Nederlandse Vereniging voor Hepatologie

Programma en abstracts

Najaarsmeeting

Nederlandse Vereniging voor Hepatologie

tevens viering 35-jarig bestaan, 1977 - 2012

4 en 5 oktober 2012, Slot Zeist te Zeist

Nederlandse Vereniging voor Hepatologie **Slotzaal**

09.00 Ontvangst, koffie in de Tuinzaal en Blauwe zaal

Voorzitters: M.J. Coenraad en R.J. de Knegt

Voordrachten in het Nederlands, spreektijd 10 minuten, discussietijd 5 minuten

09.30 Liver lesions: a prevalence study in a healthy population
M.J. Steendam[1], J.A.M. van der Palen[2], M.M.J. Guichelaar[1]Dept. of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede[1], The Netherlands. Dept. of Epidemiology, Medisch Spectrum Twente, Enschede, The Netherlands[2]

09.45 Prevalence and risk factors of severe fibrosis in the elderly: transient elastography in a population based study
E.M. Koehler[1], J. N.L. Schouten[1], B.E. Hansen[1,2], B.H. Stricker[3,4,5], L. Castera[6], H.L.A. Janssen[1],[1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Hospital, Rotterdam, The Netherlands. [2]Dept. of Public Health, Erasmus MC University Hospital, Rotterdam, The Netherlands. [3]Dept. of Epidemiology, Erasmus MC University Hospital, Rotterdam, The Netherlands. [4]Dept. of Internal Medicine, Erasmus MC University Hospital, Rotterdam, The Netherlands. [5]Dept. of Medical Informatics, Erasmus MC University Hospital, Rotterdam, The Netherlands. [6]Dept. of Hepatology, Hôpital Beaujon, Clichy, [7]Université Paris, France.

10.00 Copeptin, a surrogate marker for vasopressin, is an independent prognostic factor in cirrhosis
M.J. Coenraad, H.W. Verspaget, B.J.F. de Rooij, L.A. Verbruggen, J.J. van der Reijden, B. van Hoek, Leiden University Medical Centre, Dept of Gastroenterology and Hepatology, Leiden, The Netherlands

10.15 Complication rate in relation to the number of biopsy passes in percutaneous liver biopsy
H. Chi[1], B.E. Hansen[1,2,] J.N.L. Schouten[1], P. Taimr[1], H.L.A. Janssen[1], and R.J. de Knegt.[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Epidemiology and Biostatistics, Erasmus MC University Medical Centre, Rotterdam, The Netherlands.

10.30 Significant fibrosis in liver biopsies from HBeAg positive chronic hepatitis B patients with low ALT
W.P. Brouwer[1], M.J. Sonneveld[1], B.E. Hansen[1],[2], F.J. ten Kate[3] and H.L.A. Janssen[1], Depts of [1]Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands and [3]Pathology, Josephine Nefkens Institute, Erasmus MC University Medical Center, Rotterdam, The Netherlands

10.45 Hyponatremia is a rare side effect of terlipressin
R. Bolier, B. van Hoek, H.W. Verspaget, M.J. Coenraad, Gastroenterology Hepatology, Leiden University Medical Centre, Leiden, The Netherlands.

11.00 Koffiepauze in de Tuinzaal en Blauwe zaal

Voorzitters: S.W.M. Olde Damink en J. Blokzijl

11.30 IgG^4 positive B cell receptor clones as a potential biomarker for IgG^4 related cholangitis
L. Maillette de Buy Wenniger[1], M.E. Doorenspleet[2*], N. de Vries[2], U.H.W. Beuers[1], [1]Academic Medical Center of the University of Amsterdam, Dept of Gastroenterology and Hepatology, Tytgat Institute of Liver and Intestinal Research, Amsterdam, The Netherlands, [2]Academic Medical Center of the University of Amsterdam, Division of Clinical Immunology and Rheumatology, Amsterdam, The Netherlands.*
[*]these authors contributed equally to this work

11.45 Sarcopenia in patients with symptomatic polycystic liver disease: a more objective parameter for liver allocation?
F. Temmerman[1], J. Pirenne[2], R. Vanslembrouck[3], W. Coudyzer[3], D. Monbaliu[2], R. Aerts[2], W. Laleman[1], D. Cassiman[1], C. Verslype[1], W. Van Steenbergen[1], S. Van der Merwe[1], J. van Pelt[1], J.P. Drenth[4], F. Nevens[1]. [1]Hepatology, University Hospitals, Leuven, Belgium. [2]Abdominal Transplant Surgery, University Hospitals, Leuven, Belgium. [3]Radiology, University Hospitals, Leuven, Belgium. [4]Gastroenterology and Hepatology, Radboud University, Nijmegen, Netherlands.

12.00 Association Between Interferon Gamma Inducible Protein 10 and Liver Inflammation in Chronic Hepatitis B
W.P. Brouwer[1], M.J. Sonneveld[1], P. Arends[1], A. Boonstra[1], B.E. Hansen[1,2] and H.L.A. Janssen[1],Depts of [1]Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands and [2]Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands

12.15 Prediction of clinical disease progression in chronic hepatitis C virus infected patients with advanced hepatic fibrosis using objective variables
A.J.P. van der Meer[1], B.E. Hansen[1], J.J. Feld[2], H. Wedemeyer[3], J.F. Dufour[4], F. Lammert[5], A. Duarte Rojo[2], M.P. Manns[3], L. Kuske[4], S. Zeuzem[6], W.P. Hofmann[6], R.J. de Knegt[1], B.J. Veldt[1], H.L.A. Janssen[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands, [2]Liver centre, Toronto Western hospital, University Health Network, Toronto, Ontario, Canada [3]Dept of Gastroenterology, Hepatology, and Endocrinology, Medical

School Hannover, Hannover, Germany [4]Hepatology, Dept of Clinical research, University of Bern, Bern, Switserland [5]Dept of Medicine II, Saarland University Medical Center, Homburg/Saar, Germany [6]Medizinische Klinik 1, Klinikum der Johann Wolfgang Goethe Universität, Frankfurt am Main, Germany

12.30 Presence of Anti Interferon Antibodies is not Associated with Non Response to Peginterferon Treatment in Chronic Hepatitis B

P. Arends[1], M.J. Sonneveld[1], A.A. van der Eijk[2], B.E. Hansen[1,3], B. Haagmans[2], H.L.A. Janssen[1]. [1]Dept. of Gastroenterology & Hepatology, [2]dept. of Virology, [3]dept. of Public Health, Erasmus MC University Hospital, Rotterdam, The Netherlands

12.45 Adding peginterferon alfa 2a to entecavir increases HBsAg decline and HBeAg clearance first results from a global randomized trial (ARES)

M.J. Sonneveld[1], Q. Xie[2], N.P. Zhang[3], Q. Zhang[4], F. Tabak[5], A. Streinu[6], J.Y. Wang[3], R. Idilman[7], A. de Niet[8], M. Diculescu[9], A.J. van Vuuren[1], E. Verhey[1], B.E. Hansen[1,10], H.L.A. Janssen[1], Depts of [1]Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [2]Infectious Diseases, Ruijin Hospital, Jiaotong University, Shanghai, China; [3]Gastroenterology and Hepatology, Zhong Shan Hospital, Fu Dan University, Shanghai, China; [4]Gastroenterology and Hepatology, Shanghai Public Health Center, Fu Dan University, Shanghai, China; [5]Dept of Infectious Diseases, Cerrahpasa Medical School, Istanbul, Turkey; [6]National Institute of Infectious Disease, Bucharest, Romania; [7]Gastroenterology and Hepatology, University of Ankara, Ankara, Turkey; [8]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands; [9]Gastroenterology, Fundeni Cinical Institute, Bucharest, Romania; [10]Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

13.00 Lunchbuffet in de Tuinzaal en Blauwe zaal

Symposium NAFLD/NASH

Voorzitters: J.P.H. Drenth en H.L.A. Janssen

14.00 **Diagnosis**
Is NAFLD a disease, only a minority develops liver related complications. How do the complications compare to cardiovascular complications. Is it epidemic?
J.N.L. Schouten, Erasmus MC, Rotterdam

14.30 **Assessment & follow-up**
What is the 'gold standard' in NASH/NAFLD, should we biopsy all, is ultrasound enough. Once diagnosed, should we follow up, only if LE are elevated?
C. Day, Newcastle University, Newcastle, UK.

15.00 **Medical interventions**
When should we give drugs, only in trials. Is vitamin E ready for prime time?
V. Ratziu, APHP UPMC Liver Center, Paris, France.

15.30 **Non-medical interventions**
Is exercise the mainstay, if so what where and how. If patients are to lose weight how much, how quick? In other words: practical advice on what to tell our patients.
Surgery. Is bariatric surgery the solution for all obese?
F.L.J. Visseren, UMC Utrecht

donderdag 4 oktober 2012

Nederlandse Vereniging voor Hepatologie **Slotzaal**

16.00	Theepauze in de Tuinzaal en Blauwe zaal
16.30	Algemene Ledenvergadering NVH
17.00	**Interactieve terugblik in de tijd met de oprichters van de Nederlandse Vereniging voor Hepatologie**
17.30	Feestelijke lustrumborrel / dinerbuffet

Vrijdag 5 oktober 2012

Nederlandse Vereniging voor Hepatologie **Slotzaal**

09.00 Ontvangst, koffie in de Tuinzaal en Blauwe zaal

Voorzitters: H.L.A. Janssen en D. Sprengers

Voordrachten in het Nederlands, spreektijd 10 minuten, discussietijd 05 minuten

09.30 Response guided peginterferon therapy in HBeAg positive chronic hepatitis B using serum hepatitis B surface antigen levels: a pooled analysis of 903 patients
M.J. Sonneveld[1], B.E. Hansen[2], T. Piratvisuth[3], J.D. Jia[4], S. Zeuzem[5], E. Gane[6], Y.F. Liaw[7], Q. Xie[8], E.J. Heathcote[9], H.L.Y. Chan[10] and H.L.A. Janssen[1], Depts of [1]Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [2]Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands; [3]NKC Institute of Gastroenterology and Hepatology, Songklanagarind Hospital, Prince of Songkla University, Hat Yai, Thailand; [4]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [5]Medical Clinic 1, Johann Wolfgang Goethe University Medical Center, Frankfurt, Germany; [6]Liver Unit, Auckland City Hospital, Auckland, New Zealand; [7]Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan; [8]Dept of Infectious Diseases, Ruijin Hospital, Shanghai, China; [9]Division of Gastroenterology, University of Toronto, Toronto, Canada; [10]Dept of Medicine and Therapeutics and Institute of Digestive Disease, the Chinese University of Hong Kong, Hong Kong SAR, China

09.45 Allopurinol salvage therapy in autoimmune hepatitis: a preliminary report
Y.S. de Boer[1], G. Bouma[1], C.J.J. Mulder[1], C.M.J. van Nieuwkerk[1], [1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

10.00 Young female patients with polycystic liver disease benefit the most from somatostatin analogue therapy: an individual patient data meta analysis
T.J.G. Gevers[1], J. in 't Hout[2], A. Caroli[3], P. Ruggenenti[4,5], M.C. Hogan[6], V.E. Torres[6], F. Nevens[7], J.P.H. Drenth[1], [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands. [2]Dept of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands. [3]Dept of Biomedical Engineering, Mario Negri Institute for Pharmacological Research, Bergamo, Italy. [4]Dept of Kidney Disease, Mario Negri Institute for Pharmacological Research, Bergamo, Italy. [5]Unit of Nephrology and Dialysis, Azienda Ospedaliera Ospedali Riuniti di Bergamo, Bergamo, Italy.

[6]Division of Nephrology and Hypertension, Dept of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA. [7]Dept of Hepatology, University Hospital Leuven, Leuven, Belgium.

10.15 Peginterferon Reduces Intrahepatic HBsAg and is Associated with Histologic Response in Chronic Hepatitis B

P. Arends[1], V. Rijckborst[1], B.E. Hansen[1,2], P.E. Zondervan[3], H.L.A. Janssen[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Public Health, [3]Dept of Pathology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands.

10:30 New Insights Into Toxicity and Pharmacokinetics of Ribavirin and Cyclosporine in Liver Transplant Recipients on Boceprevir Based Antiviral Therapy – Evidence of Need for New Target Troughs for CsA and lower Dosing of Ribavirin

L. Koning[1,2], K.D.S. Watt[1], J.J. Poterucha[1], J.K. Heimbach[1], and M.R. Charlton[1] , [1]Mayo Clinic Transplant Center, Rochester MN, USA. [2]Erasmus MC, Rotterdam, The Netherlands

10.45 Hepatitis E virus among chronic hepatitis C infected patients: risk factors and clinical outcome

D.M. Hotho[1], S.D. Pas[2], B.E. Hansen[1,3], A.D.M.E. Osterhaus[2], H.L.A. Janssen[1], R.J. de Knegt[1] and A.A. van der Eijk[2], Depts of [1]Gastroenterology and Hepatology, [2]Virology and [3]Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands

11.00 Koffiepauze in Tuinzaal en Blauwe zaal

Voorzitters: J.N.L. Schouten en C.M.J. van Nieuwkerk

11.30 Genotypic resistance to entecavir in lamivudine naive patients after achieving a virological response for chronic hepatitis B

R. Zoutendijk[1], S. Diepstraten Pas[2], S. Locarnini[3], C. Boucher[2], A.A. vd Eijk[2] and H.L.A. Janssen[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Virology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands, [3]Victorian Infectious Diseases Reference Laboratory, North Melbourne, Australia

11.45 Treatment Success of Aspiration and Sclerotherapy for Hepatic Cysts depends on Cyst Diameter and Volume of Sclerosing Agent

M. Chrispijn[1], F.H. Weimer[1], Y. El Massoudi[2], T.M. van Gulik[2], A. Moelker[3], L.J. Schultze Kool[4], J.P.H. Drenth[1], [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [2]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands, [4]Division of Intervention Radiology, Dept of Radiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

12.00 Number of patients needed to treat to prevent death in genotype-1 chronic hepatitis C cirrhosis: the impact of improved interferon based therapy

A.J.P. van der Meer[1], B.J. Veldt[1], J.J. Feld[2], H. Wedemeyer[3], J F. Dufour[4], F. Lammert[5], A. Duarte Rojo[2], M.P. Manns[3], S. Zeuzem[6], W.P. Hofmann[6], R.J. de Knegt[1], B.E. Hansen[1], H.L.A. Janssen[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands, [2]Liver centre, Toronto Western hospital, University Health Network, Toronto, Ontario, Canada, [3]Dept of Gastroenterology, Hepatology, and Endocrinology, Medical School Hannover, Hannover, Germany, [4]Hepatology, Dept of Clinical research, University of Bern, Bern, Switserland, [5]Dept of Medicine II, Saarland University Medical Center, Homburg/Saar, Germany, [6]Medizinische Klinik 1, Klinikum der Johann Wolfgang Goethe Universität, Frankfurt am Main, Germany.

12.15 High relapse rates in HBeAg negative chronic hepatitis B patients after discontinuation of nucleos(t)ide analogues

B.E Hansen[1,2], M. Cornberg[3], H.L.Y. Chan[4], P. Arends[1], S. Wiegand[3], M.R. Brunetto[5], H.L.A. Janssen[1] for the Good Practice in using sAg in Chronic Hepatitis B Study Group (GPs CHB Study Group),[1]Dept of Gastroenterology and Hepatology Erasmus MC Rotterdam, The Netherlands, [2]Dept of Public Health, Erasmus MC, Rotterdam, The Netherlands, [3]Dept of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany. [4]Dept of Medicine & Therapeutics, Chinese University of Hong Kong, Hong Kong SAR, China, [5]Hepatology Unit, University of Pisa, Italy

12.30 Larger polycystic livers are associated with signs of portal hypertension and displacement of abdominal organs

M. Chrispijn[1], J.J. Hermans[2], J.P.H. Drenth[1], [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [2]Dept of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

12.45 Evaluation of 6 thioguanine therapy in Autoimmune Hepatitis
Y.S. de Boer[1], G. Bouma[1], C.J.J. Mulder[1], C.M.J. van Nieuwkerk[1], [1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

13.00 Lunchpauze in Tuinzaal en Blauwe zaal

Voorzitters: U.H.W. Beuers en B. van Hoek

14.00 Longterm follow up of inactive hepatitis B virus carriers and relation with Hepatitis B surface Antigen levels /
B.E Hansen[1],[2], H L Y Chan[3], P Arends[1], B Cherubini[7], M Cornberg[4], A.J.V. Thompson[5], [1]Dept of Gastroenterology and Hepatology Erasmus MC Rotterdam, the Netherlands, [2]Dept of Public Health, Erasmus MC, Rotterdam, The Netherlands, [3] Department of Medicine & Therapeutics, Chinese University of Hong Kong, Hong Kong SAR, China, [4]Dept of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany, [5]Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria 3051, Australia, [6]Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan.[7]Hepatology Unit, University of Pisa, Italy

14.15 An accurate formula for a quick estimate of liver volume in polycystic liver
M. Chrispijn[1], T.J.G. Gevers[1], J.P.H. Drenth[1], [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

14.30 Natural killer cell activity and function in chronic HCV-infected patients during peginterferon and ribavirin: no effect of active substance use
D.M. Hotho[1], K. Kreefft[1], Z.M.A. Groothuismink[1], H.L.A. Janssen[1], R.J. de Knegt[1], and A. Boonstra[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

14.45 Von Willebrand factor levels are independently associated with liver stiffness: results of a population-based study
E.P.C. Plompen[1], J.N.L. Schouten[1], B.E. Hansen[1,2], B.H.Ch. Stricker[3], F.W.G. Leebeek[4], H.L.A. Janssen[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Public Health, [3]Dept. of Epidemiology, [4]Dept. of Hematology, Erasmus MC University Hospital, Rotterdam, The Netherlands

15.00 The clinical relevance of secondary histological diagnoses in chronic hepatitis B and C: prevalence and impact on disease severity

H. Chi[1], B.E. Hansen[1,2], P.E. Zondervan[3], J.P.H. Drenth[4], H.L.A. Janssen[1], and R.J. de Knegt[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Epidemiology and Biostatistics, [3]Dept of Pathology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands. [4]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

15.15 ALT flares during entecavir treatment are associated with a favorable outcome in chronic hepatitis B

J.G.P. Reijnders[1], R. Zoutendijk[1], F. Zoulim[2], A. Brown[3], D. Mutimer[4], K. Deterding[5], W.P. Hofmann[6], J. Petersen[7], M. Fasano[8], M. Buti[9], T. Berg[10], M.J. Sonneveld[1], B.E. Hansen[1], H. Wedemeyer[5], H.L.A. Janssen[1] for the VIRGIL Surveillance Study Group. [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands, [2]Dept of Hepatology, Hospices Civils de Lyon, Lyon, France, [3]Dept of Hepatology and Gastroenterology, Imperial College London, London, United Kingdom, [4]NIHR Biomedical Research Unit and Centre for Liver Research, Queen Elizabeth Hospital, Birmingham, United Kingdom, [5]Dept of Gastroenterology, Hepatology, and Endocrinology, Medical School Hannover, Hannover, Germany, [6]Medizinische Klinik 1, Klinikum der Johann Wolfgang GoetheUniversität, Frankfurt am Main, Germany, [7]Ifi Institute, Asklepios Klinik St. Georg, Hamburg, Germany, [8]Clinic of Infectious Diseases, University of Bari, Bari, Italy, [9]Dept of Hepatology, Hospital Vall de Hebron, Barcelona, Spain, [10]Dept of Hepatology, University Clinic Leipzig, Leipzig, Germany

15.30 Viral hepatitis B and C: Non-invasive selection of patients with and without advanced liver fibrosis using of MR Elastography and Fibroscan

A.E. Bohte[1], A. de Niet[2], A.J. Nederveen1, S. Bipat[1], J. Verheij[3], V. Terpstra[4], C.M.J. van Nieuwkerk[5], R.J. de Knegt[6], L.C. Baak[7], P.L.M. Jansen[2], J. Stoker[1,1]AMC, dept of Radiology, [2]AMC, dept of Gastroenterology and Hepatology, [3]AMC, dept of Pathology, [4]Bronovo Ziekenhuis, department of Pathology, [5]VUmc, dept of Gastroenterology and Hepatology, [6]Erasmus MC, dept of Gastroenterology and Hepatology, [7]Onze Lieve Vrouwe Gasthuis, dept of Gastroenterology and Hepatology

15.45 Improved patient survival and its determinants in two decades of liver transplantion; a single center experience

Sebib Korkmaz K.[1], de Rooij B.-J. F.[1], Verspaget H.W.[1,] Maljaars P.W.J.[1], Coenraad M.J.[1], Ringers J.[2], Dubbeld J.[2], Baranski A.G.[2] Inderson A.[1], van Hoek B.[1],[1]Dept of Gastroenterology and Hepatology, [2]Dept of Surgery, Leiden University Medical Center, The Netherlands

16.00 Koffie/thee en gelegenheid tot napraten in de Tuinzaal en Blauwe zaal.

Liver lesions: a prevalence study in a healthy population

M.J. Steendam[1], J.A.M. van der Palen[2], M.M.J. Guichelaar[1] Dept. of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede[1], The Netherlands. Dept. of epidemiology, Medisch Spectrum Twente, Enschede, The Netherlands[2]

Background: The widespread use of modern abdominal imaging techniques has led to an increase in incidentally detected hepatic lesions. The aim of this study is to investigate the prevalence of liver lesions and simple cysts in the general population.Methods: Liver lesions and simple cysts were detected by retrospective analysis of MRI reports from all consecutive persons who underwent abdominal MRI at a center of preventive medical care between April 2010 – April 2011. The abdominal MRI is part of a medical screening and self-initiated by the participants, without doctor's referral. Anamnesis forms were studied for general demographics, medication use, medical history and abdominal complaints. Results: During the study period, 2668 persons (60% male), had abdominal MRI imaging. The mean age of the population was 53.1 ± 11.2 yrs, with a mean BMI of 25.9 ±3.7. Comparison to data of a Dutch survey study (Centraal Bureau voor de Statistiek) revealed that the study population is very similar to the general Dutch population concerning general demographics. Analysis of MRI reports showed that 759 persons (28.4%) had hepatic simple cysts. Most hepatic cysts were small (< 3 cm in 95.3%), multiple (60.9%) and more often located in the right lobe (41.8% versus 30.7% left) . The prevalence increased with age. Hepatic cysts correlated with the use of anti-diabetic medication, whereas no correlations were found with BMI or gender. Forty-eight percent of the patients with hepatic cysts also reported cysts in other organs; 40.8% had hepatic and renal cysts, 1.3% hepatic and splenic cysts, and 1.7% hepatic and pancreatic cysts. The prevalence of renal and pancreatic cysts increased with age. Hepatic hemangiomas had a prevalence of 6,4%, which was higher in female patients (F:M, 1,3:1) and were found significantly more often in the right lobe (72.3% versus 17.6% left). The prevalence of hemangiomas was not age related and correlated with oral contraceptives.

Conclusions: This study in a healthy population without major complaints revealed high prevalences of hepatic cysts and hemangiomas. In addition, also the prevalence of simple cysts in other organs was found to be high. Analysis indicated that hepatic and pancreatic cysts increased with age, and occurred often with concomitant cysts in other organs. To our knowledge this is the first study to evaluate such prevalence rates in a large, healthy population by MRI imaging. Comparison to data of a Dutch survey study indicated similar demographics which may imply that the prevalence rates are applicable to the general Dutch population.

Prevalence and risk factors of severe fibrosis in the elderly: transient elastography in a population-based study

E.M. Koehler[1], J.N.L. Schouten[1], B.E. Hansen[1,2], B.H. Stricker[3,4,5], L. Castera[6], H.L.A. Janssen[1],[1]Dept. of Gastro-enterology and Hepatology, Erasmus MC University Hospital, Rotterdam, The Netherlands. [2]Dept. of Public Health, Erasmus MC University Hospital, Rotterdam, The Netherlands. [3]Dept. of Epidemiology, Erasmus MC University Hospital, Rotterdam, The Netherlands. [4]Dept. of Internal Medicine, Erasmus MC University Hospital, Rotterdam, The Netherlands. [5]Dept. of Medical Informatics, Erasmus MC University Hospital, Rotterdam, The Netherlands. [6]Dept. of Hepatology, Hôpital Beaujon, Clichy, [7]Université Paris, France.

Transient elastography (TE) measures liver stiffness, which correlates well with histological stages of liver fibrosis. By means of TE, we aimed to assess the prevalence and risk factors of severe liver fibrosis and cirrhosis in the elderly (> 65 years). This study was based on 2317 participants of a large population-based cohort study among elderly persons. All participants underwent an interview and clinical examination that included a blood collection, abdominal ultrasound and TE (by a single operator). Nonalcoholic fatty liver disease (NAFLD) was defined as fatty liver at ultrasonography, in the absence of 1) excessive alcohol consumption (>14 drinks weekly), 2) positive HBsAg or anti-HCV, and 3) use of drugs associated with fatty liver. TE was considered reliable if ≥ 60% success rate (≥10 valid measurements) and IQR/median liver stiffness measurement (LSM) ≤0.3. LSM >9.5 kPa was taken as a cut-off for presence of severe fibrosis and 13 kPa for cirrhosis. Associations between LSM>9.5kPa or LSM as a continuous dependent variable was assessed using logistic or linear regression analysis. Failure and unreliable LSM were observed in 282 (12.1%) and 711 (29.4%) patients, respectively. Data on LSM were analysed in 1324 participants (mean age 74.0±5.6; mean BMI 26.6±3.6). In multivariable analysis, failure and unreliable LSM was associated with higher age, higher BMI and female gender (p-values<.001). The prevalence of LSM >9.5kPa and >13kPa was 4.2% and 1.1%, respectively. Higher age (OR1.12, 95%CI 1.06-1.17;p<.001), greater HOMA-IR (OR1.05, 95%CI 1.00-1.10; p=0.044), higher ALT (OR1.04, 95%CI1.02-1.06; p<.001), lower platelets (OR0.99, 95%CI 0.99-1.00; p=.03) and greater spleen size (OR1.37; 95%CI 1.13-1.66; p=.001) were associated with LSM>9.5kPa in logistic regression analysis. In total, 16 of 329 participants (4.9%) with NAFLD had LSM >9.5kPa; HOMA-IR was independently associated with elevated LSM in participants with NAFLD.

Conclusions: Our results suggest that severe fibrosis and cirrhosis may be present in 4.2% and 1.1% of the elderly population, respectively. Elevated LSM was associated with higher age, ALT, HOMA-IR, spleen size and lower platelets. Feasibility of TE in this elderly population is however disputable with either failure or unreliable results in more than one-third of the participants.

Copeptin, a surrogate marker for vasopressin, is an independent prognostic factor in cirrhosis

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MELD score is widely accepted as a prognostic score and used for organ allocation in liver transplantation. Earlier stages of portal hypertension without elevated creatinin concentration are not accounted for in the MELD score. We hypothesized that arginine vasopressin (AVP) might be an independent prognostic factor in cirrhosis. However, AVP is an instable molecule with a short half-life, whereas copeptin, a cleavage product of the C-terminal part of the AVP precursor, has a long half-life and is not bound to platelets in the circulation. The aims of the present study were (1) to evaluate the prognostic significance of plasma copeptin concentration in patients with cirrhosis and (2) to assess the relationship between plasma copeptin level and renal function, as a potential marker of end-stage portal hypertension in cirrhotic patients. In 63 patients (47M, 16F) with liver cirrhosis who were listed for liver transplantation, base plasma copeptin, sodium, creatinin, bilirubin concentration and INR measurements were performed. MELD score and MDRD-GFR were calculated based on these lab results. Copeptin measurements were performed using a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S. GmbH, Henningsdorf, Germany). Median plasma copeptin concentration in this cohort was 18.5 (IQR 7.8-34.7) pmol/l (normal value in healthy subjects: 4.2 pmol/l (1-13.8) pmol/l). Mean survival until death (n=8) or liver transplantation (n=49) was 257 ± 37 days. In univariate Cox proportional hazard model, copeptin (hazard ratio 1.006 per 1 pmol/l increase in copeptin concentration, $p<0.01$), serum bilirubin concentration (HR 1.004, $p<0.001$), INR (HR 1.710, $p<0.05$) and MELD score (HR 1.072, $p<0.01$) were significant predictors for the composite endpoint of death or liver transplantation. In multivariate Cox proportional hazard model adjusted for MELD score and INR, copeptin (HR 1.008 per 1 pmol/l increase in copeptin concentration, $p<0.05$) and bilirubin (HR 1.005, $p<0.01$) were independent predictors of death or transplantation. There was a significant correlation between copeptin and serum creatinin concentration ($r=0.826$, $p<0.001$), serum sodium concentration ($r= -0.260$, $p<0.05$) and MELD score ($r=0.443$, $p<0.001$). Copeptin was not correlated to the use of diuretics, bilirubin concentration or INR.

Conclusions. Plasma copeptin levels independently predict mortality or liver transplantation in cirrhotic patients. Furthermore, copeptin is strongly related to serum sodium, creatinin concentration and MELD score.

Complication rate in relation to the number of biopsy passes in percutaneous liver biopsy

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Background: Percutaneous liver biopsy (PLB) remains the gold standard to assess liver fibrosis. The length of a PLB should ideally be ≥25 mm for accurate fibrosis assessment with Metavir. Consequently, more than one biopsy pass may be needed. We aimed to determine whether the complication rate is affected by the number of biopsy passes. Methods: A retrospective cohort was created enrolling all PLB performed at an university medical centre in the Netherlands between January 2005 and October 2011. All biopsies were performed according to guidelines, by experienced hepatologists using abdominal ultrasound and 14-Gauge Tru-cut needle. We reviewed the medical records of the Emergency, Radiology, Gastroenterology & Hepatology, and Pathology departments up to 3 months after a PLB to identify complications. Complications were categorized into mild (event requiring hospitalization ≤2 days, and/or no intervention) and severe complications (event requiring hospitalization ≥3 days, and/or intervention). Patients without hepatitis B or hepatitis C were classified as non-viral diagnosis. Multivariate logistic regression was used to determine independent risk factors for overall and severe complications. Results: We analyzed 1382 PLB obtained from 1170 patients (median age: 45 years, male sex: 60.6%, liver transplantation: 22.1%, cirrhosis: 6.8%, liver cancer: 1.8%). The overall complication rate was 5.6% (77 cases): 55 cases (4.0%) were mild, and 22 cases (1.6%) were severe complications. One patient died (mortality: 0.07%). The overall complication rate was independently associated with the number of biopsy passes (odds ratio [OR], 1.69; p=0.04), female sex (OR, 2.25; p<0.001), platelet count ≤120*10^9/L (OR, 2.21; p=0.03) and INR ≥1.4 (OR, 3.21; p=0.03). Age, Metavir, liver cancer, liver transplantation, and non-viral diagnosis were not significantly associated with the overall complication rate. Non-viral diagnosis (OR, 3.31, p=0.04), female sex (OR, 2.50; p=0.05), and INR ≥1.4 (OR, 9.05; p<0.001) were the only independent risk factors for severe complications. The severe complication rate was not significantly related to the number of biopsy passes, age, Metavir, liver cancer, and liver transplantation.

Conclusions: PLB is a relatively safe invasive procedure to assess liver fibrosis with an overall complication rate of 5.6%. Our results suggest that patients with a high number of biopsy passes, female sex, platelet count ≤120*10^9/L, and/or INR ≥1.4 are at risk for overall complications, whereas patients with a non-viral diagnosis, female sex, and/or INR ≥1.4 are at risk for severe complications.

Significant fibrosis in liver biopsies from HBeAg-positive chronic hepatitis B patients with low ALT

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Large population based studies have shown that HBeAg-positive patients are at increased risk for the development of cirrhosis and hepatocellular carcinoma. Treatment is currently not generally recommended by AASLD for patients with ALT levels below 2 times the upper limit of normal (ULN) since they are considered to be at low risk of disease progression. This study aimed to assess the severity of liver fibrosis and hepatic inflammation in biopsies of HBeAg-positive chronic hepatitis B patients with serum ALT levels <2xULN. Hereto fibrosis (Ishak 0-6) and inflammation (HAI 0-18) were assessed in liver biopsies of 373 HBeAg-positive patients enrolled at tertiary care centers. Significant fibrosis was defined as a fibrosis stage of 3 (portal to portal septal fibrosis) or higher and significant liver inflammation was defined as an inflammation score of 6 or higher. Patients were predominantly male (75%). The median age at biopsy was 32 (IQR 25 – 43) years. Median fibrosis stage was 2 (IQR 1 – 3), inflammation score was 4 (IQR 3 – 6) and median ALT and HBV DNA at base were 106 U/L (IQR 66.5 – 206.0) and 9.1 log copies/mL. One-hundred and six patients (28%) had an ALT below 2 times ULN, of whom 29 (27%) had normal ALT. Among patients with ALT>2xULN, 144 patients (54%) had significant fibrosis and 99 (37%) had significant inflammation. Importantly, both significant inflammation and fibrosis were still commonly present in patients with ALT<2xULN: significant fibrosis was found in 32% (n=34) and inflammation in 18% (n=19). A similar rate was observed among patients with normal ALT: 8 (28%) had significant fibrosis (p=0.54 versus those with ALT >1 but <2xULN). Among patients with ALT <2xULN, those with significant fibrosis were older (p=0.04), whereas HBV DNA was not different between the two groups (p=0.65).

In conclusion, fibrosis is present in around 30% of HBeAg-positive chronic hepatitis B patients with ALT <2xULN, even in those with a normal ALT. Our findings under the importance of liver biopsy in HBeAg-positive patients even when ALT is low or normal.

Hyponatremia is a rare side effect of terlipressin

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Terlipressin, a V1a-agonist, is used as vasoconstrictive therapy in cirrhotic patients with variceal bleeding (VB) and hepatorenal syndrome (HRS). Terlipressin is also a partial agonist of the V2 receptors in the kidney. Terlipressin was recently found to cause a significant reduction in serum sodium concentration in the majority of patients with acute variceal hemorrhage, who failed to other vasoconstrictor therapy. We hypothesize that terlipressin rarely causes severe hyponatremia in patients with VB or HRS when used at lower doses. Retrospective analysis of 69 consecutive patients with cirrhosis treated between 2007 and 2011 with terlipressin: 22 patients were treated with terlipressin for VB and 47 were treated with terlipressin and albumin for HRS. Patients with VB received a bolus 2mg terlipressin iv. followed by 1 mg every 4 hours. Patients with HRS received terlipressin 0.5 mg iv. every 4 hours, with dose escalation every 3 days if there was no response.

In the whole group, serum sodium concentration did not significantly change during terlipressin therapy (difference between base and lowest sodium concentration during terlipressin therapy: + 0.63 ± 4.1 mmol/l (p=0.128)). Also when tested in the groups treated for VB (- 2.0 ± 5.27 mmol/l, p=0.115) and HRS (0 ± 3.51 mmol/l, p=0.999) separately, serum sodium concentration did not significantly change during terlipressin therapy. In 5/47 patients (11%) with HRS and in 7/22 patients with VB (32%) serum sodium decreased >5 mmol/l during terlipressin. However, none of the patients had symptomatic hyponatremia. MELD score, base serum sodium, creatinin, bilirubin concentrations and INR were not related to the serum sodium reduction in any of the groups. 3 Months survival was 64% in patients with VB and 34% in patients with HRS. 52% of HRS patients responded to terlipressin.

Conclusion. Despite partial V2 agonist effects, clinically significant hyponatremia is a rare side effect of terlipressin therapy in cirrhotic patients with variceal bleeding or hepatorenal syndrome when used at lower doses.

IgG4-positive B-cell receptor clones as a potential biomarker for IgG4-related cholangitis

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Background: IgG4-associated cholangitis (IAC) is the biliary manifestation of the recently established spectrum of IgG4-related diseases. A substantial proportion of, but not all patients have elevated serum IgG4, which limits the use of serum IgG4 as a biomarker. The source of the strongly elevated serum IgG4 has been under discussion, as well as its role in the etiology of IgG4-related disease. If elevated IgG4 serum titres would be caused by antigen-driven immune responses, clonally expanded, class-switched B-cells and plasma cells would be present. Here, we thus used a novel next-generation sequencing protocol to investigate the presence and clonality of B-cell receptors (BCR) in periperhal blood of IAC patients. Methods: The BCR repertoire was assessed in peripheral blood before and after 4 and 8 weeks of high-dose prednisolone (median 40mg, range 20-40mg) treatment of 5 prospectively included IAC patients. The BCR repertoires of 9 untreated individuals (PSC, pan-creaticobiliary cancer (CA), and age/sex-matched healthy individuals (HC), n=3 each) were analysed as controls. In one patient a (paired) duodenal papilla biopsy could be obtained at baseline. mRNA was isolated from all samples and full-repertoire analysis of the immunoglobulin heavy-chain was performed with primers for all V(ariable)- and C(onstant)-genes. The samples were analyzed using a GS-FLX/454 and custom bioinformatics algorithms (>10,000 sequences/sample). Results: Of all BCR clones a mean of 15.1% was IgG+ (similar in HC/DC) in IAC patients. Of this IgG subset, only in IAC the most dominant clones (as percentage of the total repertoire) at base were IgG4+ (mean rank of the most dominant IgG4+ clone 1st in IAC versus 63th in HC ($p<0.05$) and 55th in DC ($p<0.005$)). In all IAC patients IgG4+ BCR clones were detected among the 10 most dominant BCR clones of any immunoglobulin isotype (IgA, IgD, IgM and IgG) in blood, which was not found in any of the controls, and which was independent of serum IgG4. The BCR repertoire of the papillary biopsy comprised the same dominant IgG4 clones that were detected in the patient's blood. In all IAC patients, after 4 and 8 weeks of therapy the contribution of these specific IgG4+ clones to the BCR repertoire were negligible, mirroring sharp declines in serum IgG4 and regression of clinical symptoms.

Conclusion: We detected highly abundant IgG4+ BCR clones in blood and duodenal papilla tissue of IAC patients but not in controls, and these disappeared upon steroid treatment. Specific B cell responses may thus play a role in the pathogenesis of IAC and that expanded IgG4+ BCR clones should be explored as a biomarker for IgG4-related disease.

Sarcopenia in patients with symptomatic polycystic liver disease: a more objective parameter for liver allocation?

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Background: Invalidating polycystic liver disease (PLD) with extreme hepatomegaly can be an indication for liver transplantation (LT).In Eurotransplant, a decreased mid-upper arm circumference (MUAC) is used to give symptomatic pts priority on the waiting list (female: <23.1;men:<23.8cm). This is based on the assumption that decreased MUAC reflects malnutrition but this has never been validated in PLD.AIM: To study the prevalence of malnutrition assessed by sarcopenia (depletion of skeletal muscle) in symptomatic PLD. METHODS: Liver volume (LV); skeletal muscle area (SMA) and subcutaneous adipose tissue (SAT) at vertebra L3 were measured by single CT-scanning. Skeletal muscle area was corrected for stature (SMA-index). Sarcopenia was defined as SMA-index <38.5cm²/h² (female); <52.4cm²/h² (men).LV was corrected for body surface area (LV-index).Lean body mass was estimated from skeletal muscle area.RESULTS: Studygroup (n=43):39 women; mean age of 51y. Sarcopenia was present in 42%;a decreased MUAC in 37%. Pts were divided in 4 groups: A/decreased MUAC and sarcopenia (n=8); B/decreased MUAC and no sarcopenia (n=8); C/no decreased MUAC with sarcopenia (n=7); D/no decreased MUAC and no sarcopenia. Mann-Whitney Rank Sum Test was used to compare all groups. There was no difference regarding age & creatinine clearance. In group A, pts had larger liver volumes than group C (resp.: 6684ml (IQR:4922-8206) and 2987ml (IQR:2571-4794); p<0.05). Group C and D had normal MUAC (resp: 28.6cm (IQR:25.2-29.8) and 27.7cm (IQR: 25.3-29.4)) but also more subcutaneous fat (resp. 161.2cm² (IQR:136.7-310.8) and 204.4cm² (IQR:85.2-292.7)) compared to group A and B (resp 96.1cm² (IQR: 46.1-144) and 92.5cm²(IQR: 51.7-125.7)) (p<0.05).The LV-index in group A was higher than in group C and D (A: 4.9; C: 2.7; D:4.1; p<0.05).In group D, pts had more lean body mass and subcutaneous fat vs all other groups (p<0.05). MUAC was well correlated with subcutaneous fat (Pearson: r=0.759;P<0.0001) but less with lean body mass (Pearson: r=0.393,p=0.009). Pts were then divided in group LT (n=20) vs no LT (n=23).12 pts of group LT had no decreased MUAC, however 25% was sarcopenic.
CONCLUSION: Sarcopenia is highly prevalent is pts with symptomatic PLD (42%). MUAC is more strongly correlated with subcutaneous fat rather than lean body mass; as such a subgroup with sarcopenia despite normal MUAC exists. The SMA and LV indexes are objective parameters to asses malnutrition in PLD pts. These parameters should also be taken into consideration in the allocation for LT.

Association Between Interferon Gamma Inducible Protein 10 and Liver Inflammation in Chronic Hepatitis B

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Interferon-y-inducible protein-10 (IP-10) levels may reflect immune activity, whereas serum ALT more reflects hepatocellular damage. Recent studies have shown that wildtype (WT) HBV may be more susceptible to host immune response than non-WT (precore or core promoter mutant) HBV. Therefore, the current study aimed to investigate the association of serum levels of IP-10 and ALT with the severity of hepatic inflammation in liver biopsies of patients with CHB harboring WT or non-WT HBV. Hereto, inflammation (histology activity index; 0-18) was assessed in base liver biopsies of 276 untreated chronic hepatitis B (CHB) patients. Serum IP-10 at base was measured using a commercially available ELISA. Patients were classified as having WT or non-WT by INNO-LiPA lineprobe assay. Pearson correlation was used to assess the relationship of IP-10 and ALT with inflammation, whereas the association of IP-10 and ALT with histological inflammation was assessed using regression analysis. Of 276 patients, 167 were HBeAg-positive (72% Caucasian, 19% Asian) and 109 HBeAg-negative (95% Caucasian, 4% Asian). HBeAg-positive and negative patients had WT/non-WT in 30/70 and 5/95 percent, respectively ($p<0.001$). Median IP-10 levels were 165.5 pg/ml and 120.0 pg/ml in HBeAg-positive and negative patients, respectively ($p<0.001$). IP-10 levels significantly correlated with inflammation score in HBeAg-positive patients ($r=0.18$, $p=0.02$), particularly in patients with WT virus ($r=0.49$, $p<0.001$). Conversely, there was no association between IP-10 and liver inflammation in HBeAg-positive patients with non-WT ($r=0.10$, $p=0.31$) or HBeAg-negative patients ($r=0.06$, $p=0.54$). When adjusting for HBeAg status, HBV DNA levels and age in multivariate analysis, serum IP-10 levels ($ß=3.24$, $p=0.003$) and ALT ($ß=1.00$, $p=0.046$) were significantly associated with liver inflammation, but only in patients with WT virus.

In conclusion, serum IP-10 and ALT levels are significantly associated with the severity of hepatic inflammation, and the associations are most pronounced in patients with only WT virus. This association may reflect a better recognition of the immune system resulting in a more pronounced response directed at WT virus when compared to non-WT, which may subsequently lead to more liver inflammation.

Prediction of clinical disease progression in chronic hepatitis C virus infected patients with advanced hepatic fibrosis using objective variables

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Development of liver-related morbidity and mortality varies in chronic hepatitis C (CHC) patients with advanced fibrosis. We aimed to develop a risk score for clinical disease progression in CHC patients with advanced fibrosis and ongoing viral infection, using only objective variables. Hereto, the occurrence of events (liver failure, hepatocellular carcinoma and mortality) was assessed in our multicenter cohort of consecutive interferon-treated CHC patients with biopsy-proven advanced fibrosis (Ishak 4-6) between 1990 and 2003 from 5 tertiary care hospitals in Europe and Canada. Follow-up was completed up to 2010, if needed also by recontacting the patient or primary care physician. Patients who attained sustained virological response (SVR) on the base treatment were excluded. Initial non-SVR patients who attained SVR due to successful retreatment were censored at the time of SVR. Of the 530 treated patients 405 (76%) failed to attain SVR after the base treatment. Among non-SVR patients the median age was 48 years (IQR 42-56) and 275 (68%) were male. The Ishak fibrosis score was 4 in 105 patients (26%), 5 in 75 (19%) and 6 in 225 (56%). During follow-up (median 8.1 years, IQR 5.7-11.1) 169 patients (42%) experienced at least one event. Objective variables that significantly predicted clinical disease progression in multivariate Cox analysis, performed in 290 representative patients with available laboratory markers, were included in the following CHC disease progression risk score:
risk=5.2*age–2.8*platelets+5.17E-3*(platelets^2)+358.2*log10(AST/ALT)+83.7 for males+60.6 for hepatitis C virus genotype 3. Categorizing patients into 3 risk groups based on interquartile ranges of this risk score showed that events occurred in 1.6% in the low, 13.8% in the intermediate, and 53.1% in the high risk group after 5 years ($p<0.001$).
In conclusion, the long-term risk for clinical disease progression can be objectively and individually determined with age, gender, platelet count, AST/ALT ratio and viral genotype in CHC patients with advanced hepatic fibrosis and ongoing hepatitis C virus infection.

Presence of Anti-Interferon Antibodies is not Associated with Non-Response to Peginterferon Treatment in Chronic Hepatitis B

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The occurrence of antibodies to interferon (IFN) has been suggested to be associated with non-response to PEG-IFN treatment of chronic hepatitis C. The aim of the current study was to investigate whether presence of anti-IFN antibodies is associated with non-response to PEG-IFN in chronic hepatitis B (CHB). Presence of anti-IFN antibodies was assessed at base and at 3 and 6 months post-treatment in 323 CHB patients: 221 HBeAg-positive patients treated with PEG-IFN alfa-2b and 102 HBeAg-negative patients treated with PEG-IFN alfa-2a for one year. Anti-IFN antibodies were measured using a commercially available ELISA assay. Response was assessed at 6 months post treatment and was defined as HBeAg loss with HBV DNA <10,000 c/mL for HBeAg positive CHB and HBV DNA <10,000 c/mL with normal ALT for HBeAg negative CHB patients. Patients were predominantly male (76%), of Caucasian origin (80%) and harboured HBV genotype A in 28%, B in 6%, C in 11%, D in 52% and other genotypes in 3%. At baseline, anti-IFN antibodies were detected in 112 patients (35%). Prevalence was higher in HBeAg negative compared to HBeAg positive CHB (43% vs. 31%, respectively, p=0.030). Detection of anti-IFN antibodies at base was not associated with age, sex or HBV genotype. However, anti-IFN antibodies were more often detected in patients previously treated with IFN; 25 of 53 patients (47%) who were pre-treated with IFN versus 87 of 270 IFN-naïve patients (32%) had anti–IFN antibodies at base (p=0.037). After adjustment for HBeAg status, pre-treatment with IFN remained associated with the presence of anti-IFN antibodies at base (OR 2.0, 95%CI 1.1-3.7, p=0.025). In both HBeAg positive and -negative patients presence of anti-IFN antibodies at base was not associated with response, nor with HBV DNA or HBsAg dec at end of treatment or end of follow-up, both in the overall population (p-values>0.3), as well as in IFN-naïve patients (p-values>0.3). Fifty-six of 211 (27%) patients without anti-IFN at base developed anti-IFN antibodies after PEG-IFN treatment. Response rates did not differ between patients who developed anti-IFN antibodies and patients who did not develop anti-IFN antibodies during treatment (p>0.2).

Conclusions. Anti-IFN antibodies may frequently be detected in CHB patients, and presence is associated with previous IFN therapy. However, presence or development of anti-IFN antibodies after PEG-IFN therapy is not associated with non-response to PEG-IFN treatment in CHB.

Adding peginterferon alfa-2a to entecavir increases HBsAg dec and HBeAg clearance - first results from a global randomized trial (ARES)

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Entecavir (ETV) is a potent inhibitor of viral replication in HBeAg-positive chronic hepatitis B (CHB) patients, but serological response is infrequently achieved and indefinite therapy should therefore be anticipated in the majority of patients. Addition of peginterferon (PEG-IFN) to ETV may increase serological response rates.In this investigator-initiated randomized controlled trial 184 HBeAg-positive patients with compensated liver disease were enrolled at 15 sites in Europe and China and allocated to either ETV 0.5mg daily alone for 48 weeks or a 24 week addition of PEG-IFN alfa-2a 180 ug weekly after 24 weeks of ETV monotherapy. Response (HBeAg loss with HBV DNA <200 IU/mL) was assessed at week 48, and responders were allowed to discontinue treatment after 24 weeks consolidation treatment (week 72), with subsequent off-treatment follow-up until week 96. Results at week 48 are presented here.177 patients received at least one dose of allocated treatment, 93 ETV alone and 84 ETV with PEG-IFN add-on. Sixty-one percent of patients were of Asian ethnicity and all major HBV genotypes were present (A/B/C/D in 7/19/42/32%). A total of 160 patients had reached week 48 by June 2012, and the remaining patients will do so within 2 months. Patients were comparable with regard to important base characteristics, except for HBsAg which was higher in patients receiving combination therapy (4.28 versus 4.03 log IU/mL, p=0.05). Response, as well as HBeAg loss alone, was achieved in 18% of patients who received PEG-IFN add-on, compared to 8% of patients treated with ETV alone (p=0.07). PEG-IFN add-on resulted in more dec of HBV DNA (6.33 versus 5.91 log IU/mL, p=0.05), HBeAg (1.99 versus 1.56 log IU/mL, p=0.01) and HBsAg (0.84 versus 0.32 log IU/mL, p<0.001) at week 48. Only one patient (who received PEG-IFN add-on) had clearance of HBsAg at week 48. After adjustment for the differences in base HBsAg levels, addition of PEG-IFN was independently associated with response at week 48 (adjusted odds ratio: 3.63, 95% CI: 1.24 – 10.7, p=0.01). Add-on PEG-IFN was well-tolerated and no relevant safety concerns were raised.

Conclusion. A 24 week add-on of PEG-IFN treatment increases HBsAg dec and clearance of HBeAg and may therefore improve the chances of finite treatment in HBeAg-positive CHB patients treated with ETV.

Response-guided peginterferon therapy in HBeAg-positive chronic hepatitis B using serum hepatitis B surface antigen levels: a pooled analysis of 803 patients

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On-treatment hepatitis B surface antigen (HBsAg) levels may predict response to peginterferon (PEG-IFN) therapy in chronic hepatitis B (CHB). 803 HBeAg-positive patients treated with PEG-IFN ± lamivudine for one year in 3 global randomized studies (Peginterferon alfa-2a phase 3, Neptune and HBV 99-01) infected with HBV genotypes A through D were enrolled. A stopping-rule based on absence of a dec from base was compared to a prediction-rule that uses HBsAg levels of <1500IU/mL and >20,000IU/mL at week 12 or 24 to identify patients with high and low probabilities of response. Patients were predominantly Asian (n=580, 72%) or Caucasian (n=188, 23%) and harboured HBV genotypes A/B/C/D in 13/25/48/14%. Response (HBeAg loss with HBV DNA <2,000 IU/mL at 6 months post-treatment) was achieved in 182 (23%) and HBsAg loss in 39 (5%). Patients with an HBsAg level <1,500IU/mL at week 12 or 24 achieved response in 45 and 46%. At week 12, patients without HBsAg dec achieved a response in 14%, compared to 6% of patients with HBsAg >20,000IU/mL, but performance varied across HBV genotype. A stopping-rule based on absence of a dec at week 12 was superior for patients infected with genotypes A (NPV 88%) or D (NPV 98%), while an HBsAg level >20,000 IU/mL better identified non-responders with genotypes B (NPV 92%) or C (NPV 99%). At week 24, nearly all patients with HBsAg >20,000 IU/mL failed to achieve a response, irrespective of HBV genotype (NPV 98%). The performance of the proposed stopping-rules in patients treated with peginterferon monotherapy (n=465) was excellent (NPV >92% at week 12, >96% at week 24).Conclusions. On-treatment HBsAg level is a strong predictor of response to PEG-IFN in HBeAg-positive CHB. Discontinuation is indicated in all patients with an HBsAg level >20,000 IU/mL at treatment week 24, irrespective of HBV genotype.

Allopurinol salvage therapy in autoimmune hepatitis: a preliminary report

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Conventional corticosteroid replacement treatment with azathioprine (AZA) and 6-mercaptopurine (6-MP) therapy in autoimmune hepatitis (AIH) is unsuccessful in up to 20% of patients because of non-response or intolerance. A proportion of these patients has a 'skewed thiopurine metabolism' with low 6-thioguanine nucleotides (6-TGN) and high 6-methylmercaptopurine (6-MMP) levels. In inflammatory bowel disease, the addition of allopurinol to low dose thiopurines as salvage therapy has shown clinical improvement in refractory or intolerant patients with a skewed metabolism. We analysed prospectively collected data in a single center cohort study to assess outcome of this salvage treatment in AIH. AIH patients were included if they were either non-responsive to or intolerant for standard thiopurine therapy and had a skewed thiopurine metabolism, with high 6-MMP levels [>1 x upper limit of normal (ULN)] and low 6-TGN levels. Patients received allopurinol 100mg/day together with 25-33% of original AZA or 6-MP dose. Treatment regimes, reported side-effects and biochemical tests were recorded. A total of 8 patients were included from February 2011 until May 2012, with a median follow up of 7,8 months [interquartile range (IQR): 3,3-11,1]. There were 3 male and 5 female patients with a median age of 59 years (IQR: 43-65). 4 patients had previously been treated with AZA and 6-MP and 4 patients only with AZA. 5 patients were included because they did not respond to conventional thiopurine therapy with persistently high ALT levels (>1 x ULN). 3 patients were included because of intolerance to AZA or 6-MP, reporting persistent nausea, headache and malaise as side effects. The treatment regime was clinically effective in all patients with improvement of median base ALT levels from 62 U/L (IQR: 36-89) to 22 U/L (IQR: 20-31) at three months ($p<0.05$) and overall decreased corticosteroid usage. Median levels of 6-TGN increased from 100 (IQR: 78-162) pmol/10^8 red blood cells (RBC) at base to 167 (IQR: 127-265) pmol/10^8 RBC at one month ($p<0.05$). Simultaneously, levels of 6-MMP decreased from 6090 (IQR: 2207-8285) pmol/10^8 RBC at base to 180 (IQR: 150-240) pmol/10^8 RBC at one month ($p<0,05$). The treatment regime was well tolerated, with no reported side effects or signs of bone marrow suppression. So far none of the patients has discontinued this treatment regime. AIH patients that are non-responsive or intolerant to conventional thiopurines and have a skewed thiopurine metabolism do clinically benefit in the short term from the addition of allopurinol and low dose continuation of conventional thiopurine therapy.

Young female patients with polycystic liver disease benefit the most from somatostatin analogue therapy: an individual patient data meta-analysis

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Severe hepatomegaly due to polycystic liver disease (PLD) is a common complication in autosomal dominant polycystic liver or kidney disease (PCLD/ADPKD). Previous trials have shown that somatostatin analogues (SA) reduce polycystic liver volumes by 4.5% to 5.9%. However, it is unknown if certain patient subgroups have better treatment responses to SA. The aim of this study is to estimate the impact of age, gender, base liver volume and diagnosis (PCLD/ADPKD) on treatment response to SA in polycystic liver disease. We included all randomized controlled trials (RCTs) that compared SA with placebo in PLD patients and had change in liver volume as a primary end-point. After inclusion, we contacted the authors of the articles to collect individual patient data. Next, we performed a meta-regression analysis to estimate the impact of age, gender, base liver volume, and diagnosis on the treatment effect of SA on polycystic liver volumes. All results were corrected for study. Three short-term RCTs (6 – 12 months), including one cross-over trial, met our inclusion criteria. All authors agreed to provide individual patient data. The study population consisted of 108 patients, including 12 patients of the cross-over trial that were measured twice (SA=67, placebo=53). Women (n=86, mean 42.5 y) were on average 10 years younger than men (n=22, mean 52.3 y) at presentation and had lower polycystic liver volumes (2928 ml versus 3268 ml). SA therapy decreased polycystic liver volume with 5.3% (95% CI: 3.4 – 7.2%) when compared to placebo ($p < 0.001$) using linear modeling, and this effect was not significantly affected by diagnosis, age, base liver volume or gender. Young women (≤ 47 y) in the placebo group showed the largest growth in polycystic liver volume, with an increase of 5.3% (95% CI: 2.7 – 8.1%), whereas the polycystic liver did not notably grow in older females and male patients. Subsequently, we performed an additional subgroup analysis including subgroups for gender combined with age, using the median of 47 years as a cut-off value. Women ≤ 47 and > 47 years treated with SA experienced reductions in liver volume of 8.5% ($p < 0.001$) and 4.0% ($p = 0.017$) respectively when compared to placebo using linear modeling, with significantly better responses in the ≤ 47 years group ($p = 0.044$).

Conclusion: SA therapy is effective in PLD patients, and young female patients appear to have the most substantial benefit. The beneficial response may be the result of averting the progressive course of polycystic liver disease observed in this specific group of patients.

Peginterferon Reduces Intrahepatic HBsAg and is Associated with Histologic Response in Chronic Hepatitis B

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To date, there is limited knowledge regarding the effect of peginterferon (PEG-IFN) on the expression of intrahepatic hepatitis B virus surface antigen (HBsAg) in chronic hepatitis B (CHB), and how it correlates with serum HBsAg and histological response in the terms of necroinflammation and fibrosis scores. Fifty-two HBeAg positive CHB patients with paired liver biopsies taken at base and after 52 weeks of PEG-IFN therapy and 67 HBeAg negative CHB patients with paired liver biopsies taken at base and 24 weeks after 48 weeks of PEG-IFN therapy were studied. Necroinflammation and fibrosis were scored according to the Ishak scoring system. The degree of intrahepatic HBsAg expression was ranked on a scale of 0 to 5. Mean necroinflammatory score at base was 5.5 (± 2.2) and did not differ between HBeAg positive and -negative patients. Mean fibrosis score was 2.2 (± 1.4) and was comparable for HBeAg positive and -negative patients. Base degree of intrahepatic HBsAg did not differ between HBeAg positive and –negative patients and was not associated with necroinflammatory or fibrosis scores, nor with serum HBsAg. After PEG-IFN the degree of intrahepatic HBsAg significantly reduced in HBeAg negative patients ($p<0.001$), and a trend was seen in HBeAg positive patients ($p=0.088$). Patients with a dec in intrahepatic HBsAg had significantly more serum HBsAg dec at the end of follow-up (0.9 vs. 0.4IU/mL, $p=0.031$). A reduction in necro-inflammation (decrease ≥ 2 points) after PEG-IFN treatment was observed in 47% of HBeAg positive patients ($P=0.002$ compared with baseline) and in 52% of HBeAg negative patients ($p<0.001$ compared with baseline). Dec in intrahepatic HBsAg and a decrease in necroinflammation appeared to be associated (Spearman's ρ0.159, $p=0.096$). Improvement of fibrosis (decrease ≥ 1 point) after PEG-IFN therapy was found in 21% of HBeAg positive and 30% of HBeAg negative patients. However, a significant change in fibrosis score was only observed in HBeAg positive patients ($p=0.050$). There tended to be a correlation between a dec in intrahepatic HBsAg and fibrosis (Spearman's ρ0.174, $p=0.070$).

Conclusion. PEG-IFN reduces expression of intrahepatic HBsAg as well as necroinflammation in both HBeAg positive and -negative CHB. Dec in fibrosis was only found in HBeAg positive patients. Dec of HBsAg expression in hepatocytes after PEG-IFN was associated with a dec in serum HBsAg and showed a trend toward significance with dec in necroinflammation and fibrosis scores.

New Insights Into Toxicity and Pharmacokinetics of Ribavirin and Cyclosporine in Liver Transplant Recipients on Boceprevir-Based Antiviral Therapy – Evidence of Need for New Target Troughs for CsA and lower Dosing of Ribavirin

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Background & Aims: The use of direct-acting antiviral agents (DAA's) in liver transplant (LT) recipients with recurrence of HCV is challenging due to drug-drug interactions (DDI) with calcineurin inhibitors and subsequent risk of nephrotoxicity and hemotoxicities. In addition, the effect of DAA-based antiviral therapy (AVT) on serum ribavirin (RBV) levels in the LT setting has not been reported. We studied toxicities and pharmacokinetic profiles of boceprevir (BOC) based AVT in LT recipients. Methods: LT recipients with recurrence of HCV were treated with BOC-based AVT according to standard protocol. All patients were placed on cyclosporine A (CsA) prior to initiation of BOC. CsA dose was reduced on initiation of BOC. RBV was initially dosed at 200-1200mg/day according to a GFR-based nomogram. Drug levels, including whole blood CsA and ribavirin troughs (measured by HPLC), were measured according to protocol. Results: Fifteen patients were studied, mean age 60 yrs (range: 47-74). Maintaining CsA levels within the target trough range (75-125ng/mL) required sequential dose reductions on AVT of up to 50% on average. Week 4 RBV levels were, for all but one patient, below optimal therapeutic ranges (≥3500ng/ml). Despite this, hemoglobin decreased in a stepwise fashion, with all patients developing more severe anemia after initiation of BOC. Anemia was managed with erythropoietin (N=10), blood transfusions (N=13) and continued dose reduction of RBV. GFR decreased markedly during AVT and led to values consistent with at least stage 3 chronic renal failure in ten patients. Four patients had to discontinue AVT after initiation of BOC due to severe side effects.

Conclusion: The apparent clearance of CsA is dynamic through at least the first 16 weeks of post-LT BOC-based AVT, requiring sequential dose reductions. CsA levels cannot be predicted based on published data regarding DDI between CsA and BOC. Post-LT BOC-based AVT is associated with frequent and progressive anemia and renal impairment despite stable CsA levels and suboptimal RBV levels. Nephrotoxicity may be due to increased free CsA levels in the setting of hemolysis (CsA is sequestered in RBC). These results suggest that lowered target CsA troughs and RBV doses are needed during post-LT BOC-based AVT.

Hepatitis E virus among chronic hepatitis C-infected patients: risk factors and clinical outcome

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Background and Aims Acute hepatitis E virus (HEV) infection is emerging in industrialized countries and can cause severe hepatitis in immunocompromised patients. Data on prevalence are scarce and the exact routes of transmission in both immunocompetent and immunocompromised patients need to be determined. Furthermore, it is unclear if HEV-co-infection, like hepatitis A virus infection, could lead to worsening of liver disease in chronic hepatitis C virus (HCV) infected patients. We studied prevalence of and risk factors for HEV infection among chronic HCV-infected patients. Methods. For our analysis of risk factors, we used a well defined cohort of chronic HCV-infected patients who were treated with peginterferon/ribavirin between 2000 and 2009. Patients of whom a pretreatment serum sample was available were included. Anti-IgM-HEV and anti-IgG-HEV serum antibody detection was performed using an enzyme-linked immunosorbent assay (Wantai, Singapore).Results. 321 chronic HCV-infected patients were treated in the study period and 261 patients could be included. Mean age was 45 years (14-70) and patients were predominantly male (67%), of European origin (72%) and 59 patients (23%) had cirrhosis. Anti-IgG-HEV was positive in 54 patients (21%) and anti-IgM-HEV was positive in 1 patient (2%). Following multivariate regression analysis, older age (OR 1.0, p=0.02), Egyptian origin (OR: 6.3, p=0.02) and the absence of injecting drug use (IDU) (OR 3.0, p=0.02) were associated with positive IgG-HEV serology. Within European patients, multivariate regression analysis identified age (OR 1.1, p=0.01) but not non-IDU (p=0.06) as risk factor of positive HEV serology. Sixteen (27%) patients with and 38 patients without cirrhosis showed positive IgG-HEV serology (p=0.1). Even with correction for age, positive IgG-HEV serology was not associated with the presence of cirrhosis (p=0.6).

Conclusions. Among HCV-infected patients, HEV prevalence is high (21%) and associated with older age, Egyptian origin and the absence of a history of IDU. Patients affected do not show chronic HEV co-infection or more severe liver disease. These risk factors for positive HEV IgG-serology suggest dietary practices as route for transmission for HEV and contradict the previously reported risk of IDU for HEV infection.

Genotypic resistance to entecavir in lamivudine naive patients after achieving a virological response for chronic hepatitis B

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The risk of entecavir (ETV) resistance is low in lamivudine (LAM) naïve patients, especially after achieving an undetectable HBV DNA by sensitive PCR. EASL guidelines thus suggest decreasing frequency of expensive HBV DNA monitoring after confirming efficacy. Patients were 3-6 monthly monitored for HBV DNA and ALT. Resistance testing was performed when virological breakthrough (VB) occurred (>1 log increase in HBV DNA from the nadir). Resistance analysis was performed both by LiPA and conventional polymerase sequencing. This study describes 4 out of 108 LAM-naïve HBV patients treated with ETV who developed resistance within our centre. All 4 had wildtype at base and an HBV DNA >6.5 log IU/mL. Three were HBeAg+ and genotype A, of whom 1 was pretreated with adefovir (no resistance) and treated with 1 mg. The other was HBeAg-, with genotype D. Base analysis showed that HBV DNA was significantly higher than 104 patients who did not develop ETV resistance (7.6 vs. 6.0; p=0.001); other parameters were comparable. HBV DNA kinetics show that all 4 patients achieve a fast dec of >3 log IU/mL within the first 2-4 months. Thereafter viral dec flattens and a plateau phase with only moderate dec in HBV DNA is entered resulting in an HBV DNA after 12 months of ETV therapy ranging from 4.1-5.4 log IU/mL. HBV DNA slowly further declined within the second year resulting in a load below 3 log IU/mL for all patients. Three patients achieved a virological response (<20 IU/mL) in their third year of therapy and one achieved an HBV DNA of 45 IU/mL. Despite achieving such a low HBV DNA, all patients experienced a VB within the fourth year of therapy. At VB, all 4 patients had genotypic resistance to ETV detected both by lineprobe assay and conventional polymerase sequencing. In three patients the combination of L180M, M204V and S202G was seen and in patient 1 the combination of L180M, M204V and T184A was seen. VB was accompanied by ALT flare (>5xULN) in one patient who also experienced an increase in serum HBsAg of >1 log IU/mL. All 4 patients were switched to the combination of TDF and ETV with satisfactory results.

Conclusions: High base HBV DNA and late achievement of undetectable HBV DNA appeared related to developing ETV resistance. Infrequent monitoring of HBV DNA after achieving virological response should be re-evaluated in those achieving an undetectable HBV DNA after the first 2 years of ETV therapy.

Treatment Success of Aspiration and Sclerotherapy for Hepatic Cysts depends on Cyst Diameter and Volume of Sclerosing Agent

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Liver cysts can cause mechanical complaints through compression of adjacent organs. Aspiration and sclerotherapy (AS) reduces cyst diameter and subsequent symptoms. The aim of this study is to determine efficacy of AS in three centers and to define components that determine treatment success. We identified all patients with a dominant liver cyst that have been treated between January 2000 and January 2012 in three Dutch tertiary referral centers. All cysts were punctured US or CT guided, aspirated, and sclerosed. Treatment protocols differed with respect to type of sclerosing agent used and duration of drain presence. Cyst diameter was measured by US, CT or MRI <6 months prior and after treatment. Patient records were scrutinized for symptoms and complications. All continuous data were displayed as mean±SD. Differences between the groups were tested with ANOVA. We performed multivariable linear regression to identify predictors of treatment success. We identified 346 AS in 216 patients, 72 AS were excluded because of lack of follow-up imaging within 6 months, 39 AS were excluded because no sclerosing agent was used, 35 AS were excluded for several other reasons and in 63 AS there was more than one reason. An additional 31 AS were excluded because AS was not the first treatment episode. Eventually 106 AS in 106 patients were included. Mean age at AS was 57.1±11.5 years , 95% was female, 76% had multiple cysts and mean cyst diameter before AS was 12.9±4.2 cm. These characteristics did not differ between centers except for cyst diameter before AS (p=0.016). Mean cyst diameter diminished from 12.9±4.2 cm to 7.9±4.8 cm (mean decrease 39.5%±29.2%). Some 72.9% of patients reported dec in symptoms. Complications such as cyst bleeding or infection occurred in 10.6%. Multivariable analysis showed that cyst diameter before AS, volume of sclerosing agent, time between treatment and follow-up imaging, and dec of symptoms, predict cyst diameter after AS. AS reduces cyst diameter by ~40% and the success of treatment is better in larger cysts and with larger volumes of sclerosing agents.

Number of patients needed to treat to prevent death in genotype 1 chronic hepatitis C cirrhosis: the impact of improved interferon-based therapy

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Improved efficacy of interferon-based therapy is usually evaluated by sustained virological response (SVR) rates. We aimed to assess the improvement of therapy in cirrhotic chronic hepatitis C (CHC) genotype 1 (G1) patients with a number needed to treat (NNT) analysis for mortality. Hereto, survival was assessed in our multicenter cohort of consecutive interferon-treated CHC patients with biopsy-proven advanced fibrosis between 1990 and 2003 from 5 tertiary care hospitals in Europe and Canada. Follow-up was completed up to 2010, is needed also by recontacting the patient or primary care physician. The NNT to prevent one death was calculated with the survival probability in non-SVR patients, hazard ratio of SVR for all-cause mortality and SVR rate:
$NNT=\{1/\{[Survival_{non\text{-}SVR}(t)^{HR\ SVR}] - Survival_{non\text{-}SVR}(t)\}\} * \{100/SVR\ rate\}$. Overall 248 CHC G1 patients with cirrhosis were followed for a median of 8.3 years (IQR 6.2-11.1). At base the mean age was 50.6 years (SD 9.2), 168 (68%) patients were male and 219 (88%) treatment naive. The Ishak fibrosis score was 5 in 67 (27%) patients and 6 in 181 (73%). In total 59 (24%) patients attained SVR. The survival probability in non-SVR patients was 90.5% (95%CI 86.4-94.6) after 5 years and 69.2% (95%CI 61.6-76.6) after 10 years. Time-dependent univariate Cox analysis showed SVR was associated with reduced all-cause mortality (HR 0.20; 95%CI 0.06-0.64, p=0.007). The NNT to prevent one death within 5 or 10 years in cirrhotic CHC G1 patients declined with increasing SVR rates, assuming SVR rates ranging from 2% (NNT-5y=666, NNT-10y=212) to 40% (NNT-5y=33, NNT-10y=11) as previously reported with (peg)interferon with or without ribavirin.

In conclusion, the NNT to prevent one death among CHC G1 patients with cirrhosis has declined enormously with increasing SVR rates due to the development from interferon mono to peginterferon and ribavirin combination therapy. From a public health perspective, this finding emphasizes the clinical importance of the continuing improvement of treatment for CHC G1 patients with cirrhosis.

High relapse rates in HBeAg negative chronic hepatitis B patients after discontinuation of nucleos(t)ide analogues

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Currently, there are only few reports on the effect of stopping long-term nucleos(t)ide analogue (NA) therapy. The aims of this study were 1) to study virologic relapse (detectable HBV DNA) and restart of anti-HBV therapy after discontinuation of NA therapy in HBeAg-negative CHB and 2) to investigate serum HBsAg levels in relation to disease activity during follow-up. In this investigator-initiated project (the GPs-CHB Study Group) all consecutive HBeAg-negative CHB patients from 2000-2010, who stopped NA therapy after achievement of an undetectable HBV DNA during at least 1 year of NA therapy were studied. Data of 28 patients from 4 sites were collected. Patients were predominantly male (65%) and harbored all HBV genotypes (A:3, B:4, C:7, D:6, missing:8). Patients had been treated with LAM:16, ADV:1, ETV:5 or TDF:6. Thirteen patients stopped NA therapy in relation to protocol of previous studies, 8 were non-compliant, 6 had a continued undetectable HBV DNA and 1 patient had HBsAg loss. At base (time of discontinuation of NA therapy) mean serum ALT was 0.65 ULN, median HBsAg was 2100IU/mL (range 0-8430) and patients had been HBV DNA undetectable for a median of 15 months (range 3-84). After discontinuation of NA therapy 22 patients (79%) had a relapse (detectable HBV DNA) within 14 months. Three patients (12%) also had a flare (ALT>5xULN), of which 2 patients showed an ALT>10xULN. There were no significant differences in serum HBsAg levels at base in patients with or without a relapse (p=0.13). Patients with a relapse did not show a significant change in serum HBsAg during post-treatment follow-up (p=0.13). Of the 22 patients with a relapse, 15 patients (68%) restarted therapy, within a median of 6 months (range 2-46). HBsAg levels at restart were comparable with levels at time of discontinuation of NA therapy (p=0.47). In the 7 patients who were not retreated after relapse a significant increase in serum HBV DNA was observed in 5 cases, but ALT remained normal and serum HBsAg remained around 2000IU/mL. The other two patients showed a spontaneous HBV DNA dec and one also had a dec in HBsAg after an ALT flare. Six patients (21%) did not relapse during follow-up (median follow-up 35 months); HBsAg-levels remained <0.05IU/mL in three patients, <2000IU/mL in two and >20.000IU/mL in one.

Conclusions. Discontinuation of NA therapy, after continued suppression of HBV DNA, results in relapse and necessity of retreatment in the vast majority of HBeAg negative CHB patients. These findings suggest that NA therapy should not be discontinued in HBeAg negative disease, also not in those with long-term HBV DNA suppression.

Larger polycystic livers are associated with signs of portal hypertension and displacement of abdominal organs

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Background: Polycystic liver disease (PLD) is a disabling condition characterized by the presence of at least 20 cysts in the liver. Although cysts causing hepatomegaly dominate the phenotype, little is known on other manifestations of the disease. Aim of this observational study is to delineate the extracystic phenotype of the polycystic liver. Materials and Methods: All PLD patients from our database with at least one CT scan were considered for inclusion in the study. Patients were excluded if their CT scans were not digitally available or if they did not image the complete liver. We included one CT scan per individual patient. We defined splenomegaly as spleen diameter > 120 mm, displacement of the stomach as a deviation of at least one vertebra and diaphragm elevation as a difference of at least 20 mm between the left and right hemidiaphragm. All continuous data were displayed as median (range). Differences in liver volume between the groups were tested with the Mann Whitney U test. Results: We included 76 PLD patients for the purpose of this analysis. Mean age of the patients was 54.7±10.8 years and 87% was female. Median total liver volume was 3820mL (1084-16746mL). Median liver volume was higher in patients with splenomegaly (5567mL vs. 3569mL, $p<0.01$) and ascites (7604mL vs. 3665mL, $p<0.01$). Patients with calcifications also had higher liver volumes (4870mL vs. 3307mL, $p<0.01$). Increased liver volume resulted in displacement of the stomach (4031mL vs. 2106mL, $p<0.01$), compression of the inferior caval vein (5194mL vs. 3658mL, $p<0.05$) and diaphragm elevation (4482mL vs. 3346mL, $p<0.05$).

Conclusion: This study showed that polycystic liver disease have extracystic manifestations. We found that higher liver volume are associated with a higher proportion of splenomegaly, ascites, calcifications, displacement of the stomach, compression of the inferior caval vein and diaphragm elevation.

Evaluation of 6-thioguanine therapy in Autoimmune Hepatitis

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Azathioprine (AZA) and 6-mercaptopurine (6-MP) therapy are widely used in autoimmune hepatitis (AIH) to prevent long-term steroid related complications. However, up to 20% of patients do not respond to or tolerate this regimen. Replacement therapy of AZA or 6-MP with 6-thioguanine (6-TG) has previously shown improvement of both clinical results and 6-thioguanine nucleotides (6-TGN) levels in inflammatory bowel disease (IBD) patients. Here we report the results of our experience of 6-TG treatment in 9 AIH patients. The treatment courses of all AIH patients were retrospectively analysed. Recorded parameters included treatment regimes, side-effects, biochemical follow up and 6-TGN levels as well as initial and follow up liver biopsies. From 2003 to 2012, 9 AIH patients (6 females; 3 males) were switched to low dose (0.3 mg/kg/day) 6-TG treatment after previous treatment with conventional thiopurines (4 on AZA and 5 on 6-MP). 6 patients had been nonresponsive to AZA or 6-MP, which was marked by persistently raised alanine-aminotransferase (ALT) levels (> 1 x upper limit of normal), continued steroid dependency and low 6-TGN levels. Three other patients had experienced severe AZA and 6-MP related side-effects of nausea, alopecia and generalised abdominal pain. The median follow up was 17 months [Interquartile range (IQR): 5,5-38,7]. 6-TG treatment was initially tolerated well, leading to clinical improvement and steroid use reduction in all patients. This was illustrated by a reduction in median ALT from 65 U/L (IQR 53-141) at base to 29 U/L (IQR: 10-48) at 12 months (p=0.08). In 4 patients follow up liver biopsy was performed after more than 12 months, showing overall reduction of inflammation activity. Median 6-TGN levels increased from 108 pmol/10^8 red blood cells (IQR: 65-200) at base to 452 pmol/10^8 red blood cells (IQR: 199-652) at 3 months (p=0.07). In 2 patients 6-TG treatment was discontinued after 2 and 17 months, due to non-response and relapse respectively. In 1 patient 6-TG was eventually discontinued after 11 months at patient's request because of general weariness that he related to 6-TG therapy. During follow up there were no signs of bone marrow depression nor of nodular regenerative hyperplasia in the performed liver biopsies (4 patients).

In conclusion we observed in this case series that 6-TG treatment is effective, safe and well tolerated in AIH patients previously non-responsive or intolerant to conventional thiopurines.

Longterm follow-up of inactive hepatitis B virus carriers and relation with Hepatitis B surface Antigen levels

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Patients are considered inactive HBV carriers if HBV DNA is <2000IU/mL combined with a normal ALT. Recently a single-point HBsAg<1000IU/mL has been suggested as an additional marker too accurately identify inactive carriers after 1 year of follow-up. The aim was to validate this rule for long-term follow-up of inactive carriers. This investigator-initiated project studied the follow-up of untreated HBeAg negative HBV patients initially presenting with normal ALT-levels from 8 large centers (GPs-CHB Study Group). At base and during follow-up patients were defined as inactive carriers (IC) (HBV DNA ≤2000IU/mL and normal ALT) or active carries (AC) (HBV DNA>2000IU/mL or abnormal ALT). Survival analyses were used to analyze the transition probability from IC to AC over time. Repeated measurements of ALT, HBV DNA and quantitative HBsAg were available for 271 consecutive patients during a mean follow-up of 4.3 year. At base 170 patients (63%) were identified as IC and these patients were further studied. Total number of visits among IC was 1306. At base HBsAg was 675 IU/mL (range 0-49140) and HBV genotypes were: A 7%, B 17%, C 15%, D 44% and other 17%. Two patients had cirrhosis. At 1 year 87% remained IC, at 2 years 75% and at 5 years 63%. HBsAg<1000IU/mL at base was a strong predictor for continued IC (at 1yr 89% vs 83%, 5yr 73% vs 49% in the group with <1000 vs ≥1000IU/mL, p=0.001), as well as HBV DNA<200IU/mL (p<0.001). There were no differences in reactivation rates between HBV genotypes (p=0.72). HBsAg and HBV DNA were independent predictors of transition to AC (HR=1.4 by 1log increase and HR=2.5 by 1log increase). The combination of HBV DNA<100IU/mL and HBsAg<100IU/mL at base (n=17) gave a 100% accurate identification of IC. Overall dec of HBsAg was 0.37log in 5 years (p<0.001). Dec was not dependent on HBV DNA at base (p=0.83). In seven patients progression of liver disease was observed (2 HCC (1 with cirrhosis at baseline), 4 decompensation (1 with cirrhosis at baseline) and 1 non-liver related death). Five of those became AC prior to disease progression. The patient with non-liver related death remained IC until end of follow-up (7 years).

Conclusions. IC with a high HBsAg at base are at high risk for transition to AC and further progression of liver disease. Our date suggest to revise the definition of IC in CHB patients and to include HBsAg as a marker to accurately identify IC.

An accurate formula for a quick estimate of liver volume in polycystic liver

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Background. Patients with polycystic liver disease (PLD) have multiple liver cysts causing severe hepatomegaly. Primary aim of treatment in PLD is reduction of liver volume. The gold standard to assess total liver volume is CT liver volumetry which involves manual delineating of the liver outline. This is a time consuming method (~60 min per CT) and requires a certain level of expertise. There is a clear need for an easily accessible and fast approach to estimate polycystic liver volumes in the outpatient clinic. Materials and Methods. All PLD patients that visited our outpatient clinic from 2000-2012 and had at least one CT scan were considered for inclusion in the study. Patients were excluded if their CT scans were not available digitally or if the liver was not completely imaged. We measured the liver in transverse (T), anterioposterior (AP) and craniocaudal (CC) directions. Furthermore, we performed CT liver volumetry to assess total liver volumes. We had access to two cohorts, an inception cohort and a replication cohort. We performed multiple linear regression to predict liver volume using the three dimensions of the liver in the inception cohort. As liver volumes were very skewed, we used the logarithms of the volumes to carry out the analysis. The goodness of fit of the prediction model based on our inception cohort was assessed and stated as R^2. Finally, we validated this prediction model in our replication cohort. Results. The inception cohort included 54 PLD patients with a median base volume of 3890 mL (range 1084-13611 mL). All three diameters were significantly correlated with total liver volume ($p < 0.001$). The linear regression model resulted in the following formula: Predicted liver volume = 4,179+(0,009*T)+(0,007*AP)+(0,001*CC). Our model predicted total liver volumes very accurately in the inception cohort (R^2=0.907). We validated our prediction model in a replication cohort of 22 PLD patients (median base liver volume 3603 mL, range 1261-16746 mL). Liver volumes predicted by our model were highly correlated with liver volumes measured by CT volumetry(R^2=0.95), indicating that this model is also applicable in other patients with PLD.

Conclusion. Polycystic liver volume can easily, accurately and quickly (<1 min) be estimated by measuring the three dimensions of the liver on CT scan instead of CT volumetry.

Natural killer cell activity and function in chronic HCV-infected patients during peginterferon and ribavirin: no effect of active substance use

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Background and Aims. In Western countries, chronic hepatitis C virus (HCV)-infection mostly affects former and active substance users. The effect of active substance use on IFN-responsiveness and therapy efficacy is not well understood. We studied natural killer (NK) cell activity and function in healthy controls and chronic HCV-infected patients with and without active substance use and the effect of peg-IFN and ribavirin.Methods. Healthy controls and patients with chronic HCV-infection with and without active substance use who started on antiviral therapy consisting of peg-IFN/ribavirin were included. On day 0, NK cell activation and effector functions were assessed through measurement of CD69 levels, IFN-induced pSTAT1, IL-12/IL-18-induced IFN-gamma production, CD107-degranulation and granzyme/perforin levels expressed by NK cells. At day 7 of antiviral therapy of HCV-infected patients, the same assessments were repeated. Results. Eighteen healthy controls, 12 (42% genotype-1) HCV-infected patients with substance use and 12 (33% genotype-1) HCV-infected patients without substance use were included. Of 12 substance use patients, 6 used only heroin, 3 used heroin and cocaine, and 3 only cocaine. At baseline, the activation of NK cells (CD69 expression) was significantly lower in HCV-infected patients when compared to healthy individuals, whereas IL-12/18-induced IFN-gamma production by NK cells was comparable between all groups. The cytotoxic ability of NK cells was more potent in HCV-infected patients as compared to healthy controls, and highest in non-substance users, as demonstrated by higher granzyme levels and CD107 degranulation. Irrespective of substance use, the IFN responsiveness of NK cells (pSTAT1 induction) was lower in HCV-infected patients as compared to healthy controls, but not statistically different. Therapy-induced viral load reduction assessed early at day 7 showed similar dec in substance users and non-substance use HCV patients, with 25% substance users and 17% non-substance users testing HCV-RNA negative at day 7. During IFN-based therapy, NK cells from substance users and non-substance users showed a comparable dec of IFN-induced STAT1 phosphorylation and similar reduction of NK cells activation as demonstrated by their CD69 expression.

Conclusion. Active substance use in chronic HCV-infected patients did not affect the immune responsiveness to IFN, and thus, there is no evidence -from an immunological point of view- that antiviral therapy of HCV-infected patients with active substance use is less efficient.

Von Willebrand factor levels are independently associated with liver stiffness: results of a population-based study

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A relationship between activation of coagulation and liver fibrogenesis, possibly through the formation of intrahepatic microthrombi, has been demonstrated. Increased plasma levels of von Willebrand factor (VWF) are known to be associated with an enhanced risk of thrombosis, but the relationship with liver fibrosis is unknown. We investigated the association between VWF levels and liver stiffness measurements (LSM) in a population-based cohort and in a subgroup of participants with non alcoholic fatty liver disease (NAFLD). This cross-sectional study was part of a large population-based cohort study of elderly. Liver fibrosis was assessed by means of transient elastography. LSM were considered reliable if a success rate >60% and an interquartile range (IQR) of lower than 30% of the median stiffness value were obtained. Diagnosis of NAFLD was determined by abdominal ultrasound, according to standardized criteria, in all participants. VWF antigen levels were determined in plasma with an enzyme-linked immunosorbent assay. ABO blood group type, which is associated with VWF levels and the risk for venous thromboembolism, was acquired by DNA analysis. Genotyping was done with the Infinium HumanHap 550 K chip (Illumina). HapMap phase II, release 22 CEU, build 36 was used as reference population for imputation. Reliable LSM and VWF levels were obtained in 1228 participants. Mean age of participants was 74.0 years (SD 5.6); 49.9% were women. Median LSM was 5.1 kPa (IQR 4.1-6.3). NAFLD was detected in 395 participants (32.2%). Median VWF level was 1.11 IU/ml (IQR 0.87-1.43). VWF was significantly associated with LSM (Pearson's r=0.11; p<0.001). In a multivariate model, after adjustment for age, sex, BMI, ALT, HOMA-IR, NAFLD, spleen size and ABO blood group type, this effect remained statistically significant (p=0.016). Subgroup analysis in participants with NAFLD showed a similar association between VWF and LSM (Pearson's r=0.15; p=0.003), which also remained significant in a multivariate regression model (p=0.015).

Conclusions: In this population-based study VWF levels were independently associated with LSM, regardless of ABO blood group type. In a large subgroup of participants with NAFLD a similar association was observed. These results may provide additional support for the role of hypercoagulability in the development of liver fibrosis.

The clinical relevance of secondary histological diagnoses in chronic hepatitis B and C: prevalence and impact on disease severity.

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Background: The use of percutaneous liver biopsy (PLB) in viral hepatitis has decreased due to non-invasive diagnostics. Our aim was to determine whether a clinically relevant secondary diagnosis would be missed when PLB is excluded from the management of chronic hepatitis B (CHB) or chronic hepatitis C (CHC), and whether a secondary diagnosis affects Metavir score. Methods: We conducted a retrospective cohort study by reviewing medical records of CHB and CHC patients that underwent a PLB in two Dutch University Medical Centers between January 2005 and March 2012. Patients with co-infection (HBV/HCV, HDV, HIV), liver transplantation or liver cancer, were excluded. The chi-squared and trend tests were used. Results: We reviewed 765 PLB in 716 patients. Higher Metavir scores were found in CHC patients compared to CHB patients ($p<0.001$). A secondary diagnosis was found in 167 PLB (21.8%): nonalcoholic fatty liver disease/alcoholic liver disease (NAFLD/ALD: 95.8%; n=160), biliary hamartomas (1.8%; n=3), liver granulomas (1.2%; n=2), autoimmune hepatitis (0.6%; n=1) and primary biliary cirrhosis (0.6%; n=1). The prevalence of secondary diagnosis did not differ between CHB and CHC ($p=0.243$). A secondary diagnosis in CHB patients did not affect Metavir scores ($p=0.42$), while higher Metavir scores were found in CHC patients with a secondary diagnosis ($p=0.04$). Conclusion: The most prevalent secondary diagnosis in CHB and CHC patients is NAFLD/ALD, which can be assessed non-invasively. With a regular work-up including abdominal ultrasound and laboratory tests, no clinically relevant secondary diagnoses will be missed by excluding PLB from the management of CHB and CHC. In CHC patients, a secondary diagnosis is associated with a higher Metavir score suggesting that a secondary diagnosis (mostly NAFLD/ALD) in CHC patients contributes to liver fibrosis.

ALT flares during entecavir treatment are associated with a favorable outcome in chronic hepatitis B

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Elevations of ALT or flares during nucleos(t)ide analogue therapy are usually associated with antiviral resistance or cessation of therapy. Since entecavir (ETV) resistance is rare and therapy is rarely stopped, we aimed to investigate the frequency and outcome of on-treatment flares during ETV therapy in chronic HBV patients. Within this investigator-initiated project we studied all HBV monoinfected patients treated with ETV monotherapy from 10 large European referral centers (VIRGIL Study Group). A flare was defined as an ALT >3x level at start of ETV therapy (Flink et al, Gut 2005). ALT was measured locally using automated techniques, HBV DNA undetectability was defined as HBV DNA <80 IU/mL. A total of 366 patients were treated for a median of 19 (range 3-51) months with ETV monotherapy. Eleven (3%) patients developed a flare after a median of 6 (1-25) months, resulting in an incidence of 0.017 flares per ETV treatment year. The flares were relatively mild with a mean ALT peak of 7.3±4.0 xULN. Patients with a flare were more often HBeAg+ (73%, p=0.03). Other base characteristics (including ALT) were comparable between patients developing a flare and those not. Five (45%) patients had an ALT flare associated with a favorable event: 4 had an ALT flare accompanied by a vigorous early (week 4) HBV DNA dec and 1 patient achieved HBeAg seroconversion (flare at month 6). Three (27%) patients had a flare (month 3, 7 and 23) associated with an increase in viral load caused by non-compliance and one possibly associated with development of HCC (month 25). In 2 (18%) patients no clear association of the flare could be established. Importantly, both biochemical and virological outcome after the flares was good: 9 patients achieved ALT normalization (82%) and 10 achieved HBV DNA undetectability (91%) without treatment adaptation.

Conclusions: Flares during ETV are rare and relatively mild. The majority of flares are associated with either a vigorous dec or an increase in HBV DNA caused by non-compliance, underlining the importance of these measurements to interpret flares. After reassuring compliance and excluding other causes, ETV therapy can confidently be continued as the majority of flares have a good biochemical- and virological outcome and resolve without treatment adaptation.

Viral hepatitis B and C: Non-invasive selection of patients with and without advanced liver fibrosis using of MR Elastography and Fibroscan

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Fibroscan (FS) and MR elastography (MRE) both quantify liver fibrosis. Hepatologists who use FS predominantly perform liver biopsies in those patients in whom the obtained liver elasticity value is inconclusive. The aim of this study therefore was: At what elasticity values can FS or MRE replace liver biopsy in the pre-therapeutic assessment of liver fibrosis? And when should liver biopsy still be considered? 103 patients were consecutively included and underwent liver biopsy, MRE and FS within 6 weeks. Liver biopsies were scored by two pathologists from Metavir F0 (no fibrosis) to F4 (cirrhosis). Biopsies required ≥7 portal tracts. We defined for each technique the following two cut-offs for distinguishing F0-F1 from F2-F4: (1) the lower cut-off at which the negative predictive value (NPV) ≈ 90% (below this cut-off, 90% of patients have ≤F1). (2) the higher cut-off at which the positive predictive value (PPV) ≈ 90% (above this cut-off, 90% of patients have ≥F2). Cut-off values were determined with receiver operating characteristics (ROC) analysis. Elasticity values of FS equal approximately three times the elasticity values of MRE. Data of 86/103 patients (66 HBV, 20 HCV) were analysed. 17 patients were excluded due to incompleteness or poor biopsy quality. Mean age was 45.5±24.3 years. 56/86 were male (65%). 56 patients had F0-F1, 30 had F2-F4. Median biopsy length was 20.2 mm (range 6-60 mm). Median number of portal tracts was 14 (range 7-25). The following cut-offs were defined for F0-F1 vs F2-F4: (1)FS (cut-off 6.5 kPa): NPV 90% (82-98), PPV of 71% (57-86), sensitivity 83% (70-97) and specificity 82% (72-92). MRE (cut-off 2.2 kPa): NPV 90% (82-98), PPV 74% (59-88), sensitivity 83% (70-97) and specificity 84% (74-94). (2) FS (cut-off 8.9 kPa): PPV 88% (73-100), NPV 78% (69-88), sensitivity 50% (32-68), specificity 96% (92-100). MRE (cut-off of 2.7 kPa): PPV 89% (74-100), NPV 79% (70-89), sensitivity 53% (36-71) and specificity 96% (92-100).

Conclusion: The accuracy of MRE and Fibroscan to select patients with HBV or HCV with advanced fibrosis (≥F2) and those without advanced fibrosis (≤F1) is equal in our cohort. Using the lower cut-off, no patients with fibrosis (≥F2) would be missed for treatment if one only relies on FS or MRE. Between the lower and higher cut-off, non-invasive results are inconclusive when compared with liver biopsy.

Improved patient survival and its determinants in two decades of liver transplantion; a single center experience

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The current study analyzes long-term outcomes of nearly two decades of liver transplantation (LT). A retrospective analysis was performed on 348 LTs performed between September 1992 and March 2011 at our institution. For the current study the cohort was divided into two eras where from September 1992 until December 2001 was considered the first decade and January 2002 until March 2011 was considered the second decade. Follow-up for both groups was until December 2011. A total of 335 orthotopic LTs (OLTs) en 13 auxiliairy LTs (AXLTs) were performed in the studied time-period. (First decade: 119 LTs, Second decade: 229 LTs) Twenty-one patients were transplanted due to acute liver failure for which 10 AXLTs and 11 OLTs were performed. Alcoholic liver disease (ALD) was the main indication for OLT in the first decade (18%) whereas hepatocellular carcinoma (HCC) was the main reason for OLT in the second decade (25.3%). Hepatic artery thrombosis (HAT) and non-anastomotic strictures (NAS) were the main indications for reLT in both decades. LT with donation after brain death (DBD) had lower cold ischemic times (CIT) and lower recipient warm ischemic times (RWIT) in the second decade compared to the first decade (CIT 709 minutes vs. 591 minutes; $p<0.01$ and RWIT 42 min vs. 35 min; $p<0.01$, respectively) and LT with donors after cardiac death (DCD) had lower CIT compared to LT with DBD donation in the second decade (487 minutes vs. 591 minutes, respectively; $p<0.01$). 10-year patient and graft survival had significantly improved in the second decade versus the first decade (patient survival 82.2% vs 50.4%.; log rank $p<0.01$, graft survival 69.8% vs 32.8%.; log rank $p<0.01$). Death due to sepsis within 5 years after OLT had decreased significantly in the second as compared to the first decade (5.5% vs. 18.3%; $p<0.01$). With multivariate analysis acute liver failure, development of non-anastomotic strictures (NAS), CIT >684 minutes, RWIT, decade of transplantation, but not DCD, had a significant impact on patient survival.

Conclusions: HCC is the main reason for transplantation in the second decade. Long-term survival was significantly better in the second decade with less death due to sepsis and shorter CITs and RWITs compared to the first decade. LT with DCD donors is safe and did not impact recipient survival. HAT and NAS remain important causes for retransplantation.