDINGS: HBV DNA was detected in only one sample, resulting in an OBI rate of 2.9%. Nucleotide sequencing of the pre-S/S region was performed to genotype and analyse mutations within the HBsAg gene of this HBV DNA. The HBV in the OBI case was classified as sub-genotype A1, and a sequence analysis of the small S gene revealed 12 mutations in the major hydrophilic region compared to the consensus A1 sequence. Most of these mutations occurred in amino acid residues that have been reported as clinically relevant because they have been implicated in vaccine escape and/or inability to detect HBsAg by commercial serological assays. MAIN CONCLUSIONS: Our study suggests the importance of specific HBsAg mutations, different from those in D, B, and C genotypes, in sub-genotype A1 HBV associated with OBI.

Zhu, H. L., Li, X., Li, J. and Zhang, Z. H. "**Genetic variation of occult hepatitis B virus infection**." World J Gastroenterol **2016** 22(13): 3531-3546.

Occult hepatitis B virus infection (OBI), characterized as the persistence of hepatitis B virus (HBV) surface antigen (HBsAg) seronegativity and low viral load in blood or liver, is a special form of HBV infection. OBI may be related mainly to mutations in the HBV genome, although the underlying mechanism of it remains to be clarified. Mutations especially within the immunodominant "alpha" determinant of S protein are "hot spots" that could contribute to the occurrence of OBI via affecting antigenicity and immunogenicity of HBsAg or replication and secretion of virion. Clinical reports account for a large proportion of previous studies on OBI, while functional analyses, especially those based on full-length HBV genome, are rare.

Hayes, C. N. and Chayama, K. "**MicroRNAs as Biomarkers for Liver Disease and Hepatocellular Carcinoma**." Int J Mol Sci **2016** 17(3): 280.

Ponde RA. **Molecular mechanisms underlying HBsAg negativity in occult HBV infection**. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2015;34(9):1709-31.

Kim H, Kim BJ. **Association of preS/S Mutations with Occult Hepatitis B Virus (HBV) Infection in South Korea: Transmission Potential of Distinct Occult HBV Variants**. International journal of molecular sciences. 2015;16(6):13595-609.

REVIEW Morales-Romero J, Vargas G, Garcia-Roman R. **Occult HBV infection: a faceless enemy in liver cancer development**. Viruses. 2014;6(4):1590-611.

REVIEW Kwak MS, Kim YJ. **Occult hepatitis B virus infection**. World journal of hepatology. 2014;6(12):860-9.

Kim H, Gong JR, Lee SA, Kim BJ. **Discovery of a Novel Mutation (X8Del) Resulting in an 8-bp Deletion in the Hepatitis B Virus X Gene Associated with Occult Infection in Korean Vaccinated Individuals**. PloS one. 2015;10

Semenenko TA, Suslov AP. **[IMMUNOPATHOGENESIS OF OCCULT INFECTION CAUSED BY HEPATITIS B VIRUS]**. Zhurnal mikrobiologii, epidemiologii, i immunobiologii. 2015(6):105-13.

The concept of occult infection caused by hepatitis B virus (HBV) is determined as the presence of HBV DNA in blood sera or liver with the absence of detectable HBsAg. The actuality of this problem is associated with the fact, that occult hepatitis B (OHB) can be transmitted during hemotransfusions, cause reactivation of chronic hepatitis B in immune compromised individuals, facilitate development of liver cirrhosis and hepatocellular carcinoma. Several different hypotheses of OHB immunopathogenesis have been proposed, including a low number of copies of HBV DNA, altered immune response of the macroorganism, genetic variability of the S gene, integration of viral DNA into host genome, infection of mononuclear cells of peripheral blood, presence of immune complexes that hide HBsAg, and interference by other viruses such as HCV and HIV. Molecular mechanisms of HBV virus in HBsAg-negative individuals are not fully understood, however, viral mutations seem a very significant factor.

	Approaches of OHB prophylaxis including use of a polyvalent vaccine, that allows vaccination against wild and mutant HBV viruses, are examined.

3.2. Diagnose and Epidemiology

Session 3.2 : Diagnosis and Epidemiology

09:20 - 09:40 *Diagnosis of occult hepatitis*

Diagnostic tools for occult hepatitis B

Yuen Man-Fung *(University of Hong Kong/Queen Mary Hospital, Hong Kong)*

Mak, L. Y., Wong, D. K., Cheung, K. S., Seto, W. K., Lai, C. L. and Yuen, M. F. "**Review article: hepatitis B core-related antigen (HBcrAg): an emerging marker for chronic hepatitis B virus infection**." Aliment Pharmacol Ther **2018** 47(1): 43-54

Abstract: BACKGROUND: Chronic hepatitis B (CHB) cannot be completely eradicated due to the presence of covalently closed circular DNA (cccDNA) in the nuclei of infected hepatocytes. While quantification of intrahepatic cccDNA requires liver biopsies, serological markers can be non-invasive alternatives to reflect intrahepatic viral replicative activity. Recently, hepatitis B core-related antigen (HBcrAg) has been advocated as a novel serum marker for disease monitoring and prognostication of CHB. AIM: To examine the virological aspect and clinical application of HBcrAg with respect to the natural history and treatment of CHB. METHODS: We reviewed all papers published in the PubMed journal list and abstracts from major international meetings that included the keyword "HBcrAg" or "hepatitis B core-related antigen" until March 2017. Selected studies were compared and summarised on the basis of existing theories, as well as the authors' experience. RESULTS: HBcrAg exhibited good correlation with intrahepatic (ih) cccDNA, ih total hepatitis B virus (HBV) DNA, serum HBV DNA and to a lesser extent HBV surface antigen (HBsAg). In situations where serum HBV DNA levels become undetectable or HBsAg loss is achieved, HBcrAg can still be detectable. This marker is helpful in differentiation of HBeAg-negative chronic hepatitis from HBeAg-negative chronic infection, predicting spontaneous or treatment-induced HBeAg seroconversion, sustained response to nucleos(t)ide analogue (NA), risk of HBV reactivation in occult HBV infection under immunosuppressive therapies, and risk of hepatocellular carcinoma (HCC) development as well as post-operative HCC recurrence. CONCLUSIONS: HBcrAg is a potential surrogate marker of cccDNA. It may soon become a useful marker for disease monitoring, predicting treatment response and disease outcome of chronic hepatitis B.

Related articles (proposed by speaker)

Seto WK, Chan TSY, Hwang YY, Mak LY, Wong DKH, Fung J, Liu KSH, Cheung KS, Lai CL, Kwong YL, Yuen MF. **Monitoring and treatment of patients undergoing immunotherapy with anti-CD20 who are exposed to HBV.** Clin Gastroenterol Hepatol **2018**:S1542-3565(18)31011-5.

Seto WK, Sau-Yan Chan T, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lau EH, Cheung KS, Lie AK, Lai CL, Kwong YL, Yuen MF. **Hepatitis B reactivation in occult viral carriers undergoing hematopoietic stem cell transplantation: A prospective study.** Hepatology **2017**;65(5);1451-1461.

Seto WK, Wong DH, Chan TY, Hwang YY, Fung J, Liu KS, Gill H, Lam YF, Cheung KS, Lie AK, Lai CL, Kwong YL, Yuen MF**. Association of Hepatitis B Core-Related Antigen With Hepatitis B Virus Reactivation in Occult Viral Carriers Undergoing High-Risk Immunosuppressive Therapy**. Am J Gastroenterol **2016**;111(12):1788-1795.

Seto WK, Chan TSY, Hwang YY, Wong DKH, Fung J, Liu KSH, Gill H, Lam YF, Lie AKW, Lai CL, Kwong YL, Yuen MF. **Hepatitis B reactivation in patients with prior HBV exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study**. J Clin Oncol **2014**;32(33):3736-43.

Related articles

(Pubmed search)

Diagnositc tools – surrogate markers

Wu, T., Kwok, R. M. and Tran, T. T. "**Isolated anti-HBc: The Relevance of Hepatitis B Core Antibody-A Review of New Issues**." Am J Gastroenterol **2017** 112(12): 1780-

Vargas, J. I., Jensen, D., Sarmiento, V., Peirano, F., Acuna, P., Fuster, F., Soto, S., Ahumada, R., Huilcaman, M., Bruna, M., et al. "**Presence of anti-HBc is associated to high rates of HBV resolved infection and low threshold for Occult HBV Infection in HIV patients with negative HBsAg in Chile**." J Med Virol **2016** 88(4): 639-646.

Song, J. E. and Kim, D. Y. "**Diagnosis of hepatitis B**." Ann Transl Med **2016** 4(18): 338.

09:40 - 10:10 *Epidemiology*

Epidemiology and regional prevalence of occult HBV in Western world

Mariantonietta Pisaturo *(University of Napels, Italy)*

Overview on epidemiology

China	Zhou, S., Li, T., Allain, J. P., Zhou, B., Zhang, Y., Zhong, M., Fu, Y. and Li, C. "**Low occurrence of HBsAg but high frequency of transient occult HBV infection in vaccinated and HBIG-administered infants born to HBsAg positive mothers**." J Med Virol **2017** 89(12): 2130-2137. He S, Su C, Shen L, Niu J. **[Occult hepatitis B virus infection in normal population, Xiamen]**. Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]. 2015;49(2):132-6.
Japan	Yokoyama, K., Kumagai, H., Takahashi, M., Nagashima, S., Okamoto, H. and Yamagata, T. "**Occult hepatitis B virus infection in immunized children born to carrier mothers**." Pediatr Int **2017** 59(9): 1010-1016.
Cuba	Rodriguez Lay, L. L. A., Bello Corredor, M., Montalvo Villalba, M. C., Chibas Ojeda, A. G., Sariego Frometa, S., Diaz Gonzalez, M., Abad Lamoth, Y., Sanchez Wong, M., Sausy, A., Muller, C. P., et al. "**Hepatitis B virus infection assessed 3 to 18 years**

	after vaccination in Cuban children and adolescents born to HBsAg-positive mothers." Arch Virol **2017** 162(8): 2393-2396.
Colombia	Jaramillo, C. M., de La Hoz, F., Porras, A., di Filippo, D., Choconta-Piraquive, L. A., Payares, E., Montes, N. and Navas, M. C. "**Characterization of hepatitis B virus in Amerindian children and mothers from Amazonas State, Colombia**." PLoS One **2017** 12(10): e0181643.
Indonesia	D, H. M. "**Epidemiology of Hepatitis B and C in Republic of Indonesia**." Euroasian J Hepatogastroenterol **2017** 7(1): 55-59. Ie SI, Turyadi, Sidarta E, Sadhewa A, Purnomo GA, Soedarmono YS, Pattiiha MZ, Thedja MD, Harahap AR, Muljono DH. **High Prevalence of Hepatitis B Virus Infection in Young Adults in Ternate, Eastern Indonesia**. The American journal of tropical medicine and hygiene. 2015;93(6):1349-55. Darmawan E, Turyadi, El-Khobar KE, Nursanty NK, Thedja MD, Muljono DH. **Seroepidemiology and occult hepatitis B virus infection in young adults in Banjarmasin, Indonesia**. Journal of medical virology. 2015;87(2):199-207.
South Africa	Sondlane, T. H., Mawela, L., Razwiedani, L. L., Selabe, S. G., Lebelo, R. L., Rakgole, J. N., Mphahlele, M. J., Dochez, C., De Schryver, A. and Burnett, R. J. "**High prevalence of active and occult hepatitis B virus infections in healthcare workers from two provinces of South Africa**." Vaccine **2016** 34(33): 3835-3839 Amponsah-Dacosta E, Lebelo RL, Rakgole JN, Selabe SG, Gededzha MP, Mayaphi SH, Powell EA, Blackard JT, Mphahlele MJ. **Hepatitis B virus infection in post-vaccination South Africa: occult HBV infection and circulating surface gene variants**. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2015;63:12-7.
Iran	Baghbanian, M., Halvani, M., Roghani, H. S., Lotfi, M. H., Yazdi, M. F. and Vahedian-Ardakani, H. A. "**PREVALENCE OF OCCULT HEPATITIS B INFECTION IN IRANIAN CANCER PATIENTS BEFORE CHEMOTHERAPY TREATMENT**." Arq Gastroenterol **2016** 53(3): 175-179. .
Gabon	Bivigou-Mboumba, B., Francois-Souquiere, S., Deleplancque, L., Sica, J., Mouinga-Ondeme, A., Amougou-Atsama, M., Chaix, M. L., Njouom, R. and Rouet, F. "**Broad Range of Hepatitis B Virus (HBV) Patterns, Dual Circulation of Quasi-Subgenotype A3 and HBV/E and Heterogeneous HBV Mutations in HIV-Positive Patients in Gabon**." PLoS One **2016** 11(1): e0143869.
Taiwan	Hsu HY, Chang MH, Ni YH, Chiang CL, Wu JF, Chen HL. **Universal infant immunization and occult hepatitis B virus infection in children and adolescents: a population-based study**. Hepatology (Baltimore, Md). 2015;61(4):1183-91
Egypt	Elbahrawy A, Alaboudy A, El Moghazy W, Elwassief A, Alashker A, Abdallah AM. **Occult hepatitis B virus infection in Egypt**. World journal of hepatology. 2015;7(12):1671-8.
Mexico	Escobedo-Melendez G, Panduro A, Fierro NA, Roman S. **High prevalence of occult hepatitis B virus genotype H infection among children with clinical hepatitis in west Mexico**. Memorias do Instituto Oswaldo Cruz. 2014;109(6):728-37.

3.3. Implications of occult hepatitis

Session 3.3 : Implications of occult viral hepatitis

Chairs: XXX – XXX

10:40 - 11:00 *Clinical implication*

Occult hepatitis B virus and hepatocellular carcinoma. .

Teresa Pollicino University Hospital of Messina, Italy)

Pollicino T, Saitta C. **Occult hepatitis B virus and hepatocellular carcinoma**. World journal of gastroenterology. 2014;20(20):5951-61.

Abstract: Occult hepatitis B virus (HBV) infection (OBI) is a challenging pathobiological and clinical issue that has been widely debated for several decades. By definition, OBI is characterized by the persistence of HBV DNA in the liver tissue (and in some cases also in the serum) in the absence of circulating HBV surface antigen (HBsAg). Many epidemiological and molecular studies have indicated that OBI is an important risk factor for hepatocellular carcinoma (HCC) development. OBI may exert direct pro-oncogenic effects through the activation of the same oncogenic mechanisms that are activated in the course of an HBsAg-positive infection. Indeed, in OBI as in HBV-positive infection, HBV DNA can persist in the hepatocytes both integrated into the host genome as well as free episome, and may maintain the capacity to produce proteins-mainly X protein and truncated preS-S protein - provided with potential transforming properties. Furthermore, OBI may indirectly favor HCC development. It has been shown that the persistence of very low viral replicative activity during OBI may induce mild liver necro-inflammation continuing for life, and substantial clinical evidence indicates that OBI can accelerate the progression of liver disease towards cirrhosis that is considered the most important risk factor for HCC development.

Pollicino T, Cacciola I, Saffioti F, Raimondo G. **Hepatitis B virus PreS/S gene variants: pathobiology and clinical implications**.

Abstract: The emergence and takeover of hepatitis B virus (HBV) variants carrying mutation(s) in the preS/S genomic region is a fairly frequent event that may occur spontaneously or may be the consequence of immunoprophylaxis or antiviral treatments. Selection of preS/S mutants may have relevant pathobiological and clinical implications. Both experimental data and studies in humans show that several specific mutations in the preS/S gene may induce an imbalance in the synthesis of the surface proteins and their consequent retention within the endoplasmic reticulum (ER) of the hepatocytes. The accumulation of mutated surface proteins may cause ER stress with the consequent induction of oxidative DNA damage and genomic instability. Viral mutants with antigenically modified surface antigen may be potentially infectious to immune-prophylaxed patients and may account for cases of occult HBV infection. In addition, preS/S variants were reported to be associated with cases of fulminant hepatitis as well as of fibrosing cholestatic hepatitis, and they are associated with cirrhosis and hepatocellular carcinoma development.

Related articles

Saitta C, Tripodi G, Barbera A, Bertuccio A, Smedile A, Ciancio A, Sangiovanni A, Navarra G, Raimondo G, Pollicino T**. Hepatitis B virus (HBV) DNA integration**

(proposed by speaker)	**in patients with occult HBV infection and hepatocellular carcinoma**. Liver International. 2015, 35:2311-2317. doi: 10.1111/liv.12807. Pollicino T, Saitta C. **Occult hepatitis B virus and hepatocellular carcinoma**. World Journal of Gastroenterology 2014; 20:5951-5961 doi: 10.3748/wjg.v20.i20.5951. (see above) Pollicino T,Vegetti A, Saitta C, Ferrara F, Corradini E,Raffa G,Pietrangelo A, Raimondo G. **Hepatitis B virus DNA integration in tumour tissue of a non-cirrhotic HFE-haemochromatosis patient with hepatocellular carcinoma.** Journal of Hepatology 2013;58:190-193. doi: 10.1016/j.jhep.2012.09.005 Pollicino T, Raffa G, Costantino L, Lisa A, Campello C, Squadrito G, Levrero M, Raimondo G. **Molecular and functional analysis of occult hepatitis B virus isolates from patients with hepatocellular carcinoma**. Hepatology. 2007; 45:277-285 Pollicino T., Squadrito G., Cerenzia G., Cacciola I., Raffa G., Craxì A., Farinati F., Missale G., Smedile A., Tiribelli C., Villa E., Raimondo G. **Hepatitis B Virus (HBV) maintains its pro-oncogenic properties in case of occult HBV infection.** Gastroenterology, 2004; 126: 102-110
Related articles	Yip TC, Wong GL. **Current Knowledge of Occult Hepatitis B Infection and Clinical Implications**. Semin Liver Dis. 2019.
(Pubmed search)	Occult hepatitis B infection (OBI) is a status of undetectable serum hepatitis B surface antigen (HBsAg) yet detectable serum and/or intrahepatic hepatitis B virus (HBV) DNA. Mutations in the preS1, preS2, and S regions of the HBsAg gene may result in undetectable HBsAg. OBI may either result from a self-limiting acute hepatitis, or in patients with chronic hepatitis B who achieved HBsAg seroclearance, which refers to the loss of detectability of serum HBsAg with or without antibody to HBsAg (anti-HBs) in chronic hepatitis B (CHB) patients. HBsAg seroclearance contributes to a significant proportion of population in seropositive OBI. Both spontaneous and antiviral treatment-induced HBsAg seroclearance rarely happens; yet both types of HBsAg seroclearance are durable. CHB patients who achieve HBsAg seroclearance generally have a favorable clinical course. There is still a low yet definite risk of HCC occurrence, particularly in male CHB patients who achieve HBsAg seroclearance after being 50 years old. Clinical implications of OBI include occurrence of cirrhosis and HCC, liver transplantation, blood products transfusion, hemodialysis, and so on. A potentially life-threatening condition would be OBI reactivation in patients during immunosuppression therapy, especially in the setting of intensified immunosuppression including in onco-hematological patients (those receiving hematopoietic stem cell transplantation and treated with the anti-CD20 monoclonal antibody [e.g., rituximab]). With more new insights into these two conditions, CHB patients who achieved HBsAg seroclearance generally have benign clinical course and good prognosis. Sensitive assay for serum HBV DNA should be considered to establish the presence of OBI in the clinical settings mentioned earlier, which will affect the management plan. Eilard A, Andersson M, Ringlander J, Wejstal R, Norkrans G, Lindh M. **Vertically acquired occult hepatitis B virus infection may become overt after several years**. J Infect. 2019;78(3):226-31. Salmon, D., Mondelli, M. U., Maticic, M. and Arends, J. E. "**The benefits of hepatitis C virus cure: Every rose has thorns**." J Viral Hepat **2018** 25(4): 320-328.Division of Infectious Diseases and Immunology, Center for Diagnosis, Paris Centre University Hospitals, APHP, Paris Descartes University, Paris, France.

Wang, Q., Klenerman, P. and Semmo, N. "**Significance of anti-HBc alone serological status in clinical practice**." Lancet Gastroenterol Hepatol **2017** 2(2): 123-134

Sagnelli, C., Macera, M., Pisaturo, M., Zampino, R., Coppola, M. and Sagnelli, E. "**Occult HBV infection in the oncohematological setting**." Infection **2016** 44(5): 575-582

Huang X, Hollinger FB. **Occult hepatitis B virus infection and hepatocellular carcinoma: a systematic review**. Journal of viral hepatitis. 2014;21(3):153-62

11:00 - 11:20 *Blooddonors*

Residual risk of Hepatitis B Virus Transfusion-transmission: Need for Reappraisal of Blood Safety Measures?

Daniel Candotti *(National Institute of Blood Transfusion, Paris, France)*

Candotti D, Assennato SM, Laperche S, Allain JP, Levicnik-Stezinar S. 2019. **Multiple HBV transfusion transmissions from undetected occult infections: revising the minimal infectious dose.** Gut 68:313-21.

OBJECTIVE:

HBV infection by blood components is currently prevented in most developed countries by combining sensitive HBV surface antigen (HBsAg) assays, nucleic acid testing (NAT) and in a few of them antibodies against the HBV core antigen (anti-HBc) screening. HBV transmissions by blood components from three repeat donors tested negative for HBsAg and HBV DNA with a highly sensitive screening test (limit of detection (LOD): 3.4 IU/mL) were investigated. DESIGN: 30 of the 47 recipients of components produced from these three donors were examined. Transfusion transmission was confirmed by phylogenetic analysis of viral sequences obtained from recipients and donors following viral particle concentration. RESULTS: 9 of 31 (29%) recipients were infected: 7 infections were related to 200 mL of fresh frozen plasma and 2 infections to red blood cells containing 20 mL plasma. Transfusion transmission was confirmed by >99% identity of donor/recipient sequences in five cases, probable in three and possible in one. HBV active infection remained unsuspected for 24-57 months in three recipients. Five non-infected recipients carried anti-HBs when transfused. Six patients transfused with platelet concentrates treated with a pathogen reduction method were not infected. These data enabled to revise previous estimate of the minimal infectious dose from approximately 100 to 16 copies (or 3 IU) of HBV DNA. CONCLUSIONS: HBV transfusion transmission from occult HBV infection carrying extremely low viral loads is related to plasma volume transfused and possibly prevented by anti-HBs. HBV blood safety could be further improved by either anti-HBc screening, HBV DNA NAT with a LOD of 0.8 copies/mL (0.15 IU/mL) or pathogen reduction of blood components.

Candotti, D. and Laperche, S. "**Hepatitis B Virus Blood Screening: Need for Reappraisal of Blood Safety Measures?**" Front Med (Lausanne) **2018** 5: 29

Over the past decades, the risk of HBV transfusion-transmission has been steadily reduced through the recruitment of volunteer donors, the selection of donors based on risk-behavior evaluation, the development of increasingly more sensitive hepatitis B antigen (HBsAg) assays, the use of hepatitis B core antibody (anti-HBc) screening in some low-endemic countries, and the recent implementation of HBV nucleic acid testing (NAT). Despite this accumulation of

blood safety measures, the desirable zero risk goal has yet to be achieved. The residual risk of HBV transfusion-transmission appears associated with the preseroconversion window period and occult HBV infection characterized by the absence of detectable HBsAg and extremely low levels of HBV DNA. Infected donations tested false-negative with serology and/or NAT still persist and derived blood components were shown to transmit the virus, although rarely. Questions regarding the apparent redundancy of some safety measures prompted debates on how to reduce the cost of HBV blood screening. In particular, accumulating data strongly suggests that HBsAg testing may add little, if any HBV risk reduction value when HBV NAT and anti-HBc screening also apply. Absence or minimal acceptable infectious risk needs to be assessed before considering discontinuing HBsAg. Nevertheless, HBsAg remains essential in high-endemic settings where anti-HBc testing cannot be implemented without compromising blood availability. HBV screening strategy should be decided according to local epidemiology, estimate of the infectious risk, and resources

Candotti, D., Boizeau, L. and Laperche, S. "**Occult hepatitis B infection and transfusion-transmission risk**." Transfus Clin Biol **2017** 24(3): 189-195.**Abstract:** Advances in serology and viral nucleic acid testing (NAT) over the last decades significantly reduced the risk of transfusion-transmitted hepatitis B virus (HBV). The combination of HBsAg testing and NAT efficiently prevents the majority of HBV transmission. However, a specific residual risk remains associated with extremely low viral DNA levels in blood donors with occult HBV infection (OBI) that are intermittently or not detectable even by highly sensitive individual donation (ID) NAT. Studies have reported HBV transfusion-transmission with blood components from donors with OBI that contained low amount of viruses (<200 virions). HBV transfusion-transmission seems to depend on a combination of several factors including the volume of plasma associated with the infected blood components transfused, the anti-HBV immune status of both recipient and donor, and possibly the viral fitness of the infecting HBV strain. Models based on clinical and experimental evidences estimate a residual transmission risk of 3-14% associated with OBI donations testing HBsAg and ID-NAT non-reactive. Anti-HBc testing has the potential to improve further blood safety but it may also compromise blood availability in settings with medium/high HBV prevalence. Pathogen reduction procedures might be considered.

Related articles (proposed by speaker)

Candotti D, Assennato SM, Laperche S, Allain JP, Levicnik-Stezinar S. 2019. **Multiple HBV transfusion transmissions from undetected occult infections: revising the minimal infectious dose**. Gut 68:313-21. (see above)

Candotti D, Laperche S. 2018. **Hepatitis B virus blood screening: need for reappraisal of blood safety measures?** Front Med (Lausanne) 5:29.

Weusten J, van Drimmelen H, Vermeulen M, et al. **A mathematical model for estimating residual transmission risk of occult hepatitis B virus infection with different blood safety scenarios.** Transfusion 2017;57:841-9.

Allain JP, Mihaljevic I, Gonzalez-Fraile MI, et al. **Infectivity of blood products from donors with occult hepatitis B virus infection.** Transfusion 2013;53:1405-15.

Stramer SL, Wend U, Candotti D, et al. **Nucleic acid testing to detect HBV infection in blood donors.** N Engl J Med 2011;364:236-47

Related articles **(Pubmed search)**	Seed CR, Allain JP, Lozano M, Laperche S, Gallian P, Gross S, . . . Seifried E. **International forum on Occult hepatitis B infection and transfusion safety**. Vox sanguinis. 2019. Ramachandran S, Groves JA, Xia GL, Saa P, Notari EP, Drobeniuc J, . . . Stramer SL. **Recent and occult hepatitis B virus infections among blood donors in the United States**. Transfusion. 2019;59(2):601-11. Kiely, P., Hoad, V. C. and Wood, E. M. "**False positive viral marker results in blood donors and their unintended consequences**." Vox Sang **2018**.Australian Red Cross Blood Service, Melbourne, Victoria, Australia. Esposito, A., Sabia, C., Iannone, C., Nicoletti, G. F., Sommese, L. and Napoli, C. "**Occult Hepatitis Infection in Transfusion Medicine: Screening Policy and Assessment of Current Use of Anti-HBc Testing**." Transfus Med Hemother **2017** 44(4): 263-272. Li, L., Li, K. Y., Yan, K., Ou, G., Li, W., Wang, J., Song, N., Tian, L., Ji, X., Chen, Y., et al. "**The History and Challenges of Blood Donor Screening in China**." Transfus Med Rev **2017** 31(2): 89-93 Ghosh, K. and Mishra, K. "**Nucleic acid amplification testing in Indian blood banks: A review with perspectives**." Indian J Pathol Microbiol **2017** 60(3): 313-318 Wang, Z., Zeng, J., Li, T., Zheng, X., Xu, X., Ye, X., Lu, L., Zhu, W., Yang, B., Allain, J. P., et al. "**Prevalence of hepatitis B surface antigen (HBsAg) in a blood donor population born prior to and after implementation of universal HBV vaccination in Shenzhen, China**." BMC Infect Dis **2016** 16: 498 Seo DH, Whang DH, Song EY, Han KS. **Occult hepatitis B virus infection and blood transfusion**. World journal of hepatology. 2015;7(3):600-6.Dong Hee Seo, Labgenomics Clinical Laboratories, Seongnam-si 463-400, South Korea.

3.4. Impact of occult hepatitis on Public health, is it a threat for the elimination of hepatitis?

Session 3.4 : Recommendation to minimize impact of occult hepatitis on public health

EASL Recommendations)

Alternative : Lampertico P, Maini M, Papatheodoridis G. **Optimal management of hepatitis B virus infection - EASL Special Conference**. Journal of hepatology. 2015;63(5):1238-53..

There have been great strides in the management of chronic hepatitis B virus (HBV) infection, but considerable challenges remain. The European Association for the Study of the Liver (EASL) convened a special conference focusing on all clinical aspects of the management of this disease. Immigration patterns are having a huge effect on the incidence, prevalence and genotype predominance of HBV in many European countries. In recent years there has been significant progress in our understanding of the virology and immunopathology of HBV, particularly the identification of the entry receptor for HBV conferring its hepatotropism, sodium taurocholate co-transporting polypeptide, and a better understanding of the regulation of the covalently closed

circular DNA form of HBV - the major barrier to cure. However, more fundamental scientific research is needed. Serum biomarkers and transient elastography offer equivalent performance in the grading of disease stage and progression and monitoring of treatment. Occult HBV infection is often overlooked, but has many important implications for e.g., immuno-suppression, liver transplantation and the progression and severity of liver diseases from other causes. Hepatitis B e antigen positive immunotolerant patients, who are a significant source of horizontal and vertical transmission, are at risk for developing active chronic hepatitis B, but current treatment options are ineffective. Pegylated interferon therapy, given for a finite duration, offers sustained off-treatment responses in a minority of patients. Nucleos(t)ide analogues suppress the virus, improve liver histological lesions, reverse cirrhosis in the majority of cases, and improve survival, but 'cure' cannot be achieved. There is also a pressing need for novel HBV/hepatitis D virus co-infection therapies. Novel therapeutic strategies, e.g. immunomodulation, RNA interference and viral entry inhibition have demonstrated promising early results

Orlando R, Foggia M, Maraolo AE, Mascolo S, Palmiero G, Tambaro O, Tosone G. **Prevention of hepatitis B virus infection: from the past to the future**. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2015;34(6):1059-70. About 3-5 % of the world's population is chronically infected by hepatitis B virus (HBV) and is at risk of developing liver cirrhosis or hepatocellular carcinoma. The risk of dying prematurely because of chronic HBV infection is higher in younger people. The current strategies to prevent HBV infection involve immunization (active and/or passive) and antiviral chemoprophylaxis. The vaccines available for active immunization, containing hepatitis B surface antigen, are safe and confer long-term immunity in most healthy subjects. Since the vaccination is unsatisfactory in some patients, e.g., those with chronic kidney disease, human immunodeficiency virus infection, type I diabetes mellitus, and celiac disease, new strategies of vaccination are required. The neonatal, infant, and adolescent routine program vaccination in about 180 countries has greatly decreased the disease burden. Passive immunization with specific HBV immunoglobulins is recommended after single acute exposure, in infants born to infected mothers, and in HBV-infected patients undergoing liver transplantation combined with nucleoside/nucleotide analogues (chemoprophylaxis). Chemoprophylaxis is also indicated in HBV carrier candidates for immunosuppressive treatment and in patients with occult B infection undergoing immunosuppressive therapy or hematopoietic stem cell transplantation. Since HBV is not eradicable by an immune response or by antiviral drugs developed so far, the only preventive strategy remains global neonatal vaccination in all countries, firstly in HBV-endemic countries.

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Borzooy Z, Jazayeri SM, Mirshafiey A, Khamseh A, Mahmoudie MK, Azimzadeh P, Geravand B, Boroumand MA, Afshar M, Poortahmasebi V, Hosseini M, Streinu-Cercel A. **Identification of occult hepatitis B virus (HBV) infection and viral antigens in healthcare workers who presented low to moderate levels of anti-HBs after HBV vaccination**. Germs. 2015;5(4):134-40.. BACKGROUND: Worldwide, healthcare workers (HCWs) show different levels of response to hepatitis B virus (HBV) vaccine. One of the factors associated with vaccine unresponsiveness may be the existence of current or past HBV infection. Regardless of the presence of HBsAg (overt infection), occult HBV infection (OBI, defined as presence of HBV DNA in the absence of HBsAg) might also account for

some non- or hypo-response cases. METHODS: Sera from 120 HBsAg-negative HCWs with low and moderate levels of anti-HBs, <10 IU/mL (group I) and <100 IU/mL (group II) respectively, were selected and were examined for OBI by sensitive real-time PCR regardless of HBV serological profiles. Direct sequencing on surface genes was carried out in OBI-positive cases. RESULTS: Four (3.3%) were positive for OBI. All were negative for anti-HBc. Two of the positive cases had moderate levels of anti-HBs (>10 to <100 IU/mL). No significant differences were found between the two groups in terms of risk factors or serological data. No mutations were found in surface proteins of OBI cases. CONCLUSION: OBI in these subjects might be due to other factors rather than presence of "a" determinant mutations. Healthcare workers with inadequate to moderate levels of anti-HBs (<100 IU/mL) following vaccination, regardless of their serological profile for HBV, should be tested for the presence of HBV DNA by sensitive molecular tests. Anti-HBc is not a reliable marker for suspicion of OBI, especially in high-risk

Hsu HY, Chang MH, Ni YH, Chiang CL, Wu JF, Chen HL. **Universal infant immunization and occult hepatitis B virus infection in children and adolescents: a population-based study.** Hepatology (Baltimore, Md). 2015;61(4):1183-91.Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan; Department of Primary Care Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan.

UNLABELLED: To determine whether universal infant immunization affects occult hepatitis B virus (HBV) infection (OBI), serum samples from hepatitis B surface antigen (HBsAg)-negative subjects <18 years enrolled during six sequential seroepidemiological surveys conducted between 1984 (just before universal infant immunization) and 2009 were analyzed. Study subjects were divided into unvaccinated cohorts (born before 1984) and vaccinated cohorts (born after 1984). HBV-DNA positivity was determined by positivity of nested polymerase chain reaction in at least two of three regions (pre-S, S, and pre-core/core genes). OBI frequency was lower in vaccinated than unvaccinated antibody to hepatitis B core antigen (anti-HBc)-negative subjects (0 of 392 [0%] vs. 4 of 218 [1.8%]; P = 0.007), tended to be higher in vaccinated than unvaccinated anti-HBc-positive subjects (16 of 334 [4.8%] vs. 3 of 181 [1.7%]; P = 0.072), and was higher in vaccinated than unvaccinated subjects seropositive for both antibody to hepatitis B surface antigen (anti-HBs) and anti-HBc (13 of 233 [5.6%] vs. 3 of 170 [1.8%]; P = 0.025). By using known anti-HBc seropositivity rate in children in our serosurveys, the estimated OBI frequency per 10(4) HBsAg-negative subjects declined from 160.7 in unvaccinated cohorts to 11.5 in vaccinated cohorts. In vaccinated cohorts, OBI frequency was higher in anti-HBc-positive subjects than in anti-HBc-negative subjects (16 of 334 [4.8%] vs. 0 of 392 [0%]; P < 0.001). Subjects with OBI had much lower viral load (P < 0.001) and a trend of higher mutation rates in "a" determinant of HBsAg than age-comparable, HBsAg-positive subjects. CONCLUSIONS: Reduction of OBI in immunized subjects complements the well-documented universal infant immunization-related benefit of markedly reduced overt HBV infection. Breakthrough infections in immunized subjects seem to associate with more occurrence of OBI than natural infections in unvaccinated subjects. In the postvaccination era, anti-HBc seropositivity is a useful marker for OBI screening in HBsAg-negative subjects, and a very-low-level viral replication and HBsAg expression is the major mechanism

4. Speakers information

List of publications achieved via speaker's form, when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field. If more than 10 references were available only the most recent articles are shown.
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JOHN WARD

TASK FORCE for Global Health/ CDC – USA

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Imperial College London – UK
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STANISLAS POL

Universite Paris Descartes, Paris, France
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NAVEED JANJUA

University of British Columbia, Canada
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OLUWASEUN FALADE-NWULIA

Johns Hopkins University, Baltimore, MD, USA
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MARIO MONDELLI

University of Pavia, Italy
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Justus Liebig University Giessen, Institute of Medical Virology, National Reference Centre for Hepatitis B and D Viruses, Giessen, Germany

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PIETER MEYSMAN

University of Antwerp/Antwerp University Hospital, Belgium
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