Programma voorjaarsvergadering 19 en 20 maart 2009

Nederlandse Vereniging voor Gastroenterologie

Sectie Gastrointestinale Endoscopie
Netherlands Society for Parenteral and Enteral Nutrition
Sectie Neurogastroenterologie en Motiliteit
Sectie Experimentele Gastroenterologie
Sectie Kinder-MDL
Sectie Endoscopie Verpleegkundigen en Assistenten
Vereniging Maag Darm Lever Verpleegkundigen

★

Nederlandse Vereniging voor Hepatologie

★

Nederlandse Vereniging voor Gastrointestinale Chirurgie

★

Nederlandse Vereniging van Maag-Darm-Leverartsen

★

Locatie:
NH Koningshof Veldhoven

INHOUDSOPGAVE **pag**

PROGRAMMA DONDERDAG 19 MAART 2009

Tijdstippen diverse ledenvergaderingen donderdag:

Juniorvereniging – NVMDL (mdl-artsen i.o.) *19 maart, 12.00 uur - Zaal 82/83*
Nederlandse Vereniging voor Hepatologie *19 maart, 15.00 uur - Baroniezaal*

INHOUDSOPGAVE **pag**

PROGRAMMA VRIJDAG 20 MAART 2009

N.B. De met een asterisk gemerkte abstracts in het programma zijn ingezonden door leden van de Sectie Kinder-MDL.

Tijdstippen diverse ledenvergaderingen vrijdag:

Nederlandse Vereniging voor Gastroenterologie	*20 maart, 07.30 uur - Genderzaal*
Nederlandse Vereniging van Maag-Darm-Leverartsen	*20 maart, 12.00 uur - Genderzaal*
Vereniging Maag Darm Leververpleegkundigen	*20 maart, 11.45 uur - Auditorium*
Sectie Endoscopie Verpleegkundigen en Assistenten	*20 maart, 13.30 uur - Diezezaal*
Sectie Experimentele Gastroenterologie	*20 maart, 13.00 uur - Baroniezaal*

VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering die gehouden wordt op 19 en 20 maart a.s. in Congrescentrum Koningshof te Veldhoven. Zoals gebruikelijk wordt ons congres vooraf gegaan door het cursorisch onderwijs op 18 maart, waarvan u het programma aantreft op bladzijde 6.

Het programma zal donderdag 19 maart om 10.00 uur in het Auditorium van start gaan met een symposium van de Netherlands Society of Parenteral Nutrition, getiteld: 'Parenteral Nutrition and the Liver'. Parallel daaraan vindt in de Brabantzaal een sessie met vrije voordrachten van de Nederlandse Vereniging voor Gastroenterologie plaats en in de Baroniezaal start de 2nd Dutch Experimental Gastroenterology and Hepatology Meeting, een gezamenlijk initiatief van de sectie experimentele gastroenterologie van de NVGE en de sectie basale hepatologie van de NVH. Vanaf 12.00 organiseert de DEGH postersessies in de Meierij en Limburg Foyer. U vindt een overzicht vanaf pagina 43.
In de middag kunt u vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie en de Nederlandse Vereniging voor Gastroenterologie bijwonen in de Brabantzaal.
De DEGH vervolgt na de postersessie vanaf 13.30 het programma in de Baroniezaal. In het Auditorium zijn vrije voordrachten te volgen van de Sectie Neurogastroenterologie en Motiliteit, voorafgegaan door voordrachten van de MLDS en de Nederlandse Vereniging voor Gastroenterologie. Om 17.00 uur vindt de Tytgat Lecture plaats in de Brabantzaal. Deze lezing wordt verzorgd door prof. dr. J.P. Medema, en is getiteld: 'Colon Cancer Stem Cells; Fact of Fashion?' Aansluitend vindt om 17.30 uur de President Select plaats, zoals gebruikelijk plenair. Deze sessie duurt tot 18.30 uur en sluit daarmee het programma van de donderdag af. In de avond zijn er geen verdere lezingen meer ingepland, zodat er ruimer gelegenheid is voor diner en ontspanning.
De ledenvergadering van de NVGE vindt weer plaats op vrijdagochtend om 07.30 (inclusief ontbijtbuffet).
Op vrijdagochtend is er vanaf 08.30 uur, casuïstiek in de Brabantzaal, gevolgd door vrije voordrachten van de Sectie Gastrointestinale Endoscopie. Gedurende de gehele vrijdag zijn er behalve deze sessie met genodigde sprekers en vrije voordrachten van de DEGH, ook vrije voordrachten van de Nederlandse Vereniging voor Gastroenterologie. In respectievelijk de Diezezaal en het Auditorium tenslotte, worden door de Sectie Endoscopie Assistenten en Verpleegkundigen en de Vereniging van Maag Darm Lever Verpleegkundigen eigen programma's met lezingen verzorgd.

Graag tot ziens in Veldhoven!

Dr. R.J.F. Felt-Bersma, secretaris NVGE

Let op: *indien u gebruik maakt van overnachting in Koningshof dan dient u op de dag van vertrek de kamer* ***vóór 10.00 uur*** *te verlaten en de keycard in te leveren bij de receptie. Na dit tijdstip zullen er door Koningshof extra kosten in rekening worden gebracht. Uw bagage kunt u desgewenst in een locker deponeren. Deze vindt u nabij de hoofdingang.*

Belangrijke mededeling

over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de voorjaarsvergadering

De Nederlandse Vereniging voor Gastroenterologie kent een jarenlange samenwerking met de farmaceutische industrie. De vereniging stelt de farmaceutische industrie in de gelegenheid aanwezig te zijn bij de wetenschappelijke vergaderingen met een stand. Mede hierdoor kan de vereniging haar wetenschappelijke bijeenkomsten organiseren.
In het “besluit van 31 oktober 1994, Stb. 787, houdende regels voor reclame voor geneesmiddelen (Reclamebesluit Geneesmiddelen)” is onder andere geregeld wat wel en wat niet is toegestaan ten aanzien van gunstbetoning voor artsen door de farmaceutische industrie.
De wet zegt dat - onder strikte voorwaarden - de farmaceutische industrie alleen reclame mag maken voor receptgeneesmiddelen voor personen die bevoegd zijn om dergelijke geneesmiddelen voor te schrijven. Alle andere personen (inclusief bijvoorbeeld verpleegkundigen, endoscopie assistenten en biochemici) worden beschouwd als “publiek”. De farmaceutische industrie mag geen reclame maken voor receptgeneesmiddelen voor publiek.
De Nederlandse Vereniging voor Gastroenterologie is een wetenschappelijke vereniging voor personen die beroepsmatig betrokken zijn bij zorg, onderwijs en onderzoek ten behoeve van patiënten met maag-, darm- en leveraandoeningen. Dat betekent dat ook personen die geen arts zijn, lid van de NVGE kunnen zijn.
De aanwezigheid van artsen, niet-artsen en farmaceutische industrieën tijdens de voorjaarsvergadering kan de NVGE ongewild in aanraking brengen met de inspectie voor de gezondheidszorg, sectie reclametoezicht, en daarmee in diskrediet worden gebracht.
Dat willen wij te allen tijde voorkomen.

Wij delen u dan ook het volgende mede:
Reclame-uitingen en merkproductinformatie van farmaceutische industrieën in het voorliggende programmaboekje zijn alleen gericht op personen die bevoegd zijn om de betreffende geneesmiddelen voor te schrijven.
Al het aanwezige reclamemateriaal, reclame-uitingen en merkproductinformatie van farmaceutische industrieën die aanwezig zijn op het voorjaarscongres, zijn alleen bedoeld en alleen gericht op personen die bevoegd zijn om de betreffende geneesmiddelen voor te schrijven. Wij maken u erop attent dat het voor niet-artsen dan ook niet is toegestaan de stands van de aanwezige farmaceutische industrieën te bezoeken.

De NVGE en farmaceutische industrie (sponsoren) meent u allen, en met name de niet BIG geregistreerde personen, voldoende te hebben ingelicht en kunnen niet verantwoordelijk worden gehouden indien u geen acht slaat op deze mededeling.

Het bestuur van de NVGE

Cursuscommissie: Dr. R.A. de Man (voorzitter, MDL-arts Erasmus MC)
Dr. E. van der Harst (chirurg Maasstad Ziekenhuis)
Dr. D.J. de Jong (MDL-arts UMCN)
Prof. dr. J.H. Kleibeuker (MDL-arts UMCG)
Drs. A.D. Koch (AIOS MDL, Erasmus MC)
Dr. R. Timmer (MDL-arts, Antonius Ziekenhuis)
Drs. H. Telleman (AIOS MDL, VUMC)

Hepatologie

15.00 - 15.15	Evaluatie toets hepatologie
15.15 - 15.45	Management algoritme bij verhoogde serum leverwaarden *Prof. dr. U. Beuers, MDL-arts, AMC, Amsterdam*
15.45 - 16.15	Osteoporose en hepatische osteodystrofie: vaak vergeten *Mw. dr. M. Guichelaar, MDL-arts i.o. UMC Groningen*
16.15 - 16.45	Stapsgewijs management van ascites: van dieet tot TIPS *Prof. dr. P.L.M. Jansen, MDL-arts, AMC, Amsterdam*
16.45 - 17.15	**Pauze**
17.15 - 17.45	Spontane bacteriële peritonitis en hepatorenaal syndroom *Dr. K.J. van Erpecum, MDL-arts, UMC Utrecht*
17.45 - 18.15	Kleine ingrepen met grote gevolgen: operatief risico bij cirrose *Dr. G. Kazemier, chirurg, Erasmus MC, Rotterdam*
18.15 - 18.45	Behandeling van chronische HCV infectie *Dr. R.J. de Knegt, MDL- arts, Erasmus MC, Rotterdam*
18.45 - 19.45	**Dinerbuffet**

19.45 - 20.15	Behandeling van chronische HBV infectie *Prof .dr. H.L.A. Janssen, MDL-arts, Erasmus MC, Rotterdam*
20.15 - 20.45	Pathogenese en behandeling van NASH *Prof. dr. J.PH. Drenth, MDL-arts, UMC St Radboud, Nijmegen*
20.45 - 21.15	Levertransplantatie anno 2008 *Prof. dr. X. Rogiers, Universiteit Gent*
21.15 - 21.45	Discussie casuïstiek *Panel:* *Prof. dr. P.L.M. Jansen, MDL-arts, AMC,* *Prof. dr. H.L.A. Janssen, MDL-arts, Erasmus MC* *Presentatie:* *Tessa Uiterwaal, aios VUMC,* *Ardi Oberndorff, aios AZM*
21.45 - 22.00	Afsluitende kennistoets

De cursuscommissie verwacht van de MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie (NVH) éénmaal bezoeken in het tweede deel van de MDL-opleiding (jaar vier tot zes).

Programma donderdag 19 maart 2009

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
10.30 – 12.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 10	DEGH-Meeting Genodigde spreker: Prof. L. Fabris (Italy) p. 13	Geen programma in deze zaal op donderdag	**Symposium 'Parenteral Nutrition and the Liver'** p. 12	Geen programma in deze zaal op donderdag
12.00 – 13.00	Lunchbuffet expositiehal	Lunchbuffet- postersessie p 43			
13.00 – 15.00	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 14	DEGH-Meeting v.a. 13.30 Genodigde spreker: Prof. G. Hansson (Sweden) p. 24		Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie en voordrachten MLDS p. 19-21	
15.00 – 15.30	Theepauze	Theepauze / Ledenverg. NVH		Theepauze	
15.30 – 17.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 16	DEGH-Meeting (vervolg) p. 25		Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit, tot 17.30 uur p. 21	
17.00 – 17.30	**Tytgat-lecture** door Prof. dr. J.P. Medema p. 17	Einde programma in deze zaal		Vervolg programma	
17.30 – 18.30	**President Select** p. 17			Einde programma in deze zaal	
18.30 – 19.30	Congresborrel expositiehal				
19.30 – 22.00	Diner in Genderzaal				
22.00 – 01.00	Borrel / Muziek in de foyer				

Programma vrijdag 20 maart 2009

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
07.30 – 08.30	Ledenvergadering NVGE in Genderzaal – met ontbijtbuffet				
08.30 – 09.00	Casuïstiek p. 27	DEGH-Meeting p. 37	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 32		
09.00 – 10.30	Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 27	DEGH Meeting Genodigd spreker: Dr. A.M. Mowat (UK) p. 37	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 32	Programma Vereniging voor Maag-Darm-Lever Verpleegkundigen (09.30) p. 41	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 40 (aanvang 10.30)
10.30 – 11.00	Koffiepauze	Koffiepauze	Koffiepauze	Koffiepauze	Koffiepauze
11.00 – 13.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 29	DEGH Meeting, Genodigd spreker: Dr. K. Schoonjans (Switzerland) p. 38	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 34	Programma Vereniging voor Maag-Darm-Lever Verpleegkundigen p. 41	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 40
13.00 – 14.30	Lunchbuffet expositiehal Ledenvergadering NVMDL	Prijsuitreikingen gevolgd door ledenvergadering SEG.	Lunchbuffet expositiehal	Lunchbuffet expositiehal (12.45 – 14.00 uur)	Lunchbuffet expositiehal
	Koffie/thee expositiehal	Koffie/thee expositiehal	Koffie/thee expositiehal	Einde programma 15.30	Einde programma 15.05

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

10.00 Inschrijving, koffie

Voorzitters: A. Cats en A.A.M. Masclee

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

10.30 Losses of chromosome 5q and 14q mark a subset of gastric cancers with good clinical outcome (p. 56)

T.E. Buffart[1], B. Carvalho[1], N.C. Van Grieken[1], W.N. Van Wieringen[2], M. Tijssen[1], E. Klein Kranenbarg[3], H. Grabsch[4], B. Ylstra[1], C.J. Van de Velde[3], G.A. Meijer[1], [1]VU University Medical Center Amsterdam, Amsterdam, Netherlands; [2]Vrije Universiteit, Amsterdam, Netherlands; [3]Leiden University Medical Center, Leiden, Netherlands; [4]Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds, United Kingdom

10.40 Grading and staging gastritis with the OLGA system: intestinal metaplasia as a reproducible alternative (p. 57)

L.G. Capelle[1], A.C. de Vries[1], J. Haringsma[1], F. ter Borg[2], R. de Vries[3], M. Bruno[1], H. Van Dekken[4], J. Meijer[5], N.C.T. Van Grieken[6], E.J. Kuipers[1], [7,1]Depts of Gastroenterology and Hepatology, [4]Pathology, and [7]Internal Medicine, Erasmus MC University Medical Center, Rotterdam, [2]Dept of Hepato-gastroenterology, Deventer Hospital, Deventer, [3]Dept of Internal Medicine, University Medical Center, Groningen, [5]Dept of Pathology, Rijnstate Hospital, Arnhem, [6]Dept of Pathology, VU University Medical Center, Amsterdam, the Netherlands

10.50 Changes in overuse and underuse of prophylactic strategies with NSAID treatment over the past decade; further improvement is needed (p.58)

V.E. Valkhoff[2,1], E.M. van Soest[1], M.C.J.M. Sturkenboom[1,4], E.J. Kuipers[2,3] [1]Medical Informatics, Erasmus Medical Centre, Rotterdam, The Netherlands; [2]Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands; [3]Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands; [4]Epidemiology and Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands

11.00 Underutilization of proton pump inhibitors in short-term NSAID users in a large population in the Netherlands (p.59)

O.S. van Boxel[1], M.P. Hagenaars[2], A.J.P.M. Smout[1] and P.D. Siersema[1], [1]University Medical Centre Utrecht, the Netherlands[2] Achmea Health Insurance, Leiden, the Netherlands

11.10 Premalignant gastric lesions in patients with gastric MALT lymphoma and metachronous gastric carcinoma: a case-control study (p.60)

C.M. den Hoed[1], L.G. Capelle[1], K. Biermann[3], M.K. Casparie[4], E.J. Kuipers[1,2], Depts of [1]Gastroenterology and Hepatology, [2]Internal Medicine, and [3]Pathology, Erasmus MC University Medical Center, Rotterdam, Netherlands, [4]Foundation PALGA, Utrecht, the Netherlands

11.20 Abdominal Migraine, a new and treatable disorder mimicking functional dyspepsia (p. 61)

M. Bigirwamungu-Bargeman[1], R.H. Geelkerken[2], A.B. Huisman[3], J.J. Kolkman[1], Depts of [1]Gastroenterology, [2]Vascular Surgery and [3]Radiology, Medical Spectrum Twente, Enschede, the Netherlands

11.30 Short term efficacy of the new D-Weave Niti-S™ stent in malignant gastric outlet obstruction: results of the first European prospective, multicenter study (p. 62)

J.E. van Hooft[1], S.M. Jeurnink[2], M.J. Bruno[1], M. Dijkgraaf[3], P.D. Siersema[2], P. Fockens[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [3]Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, The Netherlands

11.40 Endoscopic visible light spectroscopy: a new minimally invasive technique for the diagnosis of chronic gastrointestinal ischemia (p. 63)

D. van Noord[1], D.A. Benaron[2], P.M.T. Pattynama[3], H.J.M. Verhagen4, E.J. Kuipers[1], P.B.F. Mensink[1], Depts of Gastroenterology and Hepatology[1], Intervention Radiology[3], Vascular Surgery[4], Erasmus MC - University Medical Center, Rotterdam, The Netherlands, Standford University School of Medicine, Palo Alto, CA, USA[2]

11.50 Evaluation of molecular changes in sporadic duodenal adenomas (p. 64)

D. Ramsoekh[1], M. Theeuwes[1], W. van Veelen[1], R. Smits[1], W.N.M. Dinjens[2], E. Dekker[3], K. Boparai[3], E.J. Kuipers[1] and M.E. van Leerdam[1], Depts. of [1]Gastroenterology and Hepatology and [2]Molecular Pathology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [3]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

12.00 Lunchpauze

Parenteral Nutrition and the Liver

A symposium in honour of the retirement of Prof. dr. H.P. Sauerwein
internist/endocrinologist, Academic Medical Center Amsterdam
Chair NESPEN (SVEM) 1988 – 1998.

Chair: U. Beuers / G. Wanten

10.00 Welcome and Opening Remarks or Comments :
Dr. G. Wanten, UMCN (Committee Member NESPEN)

10.05 Optimal Parenteral Nutrition
Prof. dr. H.P. Sauerwein, AMC Amsterdam

10.30 Are serum liver test abnormalities during parenteral nutrition predictors of liver cirrhosis?
Prof. dr. A. Forbes, University College Hospital Maple House London

11.00 Observations about the practice of parenteral nutrition: should we act as we do?
Prof. dr. H.P. Sauerwein, AMC Amsterdam

11.30 How to keep the liver in a healthy state?
Prof. dr. U. Beuers, AMC Amsterdam

11.55 Closing remarks: Dr. W. van Gemert, UMCM
(Chair NESPEN)

12.00 End of session

12.00 Lunch buffet in exhibition hall

DEGH-Meeting **Baroniezaal**

Voorzitters: L. Fabris en J.P.H. Drenth

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

10.30 MMP-14/MT1-MMP mediates endoglin shedding in colorectal cancer (p. 65)
L.J.A.C. Hawinkels[1,2], P. Kuiper[1], H.W. Verspaget[1], R. Hanemaaijer[3], P. ten Dijke[2], C.F.M. Sier[1], Depts of Gastroenterology-Hepatology[1] and Molecular Cell Biology and Centre for Biomedical Genetics[2], Leiden University Medical Center, TNO Quality of Life BioSciences[3], Leiden, the Netherlands

10.45 Depletion of the colonic epithelial precursor cell compartment upon conditional activation of the Hedgehog pathway (p. 66)
W.A. van Dop[1,2], A. Uhmann[3], M. Wijgerde[4], E. Sleddens-Linkels[4], G.J. Offerhaus[5], G.E. Boeckxstaens[1], M.A. van den Bergh Weerman[1], D.W. Hommes[2], J.C. Hardwick[2], H. Hahn[3], G.R. van den Brink[1,2] ,[1]AMC, Amsterdam, The Netherlands, [2]UMC Leiden, Leiden, The Netherlands, [3]University of Göttingen, Göttingen, Germany, [4]Erasmus MC, Rotterdam, The Netherlands, [5]UMC Utrecht,, The Netherlands

11.00 Optimization of aav liver-directed gene therapy for the treatment of crigler-najjar syndrome (p. 67)
P. Miranda, L. ten Bloemendaal, C. Kunne, S. Duijst, P. Bosma, AMC Liver Center, Amsterdam, The Netherlands

11.15 Tissue repair induces cancer in p53 and Rb deficient livers (p. 68)
M.J.M. Toussaint[1], R.B. Matondo[1], S. Pandit[1], P.C.J. Tooten[1], R. Kisjes[1], T. Roskams[2] and A. de Bruin[1], [1]Dept of Pathobiology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands and Dept of Morphology and Molecular Pathology, University of Leuven, Belgium

11.30 Invited Speaker
Pathophysiology of cholangiopathies
Prof. L. Fabris (Italy)

12.00 Lunchbuffet

Postersessie DEGH **Meierij en Limburg Foyer**

12.00 De postersessie van de DEGH vindt plaats tussen 12.00 en 13.30 uur met vanaf 12.30 de mogelijkheid om u aan te sluiten bij een begeleide sessie langs geselecteerde posters. U vindt een overzicht van deze geselecteerde posters vanaf pagina 43 in dit programma. Vervolg DEGH-programma, om 13.30 uur zie pagina 24.

Nederlandse Vereniging voor Gastrointestinale Chirurgie — Brabantzaal

Voorzitters: G.J.D. van Akker en E.J. Hazebroek

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

13.00 Endoscopic mucosal resection appears equally effective, but is associated with less morbidity than transanal endoscopic microsurgery for the treatment of large rectal adenomas. (p. 69)
F.J.C. van den Broek[1], J. van Schooten[1], W.A. Bemelman[2], E.J.R. de Graaf[3], P. Fockens[1], E. Dekker[1], for the TREND-study group, Depts. of [1]Gastroenterology and Hepatology, and [2]Surgery, Academic Medical Center Amsterdam, [3]dept. of Surgery, IJsselland hospital Cappelle a/d IJssel, the Netherlands

13.10 Intestinal barrier function in patients undergoing open or laparoscopic (sub)total colectomy: a randomized trial (p.70)
M.S. Vlug[1], G.M.P. Diepenhorst[2], P.J. van Koperen[1], J.F. Slors[1], M.A. Boermeester[1], W.A. Bemelman[1], [1]Dept of Surgery, Academic Medical Center, [2]Dept of Surgery, Surgical Laboratory, Academic Medical Center, University of Amsterdam, the Netherlands

13.20 DNA copy number changes predict clinical outcome in Stage II Colon cancer (p. 71)
R.P.M. Brosens[1], T. Buffart[2], A.F. Engel[3], M.A. Cuesta[1], G.A. Meijer[2], [1]Dept of Surgery, VU University Medical Centre, Amsterdam, The Netherlands [2]Dept of Pathology, VU University Medical Centre, Amsterdam, The Netherlands, [3]Dept of Surgery, Zaans Medical Centre, Zaandam, The Netherlands

13.30 Stroma production and downregulation of SMAD4 correlates with worse survival for stage I-II colon cancer patients (p. 72)
W.E. Mesker[1], G.J. Liefers[1], J. Morreau[2], R.A.E.M. Tollenaar[1], [1]Dept of Surgery and [2]Dept of Pathology, Leiden University Medical Center (LUMC), Leiden, the Netherlands

13.40 Long-term symptomatic and anatomical outcome of laparoscopic para-oesophageal hiatal herniation repair (p. 73)
E.J.B. Furnée[1], W.A. Draaisma[2], H.G. Gooszen[1], G. Stapper[3], I.A.M.J. Broeders[2], Dept of Surgery[1], University Medical Centre Utrecht, the Netherlands, Dept of Surgery[2], Meander Medical Centre, Amersfoort, the Netherlands, Dept of Radiology[3], University Medical Centre Utrecht, the Netherlands

13.50 A multi-center randomized efficacy study of the EndoBarrier for pre-surgical weight loss in bariatric surgery (p. 74)
R. Schouten[1], C. Rijs[3], N.D. Bouvy[1], W. Hameeteman[2], G.H. Koek[2], I. Jansen[3], J.W.M. Greve[1], [1]Dept of General Surgery, University Hospital Maastricht, [2]Dept of Gastroenterology and Hepatology, University Hospital Maastricht, [3]Dept of Surgery, Rijnstate Hospital, Arnhem, The Netherlands

14.00 Intrathoracic manifestations of cervical anastomotic leaks and risk factors for development of benign cervical strictures after oesophagectomy (p. 75 + p. 76)

M. van Heijl MD[1], J.A.H. Gooszen[1], A.K.S. van Wijngaarden[1], S.M. Lagarde[1], O.R.C. Busch[1], J.J.B. van Lanschot[3], M.I. van Berge Henegouwen[1], 1Dept of Surgery, Academic Medical Centre, Amsterdam, [2]Dept of Gastroenterology Academic Medical Centre, Amsterdam, [3]Dept of Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

14.10 Mortality rates for gastric cancer surgery in the Southwest of the Netherlands (p. 77)

B.P.L. Wijnhoven[1], C. Schroten[2], P.D. de Rooij[3], R.A.M. Damhuis[2], [1]Erasmus MC, Dept of Surgery, Rotterdam, [2]Comprehensive Cancer Centre IKR, Rotterdam, [3]Maasstad Ziekenhuis, Dept of Surgery, Rotterdam, The Netherlands

14.20 Fast intestinal barrier recovery following ischemia/reperfusion damage in the human gut: myosin light chain kinase mediated closure of the villus tip (p. 78)

G. Thuijls[1], J. Grootjans[1], J.P.M. Derikx[1], F. Heyers[1], R. Matthijsen[1], E. Heineman[1], R.M. van Dam[1], C.H.C. Dejong[1], W.A. Buurman1 ,1Dept of Surgery, Maastricht University Medical Centre and Nutrition and Toxicology Research Institute Maastricht (NUTRIM), the Netherlands

14.30 Laparoscopic cholecystectomy for acute cholecystitis for laparoscopic surgeons only? (p. 79)

K. Kortram, D. Boerma, M.J. Wiezer, P.M.N.Y.H. Go, B. van Ramshorst, St. Antonius Ziekenhuis Nieuwegein, the Netherlands

14.40 Quality of life and pancreatic function after resection of pancreatic cysts (p. 80)

N.A. van der Gaag[1], O. Berkhemer[1], O.R.C. Busch[1], T.M. van Gulik[1], D.J. Gouma[1], 1Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

14.50 In-hospital mortality decreased significantly after regionalization of pancreatic surgery in the south-east of The Netherlands (p. 81)

S.W. Nienhuijs[1], H.J.T. Rutten[1], E.J.T. Luiten[2], O.J. Repelaer van Driel[3], P.H.M. Reemst[3], V.E.P.P. Lemmens[4], I.H.J.T. de Hingh[1], [1]Dept of Surgery, Catharina Hospital, Eindhoven, [2]Dept of Surgery, St. Anna Hospital, Geldrop, [3]Dept of Surgery, Maxima Medical Center, Veldhoven, [4]Comprehensive Cancer Centre South, Eindhoven Cancer Registry, Eindhoven

15.00 Theepauze

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

Voorzitters: R.J.F. Felt-Bersma en A.J.P. van Tilburg

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

15.30 Incomplete colonoscopy: significant findings in a mixed referral population during follow up (p. 82)

M. Neerincx[1], J.S. Terhaar sive Droste[1], M. Räkers[1], J.F.W.M. Bartelsman[2], R.J. Loffeld[3], H.A.R.E. Tuynman[4], C.J.J. Mulder[1], R.W.M. van der Hulst[5], Dept. of Gastroenterology and Hepatology[1], VU University Medical Center, Amsterdam, Dept. of Gastroenterology and Hepatology[2], Academic Medical Center, Amsterdam, Dept. of Internal Medicine[3], Zaans Medical Center, Zaandam, Dept. of Gastroenterology and Hepatology[4], Medical Center Alkmaar, Alkmaar, Dept. of Gastroenterology and Hepatology[5], Kennemer Gasthuis, Haarlem, The Netherlands

15.40 High Cumulative Risk of Intussusceptions in patients with Peutz-Jeghers Syndrome (p. 83)

M.G.F. van Lier[1], A. Wagner[2], A.M. Westerman[3], J.H.P. Wilson[3], F.W.M. de Rooij[3], E.J. Kuipers1,3, M.E. van Leerdam[1], Dept of Gastroenterology and Hepatology[1], Dept of Clinical Genetics[2] and Dept of Internal Medicine[3], Erasmus MC, University Medical Center, Rotterdam, the Netherlands

15.50 Is colonoscopy screening mandatory for post-LTx recipients? (p. 84)

J. Sint Nicolaas[1], S.W.A. Tjon[1], H.J. Metselaar[1], E.J. Kuipers[1], R.A. de Man[1], M.E. van Leerdam[1], 1Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

16.00 The burden of colonoscopy: gastroenterologists' ability to assess patients' most important issues of concern (p. 85)

M.J. Denters[1], M. Deutekom[2], H.H.F. Derkx[3], E. Dekker[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of Social Medicine, Academic Medical Center, Amsterdam, [3]Dept of Pediatrics, Academic Medical Center, Amsterdam, The Netherlands

16.10 First population-based study on the incidence and prognosis of patients suffering from synchronous peritoneal carcinomatosis of colorectal origin (p.86)

Y.L.B. Klaver[1], V.E.P.P. Lemmens[2], V.J. Verwaal[3], H.J.T. Rutten[1], J.W. Coebergh[2], I.H.J.T. de Hingh[1], [1]Dept of Surgery, Catharina Hospital, Eindhoven, [2]Dept of Research, Comprehensive Cancer Centre South, Eindhoven Cancer Registry, [3]Dept of Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

16.20 Population based survival of patients suffering from peritoneal carcinomatosis does not improve over time despite increasing usage of palliative chemotherapy (p.87)

Y.L.B. Klaver[1], G.J. Creemers[2], V.E.P.P. Lemmens[3], S.W. Nienhuijs[1], I.H.J.T. de Hingh[1], [1]Dept of Surgery, Catharina Hospital, Eindhoven, [2]Dept of Internal Medicine, Catharina Hospital, Eindhoven, [3]Dept of Research, Comprehensive Cancer Centre South, Eindhoven Cancer Registry, The Netherlands

16.30 Endoscopically removed malignant colorectal polyps with uncertain histological radicality: surgery or endoscopic follow-up? (p. 88)

L. van Nunspeet[1], J.W. Arends[2], F. ter Borg[1], E.J. Kuipers[3], Depts. of Gastroenterology[1] and Pathology[2], Deventer Ziekenhuis, Deventer, [3]Dept of Gastroenterology, Erasmus Medical Centre, Rotterdam, The Netherlands

16.40 Inter-observer variation in the histological diagnosis of polyps in colorectal cancer screening (p. 89)

P.G. van Putten[1], L. Hol[1], H. van Dekken[2], J.H. van Krieken[3], M. van Ballegooijen[4], M.E. van Leerdam[1] and E.J. Kuipers[1,5], [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [2]Dept of Pathology, St. Lucas Andreas Hospital, Amsterdam, [3]Dept of Pathology, University Nijmegen Medical Center, Nijmegen, [4]Dept of Public Health, Erasmus University Medical Center, Rotterdam,[5]Dept of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

16.50 A Gly82Ser polymorphism of RAGE is not associated with gastric or colorectal cancer in a Western population (p.90)

E. Hoff, J.J. van der Reijden, A.A. Dihal, H.W. Verspaget, D.W. Hommes, G.R. van den Brink, Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands

17.00 **Tytgat Lecture**

Colon Cancer Stem Cells; Fact or Fashion?

Prof. dr. J.P. Medema, Laboratory for Experimental Oncology and Radiobiology, CEMM, Academic Medical Center, Amsterdam

De Tytgat Lecture wordt gesponsord door Tramedico BV.

President Select (plenaire sessie) — Brabantzaal

Voorzitter: C.J.J. Mulder

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

17.30 Early or delayed laparoscopic cholecystectomy after endoscopic sphincterotomy for common bile duct stones: A prospective randomized multicentre trial (p. 91)

J.S.K. Reinders[1], A. Goud[1], R. Timmer[2], Ph.M. Kruijt[3], B.J.M. Witteman[4], N. Smakman[5], R. Breumelhof[6], S.C. Donkervoort[7], J.M. Jansen[8], B. van Ramshorst[1], D. Boerma[7].,Depts of Surgery[1] and Gastroenterology[2], St. Antonius Hospital Nieuwegein, Depts of Surgery[3] and Gastroenterology[4], Hospital Gelderse Vallei, Ede, Depts of Surgery[5] and Gastroenterology[6], Diakonessenhuis, Utrecht, Depts of Surgery[7] and Gastroenterology[8], Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Donderdag 19 maart 2009

17.45 Are hyperplastic polyps precursors of colorectal cancer? A long-term, retrospective study (p. 92)

M. Bouwens[1], E. Rondagh[1], B. Winkens[2], A. Driessen[3], A. De Bruine[3], A. Masclee[1], S. Sanduleanu[1], Dept of Gastroenterology and Hepatology[1], Dept of Methodology and Statistics[2], Dept of Pathology[3], Maastricht University Medical Center, Maastricht, the Netherlands

18.00 Adult human liver contains residential mesenchymal stem cells which mobilize during liver transplantation and contribute to immunomodulation and hepatic regeneration (p.93)

Q. Pan[1], S.M.G. Fouraschen[2], F.S.F. Aerts-Kaya[3], M.M.A. Verstegen[3], A. van der Sloot[2], R. Smits[1], J. Kwekkeboom[1], H. Metselaar[1], H.W. Tilanus[2], G. Wagemaker[3], H.L.A. Janssen[1] and L.J.W. van der Laan[2], Depts of [1]Gastroenterology & Hepatology; [2]Surgery and [3]Hematology, Erasmus MC - University Medical Center Rotterdam, The Netherlands

18.15 Genetic and mucosal expression analysis shows important roles for JAK2 and MST1 in the pathogenesis of ulcerative colitis and identifies more susceptibility loci (p. 94)

E.A.M. Festen[1,2], P.C. Stokkers[3], M.C. Wapenaar[2], C.C. van Diemen[2], A.A. van Bodegraven[4], M. Bruinenberg[2], H.M. Boezen[5], J.B.A. Crusius[6], D.W. Hommes[7], C.J. van der Woude[8], T. Balschun[9], H.W. Verspaget[7], S. Schreiber[9], D.J. de Jong[10], A. Franke[9], K.N. Faber[1], G. Dijkstra[1], C. Wijmenga[2], and R.K. Weersma[1],*, [1]Dept of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands [2]Dept of Genetics, University Medical Centre Groningen and University of Groningen, Groningen, the Netherlands, [3]Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, the Netherlands, [4]Dept of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, the Netherlands, [5]Dept of Epidemiology, University Medical Centre Groningen and University of Groningen, Groningen, the Netherlands, [6]Dept of Immunogenetics, VU University Medical Centre, Amsterdam, the Netherlands, [7]Dept of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, the Netherlands, [8]Dept of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, the Netherlands, [9]Institute for Clinical Molecular Biology, Christian Albrechts- University, Kiel, Germany, [10]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands. *These authors contributed equally to this work.*

18.30 Einde programma, congresborrel in de expositiehal

19.30 Diner in de Genderzaal

Nederlandse Vereniging voor Gastroenterologie **Auditorium**

Voorzitters: W. van Gemert en H.J. Verkade

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

13.00 Preservation of intestinal integrity precedes anti-inflammatory actions of lipid-rich enteral nutrition (p. 95)

J. de Haan[1], G. Thuijls[1], T. Lubbers[1], M. Hadfoune[1], J.P.M. Derikx[1, 3], M.D. Luyer[1,3], W.A. Buurman[1], J.W.M. Greve[2,1], [1]Surgery, Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University Medical Center, Maastricht; [2]Surgery, Atrium Medical Center, Heerlen; [3]Surgery, Maaslandziekenhuis, Sittard, the Netherlands

13.10 Central venous catheter related complications and experienced problems in HPN dependent patients (p. 96)

G. Huisman-de Waal[1], L. Schoonhoven[1], G. Wanten[2] , J. Jansen[2], H. Sauerwein[3], T. van Achterberg[1], [1]IQ Healthcare, Nursing Science, [2]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, [3]Dept of Endocrinology and Metabolism, University Medical Centre Amsterdam, the Netherlands

13.20 Effects of corticosteroids on bone metabolism in patient with active Crohn's disease (p. 97)

D.J. de Jong[1], C.G.J. Sweep[2], A.R.M.M. Hermus[3], R. Greinwald[4], R. Mohrbacher[4], A.H.J. Naber[5], Depts of [1]Gastroenterology and Hepatology, [2]Chemical endocrinology, [3]Endocrinology, Radboud University Nijmegen Medical Centre, Nijmegen, [4]Dept of Research and Development, Dr. Falk Pharma Gmbh, Freiburg, [5]Dept of Gastroenterology, Tergooi Hospital Hilversum, the Netherlands

13.30 Detection of Tropheryma whipplei DNA in intestinal biopsy specimens with a novel real-time PCR (p. 98)

M.E. Grasman[1], A.M. Pettersson[2], A.G. Koek[2], C.J. Mulder[1], P.H.M. Savelkoul[2], A.A. van Bodegraven[1], [1]Dept of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, [2]Dept of Medical Microbiology and Infection Control, VU University Medical Centre, Amsterdam, the Netherlands

13.40 Ten-year Outcome of Laparoscopic and Conventional Nissen Fundoplication: Randomized Clinical Trial (p. 99)

J.A.J.L. Broeders[1], H.G. Rijnhart – de Jong[1], W.A. Draaisma[1], A.J. Bredenoord[3], A.J.P.M. Smout[2], H.G. Gooszen[1], Gastro-enterologische onderzoeksgroep van het Universitair Medisch Centrum Utrecht Afdeling Heelkunde[1] en Maag-Darm-Leverziekten[2] Afdeling Maag-Darm-Leverziekten, St. Antonius Ziekenhuis, Nieuwegein[3], The Netherlands

13.50 The current situation on the use of sedation during gastrointestinal endoscopy in the Netherlands (p.100 + p. 101)

R.W.F. ter Steege[1], P. Fockens[2], S. van den Hazel[3], J.J. Kolkman[1], [1]Gastroenterology, Medical Spectrum Twente, Enschede, the Netherlands, [2]Gastroenterology and hepatology, Academic Medical Centre, Amsterdam, [3]Gastroenterology Slingeland Hospital, Doetinchem, the Netherlands

14.00 Preoperative biliary drainage versus direct operation for pancreatic tumors causing obstructive jaundice (DROP-Trial) (p. 102)

N.A. van der Gaag[1], E.A. Rauws[2], C.H. van Eijck[3], M.J. Bruno[4], E. van der Harst[5], J.J. Gerritsen[6], J.W. Greve[7], M.F. Gerhards[8], I.H. de Hingh[9], J.H. Klinkenbijl[10], C.Y. Nio[11], S.M. de Castro[1], O.R. Busch[1], T.M. van Gulik[1], P.M. Bossuyt[12], D.J. Gouma[1], [1]Surgery, Academic Medical Center, Amsterdam, [2]Gastroenterology, Academic Medical Center, Amsterdam, [3]Surgery, Erasmus Medical Center, Rotterdam, [4]Gastroenterology, Erasmus Medical Center, Rotterdam, [5]Surgery, Maasstad Hospital, Rotterdam, [6]Surgery, Medisch Spectrum Twente, Enschede, [7]Surgery, University Hospital Maastricht, Maastricht, [8]Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, [9]Surgery, Catharina Hospital, Eindhoven, [10]Surgery, Rijnstaete Hospital, Arnhem,[11]Radiology, Academic Medical Center, Amsterdam, [12]Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, The Netherlands

14.10 Bacterial translocation in patients undergoing pancreatic surgery and the influence of prophylactic use of probiotics and selective decontamination of the digestive tract in a randomized placebo-controlled trial (p.103)

G.M.P. Diepenhorst[1], O. van Ruler[2], M.G.H. Besselink[3], H.C. van Santvoort[3], P.R. Wijnandts[4], D.J. Gouma[2], H.G. Gooszen[3], M.A. Boermeester[2], [1]Dept of Surgery (Surgical Laboratory), Academic Medical Center, and Dept of Immunopathology, Sanquin Research, Amsterdam, [2]Dept of Surgery, Academic Medical Center, Amsterdam, and Dutch Acute Pancreatitis Study Group, Utrecht,[3]Depts of Surgery, University Medical Center Utrecht and Dutch Acute Pancreatitis Study Group, Utrecht, [4]Dept of Anaesthesiology, Academic Medical Center, The Netherlands

14.20 Prevalence of pancreatic cysts in individuals undergoing preventive medical examination by Magnetic Resonance Imaging (MRI). (p. 104)

K. de Jong[1], C.Y. Nio[2], J. Hermans[3], M.G. Dijkgraaf[4], D.J. Gouma[5], C.H.J. van Eijck[6], E. van Heel[7], G. Klaß[8], P. Fockens[1], M.J. Bruno[9], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of Radiology, Academic Medical Center, Amsterdam, [3]Dept of Radiology, Erasmus Medical Center, Rotterdam, [4]Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, [5]Dept of Surgery, Academic Medical Center, Amsterdam, [6]Dept of Surgery, Erasmus Medical Center, Rotterdam, [7]Prescan Nederland, Hengelo, [8]Dept of Radiology, Mathias Spital Hospital, Rheine, Germany, [9]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

14.30 Genetic variants of Myosin IXB and Pard3 predispose to acute pancreatitis (p. 105)

R.M. Nijmeijer[1], H.C. van Santvoort[1], A. Zhernakova[2], M.G.H. Besselink[1], M.C. Wapenaar[3], M.A. Boermeester[4], H.G. Gooszen[1], L.M.A. Akkermans[1], C. Wijmenga[2,3], on behalf of the Dutch Pancreatitis Study Group, [1]Dept of Surgery, University Medical Center Utrecht, The Netherlands; [2]Complex Genetics Section, Dept of Medical Genetics, University Medical Center Utrecht, The Netherlands; [3]Dept of Genetics, University Medical Center Groningen and University of Groningen, The Netherlands; [4]Dept of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Voordrachten MLDS-projecten — Auditorium

Voorzitters: W. van Gemert en H.J. Verkade

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

14.40 A mouse model of Juvenile Polyposis shows that Colorectal Cancer can arise due to a landscaper defect (MLDS project 04-06) (p. 106)
L.A.A. Brosens[1], W.A. van Hattem[1,2], W.W.J. de Leng[1], F.M. Morsink[1], G.J.A. Offerhaus[1,2] , [1]Dept of Pathology, University Medical Center, Utrecht, [2]Dept of Pathology, Academic Medical Center, Amsterdam, the Netherlands

14.50 Reduced responsiveness of the steatotic liver to FGF19 (MLDS-project 05-03) (p. 107)
P.J. Jansen[1], K. van den Oever[1], W. Patsch[2], P.L.M. Jansen[1,3], F,G. Schaap[1],Academic Medical Center, [1]AMC Liver Center, [3]Dept of Gastroenterology and Hepatology, Amsterdam, The Netherlands, [2]Dept of Laboratory Medicine, Paracelsus Medical University, Salzburg, Austria

15.00 Theepauze

Sectie Neurogastroenterologie en Motiliteit — Auditorium

Voorzitters: A.J.P.M. Smout en J.W. Straathof

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

15.30 The position of the acid pocket as risk factor to have acid reflux during a TLESR (p. 108)
H. Beaumont[1], R.J. Bennink[2], J.W. Jong[2], G.E. Boeckxstaens[1,3], Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands[1], Dept of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands[2], Dept of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium[3]

15.40 Speech therapy in patients with excessive supragastric belching (p. 109)
G.J.M. Hemmink[1], L. ten Cate[2], A.J. Bredenoord[1,3], R. Timmer[1], B.L.A.M. Weusten[1], A.J.P.M. Smout[3], [1]Dept of Gastroenterology, Sint Antonius Hospital, Nieuwegein, the Netherlands, [2]Practice for Speech and Voice Therapy, L. ten Cate, Utrecht, [3]Gastrointestinal Research Center, University Medical Center, Utrecht, the Netherlands

15.50 Characterization of gastro-esophageal motor function following esophageal atresia repair (p. 110)

M.P. van Wijk[1], F.M.C. Knüppe[1], T.I. Omari[2], D.C. Aronson[3], J.A. Deurloo[3], M.A. Benninga[1], [1]Paediatric Gastroenterology and Nutrition, Emma Children's Hospital / Academic Medical Centre , Amsterdam, Netherlands, [2]Centre for Paediatric and Adolescent Gastroenterology, Children, Youth and Women's Health Services, Adelaide, SA, Australia, [3]Amsterdam Centre for Paediatric Surgery, AMC / VUmc, Amsterdam, the Netherlands

16.00 Non-invasive measurement of early postprandial volume and accommodationresponse in health and functional dyspepsia using Magnetic Resonance Imaging (p. 111)

J.J.L. Haans[1], I.M. de Zwart[2], A. de Roos[2], A.A.M. Masclee[1], [1]Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [2]Dept of Radiology, Leiden University Medical Center, Leiden, The Netherlands

16.10 CRH-receptor antagonism prevents the development of stress-induced visceral hypersensitivity but fails to affect established hypersensitivity (p. 112)

O.I. Stanisor[1], S.A. van Diest[1], O. Welting[1], W.J. de Jonge[1], G.E. Boeckxstaens[1,2], R.M. van den Wijngaard[1], Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands[1], Dept of Gastroenterology, University Hospital Gasthuisberg, Catholic University of Leuven, Leuven, Belgium[2]

16.20 Rectal butyrate administration dose-dependently lowers visceral sensitivity in healthy humans (p. 113)

*S. Vanhoutvin[1,2] *, F. Troost[1,2], P. Lindsey[3], T. Kilkens[2], H. Hamer[1,2], D. Jonkers[1,2], K. Venema[1,4], R.J. Brummer[1,2,5], [1]TIFood and Nutrition, Wageningen, The Netherlands, [2]Maastricht University, Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht, The Netherlands, [3]Maastricht University, Dept of Population Genetics, Genomics and Bioinformatics, Maastricht, The Netherlands, [4]TNO Quality of Life, Dept of Biosciences, Zeist, The Netherlands, [5]Örebro University, School of Health and Medical Sciences, Örebro, Sweden. *s.vanhoutvin@intmed.unimaas.nl*

16.30 Does the presence of a hiatal hernia affects the efficacy of the reflux inhibitor baclofen? (p. 114)

H. Beaumont[1], G.E.E. Boeckxstaens[1,2] Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands[1], Dept of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium[2]

16.40 Colonic manometry in children with defecation disorders: should we measure for 24 hours? * (p. 115)

O. Liem[1,2], R. Burgers[1,2], F. Connor[3], M. Benninga[2], S. Reddy[4], H. Mousa[1], C. Di Lorenzo[1], [1]Nationwide Children's Hospital, Columbus, OH, USA, [2]Emma Children's Hospital, Amsterdam Medical Center, Amsterdam, Netherlands, [3]Royal Children's Hospital, Brisbane, QL, Australia, [4]Sriram Motility Clinic, Hyderabad, India

16.50 Muscularis mucosae of the rectum in children with Hirschsprung's disease & functional constipation * (p. 116)

N. Bekkali[1], M.M. Tabbers[1], J.C.H. Wilde[2], M.W.N. Oomen[2], M.A. Benninga[1], F.J.W. ten Kate[3], [1]Dept of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre, Amsterdam, the Netherlands, [2]Dept of Paediatric surgery, Emma Children's Hospital, Academic Medical Centre, Amsterdam, the Netherlands, [3]Dept of Pathology, Academic Medical Centre, Amsterdam, the Netherlands*

17.00 Treatment of rectal fecal impactiona - a randomized controlled trial: enemas versus high doses of PEG 3350 * (p. 117)

Bekkali[1], M.G.W. Dijkgraaf[2], M.M. van den Berg[1], M.P. van Wijk[1], M.E.J. Bongers[1], O. Liem[1], M.A. Benninga[1], [1]Dept of Pediatric gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre, Amsterdam, the Netherlands, [2]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, Amsterdam, the Netherlands

17.10 Effect of weight reduction on NAFLD in children: results of a Dutch second line weight reduction program * (p. 118)

B.G.P. Koot[1], O.H. van der Baan-Slootweg[2], T.H. Pels Rijcken[3], P.L.M. Jansen[4], M.A. Benninga[1], [1]Academic Medical Centre (AMC), Dept of Pediatric gastro-enterology, [2]Heideheuvel Obesity Clinic, Hilversum, [3]Ter Gooi Ziekenhuizen, Dept of Radiology, [4]AMC, Dept of Hepatology, the Netherlands

17.20 Constipation and colonic transit time in morbidly obese children * (p. 119)

O. Liem[1], O.H. vd Baan-Slootweg[1,2], N. Bekkali[1], W.M.C. van Aalderen[3], T.H. Pels Rijcken[4], M.A. Benninga[1,1]. Dept of pediatric gastroenterology and nutrition, Emma's Children's Hospital/AMC, Amsterdam, the Netherlands[2], Childhood Obesity Centre Heideheuvel, Hilversum, the Netherlands[3], Dept of pediatric pulmonology, Emma's Children's Hospital/ AMC, Amsterdam, the Netherlands[4], Dept of radiology, Tergooiziekenhuizen, Hilversum, the Netherlands

17.30 Voor de **President Select** kunt u zich begeven naar de Brabantzaal

18.30 Einde programma, congresborrel in de expositiehal

19.30 Diner Genderzaal

DEGH-Meeting **Baroniezaal**

Voorzitters: G. Hansson en A.A. te Velde

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

13.30 Intestinal flora directs infiltrate composition and disease severity in a novel zebrafish colitis model (p. 120)

S. Brugman[1], K-Y. Liu[1], D. Lindenbergh-Kortleve[1], J.N. Samsom[1], G.T. Furuta[2], S.A. Renshaw[3], R. Willemsen[4], E.E.S. Nieuwenhuis[1] ,[1]Laboratory of Pediatrics, Dept of Pediatric Gastroenterology, Erasmus Medical Center, Rotterdam, the Netherlands, [2]Section of Gastroenterology, Hepatology and Nutrition, The Children's Hospital, Aurora, Colorado, USA, [3]MRC Centre for Developmental and Biomedical Genetics, University of Sheffield, UK, [4]Dept of Clinical Genetics, Erasmus Medical Center, Rotterdam, the Netherlands

13.45 A polymorphism in the coding region of il12b promotes IL-12p70 heterodimer formation in colitis sensitive SJL/J mice (p. 121)

A. Zwiers[1,2], D. Seegers[3], T. Konijn[2], B.J. Verwer[1], J.J.B. Garcia-Vallejo[2], J. Samsom[4], I. Fuss[3], W. Strober[3], G. Kraal[2] and G. Bouma[1], Dept. of Gastroenterology[1] and Molecular Cell Biology and Immunology[2], Vrije Universiteit Medical Center, Amsterdam, the Netherlands, [3]The Mucosal Immunity Section, National Institutes of Health, Bethesda, MD, USA, [4]Dept. of Pediatric Gastroenterology and Nutrition, Erasmus University Medical Centre–Sophia Children's Hospital, Rotterdam, The Netherlands

14.00 5-Aminosalicylic acid suppresses colitis-associated but not sporadic colorectal cancer (p.122)

P.J. Koelink[1], E.C. Robanus-Maandag[2], J.A.D. Jankie[2], C.B.H.W. Lamers[1], D.W. Hommes[1] and H.W. Verspaget[1], Depts of [1]Gastroenterology-Hepatology and [2]Human Genetics, Leiden University Medical Center, Leiden, the Netherlands

14.15 Generation of a tightly regulated doxycycline-inducible model for studying mouse intestinal biology (p. 123)

S. Roth[1], P. Franken[1], W. van Veelen[2], L. Blonden[1], L. Raghoebir[3], B. Beverloo[4], E. van Drunen[4], E.J. Kuipers[2,5], R. Rottier[3], R. Fodde[1], and R. Smits[2] ,[1]Dept of Pathology, Josephine Nefkens Institute, Erasmus MC, Rotterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, [3]Dept of Cell Biology, [4]Dept of Clinical Genetics, [5]Dept of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

14.30 Invited Speaker
Role of mucus in ulcerative colitis
Prof. G. Hansson (Sweden)

15.00 Theepauze en Ledenvergadering NVH

DEGH-Meeting **Baroniezaal**

Voorzitters: J. Kwekkeboom en E.H.H.M. Rings

15.30 Intravenous Immunoglobulins trigger direct functional activation of CD4+CD25+ Foxp3+ regulatory T cells and promote skin allograft acceptance (p. 124)

T. Tha-In[1,2], A.R. Bushell[2], H.J. Metselaar[1], K.J. Wood[2], J. Kwekkeboom[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam and [2]Nuffield Dept of Surgery, University of Oxford, Oxford, UK

15.45 Wilson disease is a novel target for pharmacological folding chaperones 4-phenylbutyrate and curcumin (p. 125)

P.V.E. van den Berghe[1], E. Spijker[1], E. van Beurden[1], R.E.A. de Groot[1], J.M. Stapelbroek[1], S.F.J. van de Graaf[1], P. de Bie[1], R. Berger[1], L.W.J. Klomp[1], [1]Dept of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, the Netherlands

16.00 Microvillus inclusion disease is caused by mutations in apical recycling endosome-associated myosin Vb * (p.126)

A.M. Szperl[1,8], M.R. Golachowska[2,8], M. Bruinenberg[1], R. Prekeris[3], A.M. Thunnissen[4], D. Hoekstra[2], C. Wijmenga[1,5], J. Ksiazyk[6], E.H. Rings[7,9], M.C. Wapenaar[1,9], S.C. van IJzendoorn[2,9], Depts of [1]Genetics, [2]CellBiology/Membrane Cell Biology and [7]Pediatrics, University Medical Center Groningen and University of Groningen, Groningen, the Netherlands, [3]Dept of Cellular and Developmental Biology, School of Medicine, University of Colorado Health Sciences Centre, Denver, Colorado, USA, [4]Dept of Biophysical Chemistry, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, The Netherlands, [5]Dept of Medical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [6]Dept of Pediatrics, Children's Memorial Health Institute, Warsaw, Poland. [8,9] These authors contributed equally

16.15 COMMD1 is a novel inhibitor of the CCS-dependent activation of Copper/ Zinc Superoxide Dismutase (p. 127)

W.I.M. Vonk[1,2], B. van de Sluis[1,2,3], R. Berger[1], C. Wijmenga[2,4], L.W.J. Klomp[1], [1]Dept of Metabolic and Endocrine Diseases, University Medical Center Utrecht, and Netherlands Metabolomics Center, the Netherlands, [2]Complex Genetics Section, University Medical Center Utrecht, the Netherlands, [3]Dept of Pathology and Laboratory Medicine, University Medical Center Groningen, the Netherlands, [4]Dept of Genetics, University Medical Center Groningen, the Netherlands

16.30 Angiotensin II protects rat hepatocytes from bile acid- induced apoptosis (p. 128)

G. Karimian, M. Buist-Homan, R. Henning, K.N. Faber, H. Moshage, Dept. Gastroenterology and Hepatology and *Dept. Clinical Pharamcology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

16.45 NK-cell chimerism is a unique feature of liver transplantation and may modulate the recipient's immune response against the graft (p. 129)

V. Moroso[1], H.J. Metselaar[1], B.M. Bosma[1], S. Mancham[1], L.J.W. van der Laan[2], N.M. van Besouw[3], H.W. Tilanus[2], E.J. Kuipers[1], D. Eissen[4], A.van der Meer[4], I. Joosten[4], J. Kwekkeboom[1], Depts of [1]Gastroenterology and Hepatology, [2]Surgery and [3]Internal Medicine, Erasmus MC, Rotterdam, and [4]Dept of Blood Transfusion and Transplantation Immunology, UMC St Radboud, Nijmegen., the Netherlands

17.00 Congresborrel in de expositiehal

Nederlandse Vereniging voor Gastroenterologie — Genderzaal

07.30 **Ledenvergadering NVGE**
Onbijtbuffet in de zaal

08.30 Sluiting

Casuïstiek — Brabantzaal

Voorzitter: W. Hameeteman

08.30 Casuïstische Patiëntenbespreking

Sectie Gastrointestinale Endoscopie — Brabantzaal

Voorzitters: W. Hameeteman en M.A.J.M. Jacobs

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

09.00 Systematic evaluation of the Over-The-Scope-Clip (OTSC) for NOTES gastric closure (p. 130)
R.P. Voermans[1,2], M.I. van Berge Henegouwen[2], W.A. Bemelman[2], P. Fockens[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, [2]Dept. of Surgery, Academic Medical Center, University of Amsterdam, the Netherlands

09.10 Preliminary experience with the novel Spyglass peroral cholangioscopy system (p. 131)
R.K.Weersma, Dept of Gastroenterology and HepatologyUniversity Medical Center Groningen, the Netherlands

09.20 Performance of endoscopic ultrasound-guided fine-needle aspiration in patients with mediastinal lymphadenopathy during routine patient care (p. 132)
M.M. Hirdes[1], M.P. Schwartz[1,4], K.M. Tytgat[1], N.J. Schloesser[2], D.M. Sie Go[3], M. Brink[4], B. Oldenburg[1], P.D. Siersema[1], F.P. Vleggaar[1], Depts of Gastroenterology & Hepatology[1], Pulmonary Medicine[2] and Pathology[3], University Medical Center Utrecht, the Netherlands, Dept of Gastroenterology[4], Meander Medical Center, Amersfoort, the Netherlands

Vrijdag 20 maart 2009

09.30 How effective and safe is EUS-guided Fine Needle Aspiration (EUS-FNA) in the evaluation of cystic lesions of the pancreas? (p. 133)

K. de Jong[1], M.J. Bruno[2], M. Visser[3], C.Y. Nio[4], D.J. Gouma[5], J.J. Hermans[6], C.H.J van Eijck[7], J.W. Poley[2], P. Fockens[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [3]Dept of Pathology, Academic Medical Center, Amsterdam, [4]Dept of Radiology, Academic Medical Center, Amsterdam, [5]Dept of Surgery, Academic Medical Center, Amsterdam, [6]Dept of Radiology, Erasmus Medical Center, Rotterdam, [7]Dept of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands

09.40 The value of endoscopic ultrasound in detecting periampullary tumors after a negative CT (p. 134)

N.A. van der Gaag[1], C.Y. Nio[2], J. Hoogmoed[1], O.R.C. Busch[1], M.J. Bruno[3], P. Fockens[4], T.M. van Gulik[1], P.M.M. Bossuyt[5], D.J. Gouma[1],[1]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands. [2]Dept of Radiology, Academic Medical Center, Amsterdam, the Netherlands, [3]Dept of Gastroenterology, Erasmus Medical Center, Rotterdam, the Netherlands, [4]Dept of Gastroenterology, Academic Medical Center, Amsterdam, the Netherlands, [5]Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, the Netherlands

09.50 Endoscopic Tri-Modal Imaging improves the detection of early neoplasia in Barrett esophagus; an international multi-center randomized cross-over study (p. 135)

W.L. Curvers[1], L. Alvarez Herrero[1,2], H.C. Wolfsen[3], V. Subramanian[4], G.A. Prasad[5], M.B. Wallace[3], K. Ragunath[4], L-M. Wong Kee Song[5], P. Fockens[1], B.L.A.M. Weusten[2], J.J.G.H.M. Bergman[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, Netherlands, [2]Dept of Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, Netherlands, [3]Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, USA, [4]Wolfson Digestive Disease Centre, Queen's Medical Centre, Nottingham, United Kingdom, [5]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

10.00 Endoscopic radiofrequency ablation for very long segments of Barrett esophagus containing neoplasia (p. 136 + 137)

L. Alvarez Herrero[1,2], R. Pouw[1], F.G. van Vilsteren[1], C.M. Sondemeijer[1], F.J. ten Kate[3], P. Fockens[1], B. Weusten[2], J.J. Bergman[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Netherlands, [2]Dept of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, Netherlands, [3]Dept of Pathology, Academic Medical Center, Amsterdam, the Netherlands

10.10 Patient-based assessment of prolonged colonoscopy simulator training (p.138)

A.D. Koch[1], J. Haringsma[1], E.J. Schoon[2], R.A. de Man[1], E.J. Kuipers[1], [1]Erasmus MC, Rotterdam, [2]Catharina Hospital, Eindhoven, the Netherlands

10.20 Autofluorescence endoscopy allows better differentiation than white light video colonoscopy in classifying adenomatous and non-adenomatous colorectal polyps (p.139)

P.G. van Putten[1], D. Ramsoekh[1], J. Haringsma[1], J.W. Poley[1], H. van Dekken[2], E.W. Steyerberg[3], M.E. van Leerdam[1] and E.J. Kuipers[1,4], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Dept of Pathology, St. Lucas Andreas Hospital, Amsterdam, The Netherlands, [3]Dept of Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [4]Dept of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

10.30 Koffie/thee in de expositiehal.

Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

Voorzitters: M.J. Bruno en P.D. Siersema

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

11.00 Outcome of a progressive stenting protocol inthe treatment of anastomic strictures after orthotopic liver transplantation (p. 140)

J.W. Poley[1], G. Kazemier[2], H.J. Metselaar[1], E.J. Kuipers[1], M.J. Bruno[1], Depts of Gastroenterology & Hepatology[1] and Surgery[2], Erasmus MC, University Medical Center Rotterdam, the Netherlands

11.10 Risk of esophageal adenocarcinoma and mortality in patients with Barrett esophagus: a systematic review and meta-analysis (p. 141)

M. Sikkema[1], P.J.F. de Jonge[1], E.W. Steyerberg[2], E.J.Kuipers[1,3] ,Depts of Gastroenterology and Hepatology[1], Public Health[2] and Internal Medicine[3], Erasmus MC – University Medical Center, Rotterdam, The Netherlands

11.20 P53 protein overexpression by immunocytochemistry (ICC) and p53 gene locus loss by DNA Fluorescent in situ hybridization (FISH) are complimentary tools for detecting abnormal P53 status in Barrett's esophagus patients (p.142)

A.L. Davelaar[1], A.M. Rygiel[1], F. Milano[1], J.J.G.H.M. Bergman[2], B. Elzer[2], P. Fockens[2], K.K. Krishnadath[2], [1]Labolatory of Experimental Gastroenterology, [2]Dept of Gastroenterology, Academic Medical Centre, Amsterdam, the Netherlands

11.30 Quality of life as a predictor for survival in patients with oesophageal cancer (p. 143)

M. van Heijl[1], A.G.E.M. de Boer[2], J.B. Reitsma[3], O.R.C. Busch[1], H.W. Tilanus[4], M.A.G. Sprangers[2], J.J.B. van Lanschot[4], M.I. van Berge Henegouwen[1], [1]Dept of Surgery, [2]Dept of Medical Psychology, [3]Dept of Clinical Epidemiology, Academic Medical Centre, Amsterdam, [4]Dept of Surgery, Erasmus Medical Centre, Rotterdam, the Netherlands

11.40 Overexpression of p53 and Ki67 and aneuploidy as markers for neoplastic progression in Barrett esophagus: a nested case-control study (p. 144)

M.Sikkema[1], M. Kerkhof, H. van Dekken[3], J.G. Kusters[1], E.W. Steyerberg[2], C.W.N. Looman[2], P.D. Siersema[1], E.J. Kuipers[1,4] on behalf of the CYBAR-study group, Depts of Gastroenterology and Hepatology[1], Public Health[2], Pathology[3] and Internal Medicine[4], Erasmus MC – University Medical Center, Rotterdam, The Netherlands

11.50 Improving the quality of the pre-operative work-up of patients with esophageal carcinoma; implementation of a fast-track staging protocol (p. 145)

P. Didden[1], M.C.W. Spaander[1], B.P.L. Wijnhoven[2], E.J. Kuipers[1], M.J. Bruno[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Dept of Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands

12.00 Risk of Malignant Progression in Patients with Barrett's Esophagus; a Dutch Nationwide Cohort Study (p.146)

P.J.F. de Jonge[1], M. van Blankenstein[1], C.W.N. Looman[2], M.K. Casparie[3], G.A. Meijer[4], E.J. Kuipers[1,5], [1]Depts. of Gastroenterology and Hepatology, [2]Public Health and [5]Internal Medicine, Erasmus MC - University Medical Center Rotterdam, [3]Stichting PALGA, Utrecht, [4]Dept. of Pathology, VU University Medical Center, Amsterdam, The Netherlands

12.10 A Multi-Center Randomized Trial Comparing Stepwise Radical Endoscopic Resection versus Radiofrequency Ablation for Barrett Esophagus containing High-Grade Dysplasia and/or Early Cancer (p. 147)

F.G.I. van Vilsteren[1], R.E. Pouw[1], S. Seewald[2], L.A.H. Alvarez Herrero[3], C.M.T. Sondermeijer[1], F.J. ten Kate[4], P. Fockens[1], K. Yu Kim Teng[2], T. Rösch[2], N. Soehendra[2], B.L. Weusten[3], J.J. Bergman[1], [1]Gastroenterology, Academic Medical Center, Amsterdam, the Netherlands, [2]Interdisciplinary Endoscopy, University Medical Center Hamburg-Eppendorf, Germany, [3]Gastroenterology, Sint Antonius Hospital, Nieuwegein, Netherlands, [4]Pathology, Academic Medical Center, Amsterdam, the Netherlands

12.20 The effect of operator experience on outcome of laparoscopic Nissen fundoplication (p. 148)

J.A.J.L. Broeders[1], W.A. Draaisma[1], H.G. Rijnhart–de Jong[1], A.J.P.M. Smout[2], J.J.B. van Lanschot[3], I.A.M.J. Broeders[4], H.G. Gooszen[1], Gastrointestinal Research Unit of the University Medical Center Utrecht, Depts of Surgery[1] and Gastroenterology[2], Dept of Surgery[3], Erasmus Medical Center, Rotterdam; Dept of Surgery[4], Meander Medical Center, Amersfoort, the Netherlands

12.30 Surveillance in a prospectively followed cohort of patients with Barrett esophagus in the Netherlands: a cost-effectiveness analysis (p. 149)

M. Sikkema[1], E.W. de Bekker-Grob[2], M. Kerkhof[1], M.J.C. Eijkemans[2], C.W.N. Looman[2], J.B.Wong[4], D.T. Provenzale[5], E.J. Kuipers[1,3], P.D. Siersema[1,6], E.W. Steyerberg[2] on behalf of the CYBAR study group, Depts. of Gastroenterology and Hepatology[1], Public Health[2] and Internal Medicine[3], Erasmus MC - University Medical Center, Rotterdam, The Netherlands, Dept. of Medicine: Division of Clinical Decision Making[4], Tufts-New England Medical Center, Boston, USA, Dept. of Clinical Health Policy Research[5], Duke University Medical Center, Durham, USA, Dept. of Gastroenterology and Hepatology[6], University Medical Center Utrecht, The Netherlands

12.40 Predictors for neoplastic progression in patients with Barrett Esophagus: a prospective cohort study (p. 150)

M. Sikkema[1], M. Kerkhof[1], C.W.N. Looman[2], E.J. Kuipers[1,3], P.D. Siersema[1] on behalf of the CYBAR-study group, Depts. of Gastroenterology and Hepatology[1], Public Health[2], Internal Medicine[3], Erasmus- University Medical Center, Rotterdam, The Netherlands

12.50 Long-term results of endoscopic ablation therapy for early Barrett's cancer (p. 151)

N.C.M. van Heel, J. Haringsma, E.J. Kuipers, Erasmus MC University Medical Center, Rotterdam, the Netherlands

13.00 Lunchbuffet (expositiehal)

Nederlandse Vereniging voor Gastroenterologie — Parkzaal

Voorzitters: B. Oldenburg en A.A. van Bodegraven

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

08.30 Low frequency of Inflammatory Bowel Disease-related Colorectal Carcinoma (CRC) in non-tertiary centers: final results of a nation wide long-term survey (p.152)

J.E. Baars[1], E.J. Kuipers[1], R. Beukers[2], A. Tan[3], B. Weusten[4], M.K. Casparie[5], C.J. van der Woude[1], Depts of Gastroenterology & Hepatology, Erasmus MC, Rotterdam[1], Albert Schweitzer Hospital, Dordrecht[2], Canisius Wilhelmina Hospital, Nijmegen[3], St Antonius Hospital, Nieuwegein[4], Nation-wide network and registry of histo-and cytopathology, Utrecht[5], the Netherlands

08.40 Sex-related Differences in the Medication Use and Surgery for Inflammatory Bowel Diseases (p. 153)

Z. Zelinkova, L. Vogelaar, C. Bouziane, E.J. Kuipers, C.J. van der Woude, Dept of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, The Netherlands

08.50 Low yield of neoplasia and lack of clinical consequences of random biopsies do not warrant their use in colonoscopic surveillance of patients with ulcerative colitis (p. 154)

F.J.C. van den Broek, R.P.B. Boltjes, S.C.S. Wolfkamp, P. Fockens, C.Y. Ponsioen, P.C.F. Stokkers, E. Dekker, Dept.of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands

09.00 Mortality in Inflammatory Bowel Disease in the Netherlands 1991 - 2002. Results of a population based study; the IBD South-Limburg cohort (p. 155)

M.J.L. Romberg-Camps[1,5], E.M.M. Kuiper[2], L.J. Schouten[3], A.D.M. Kester[4], M.A.M. Hesselink-van de Kruijs[1], L.P. Bos[5], J. Goedhard[6], W.H.A. Hameeteman[1], F. Wolters[7], M.G.V.M. Russel[8], R.W. Stockbrügger[1], P.C. Dagnelie[3], [1]Dept of Gastroenterology and Hepatology, Maastricht University Medical Center, [2]Dept of Gastroenterology, Erasmus University Medical Centre, [3]Dept of Epidemiology, Maastricht University, [4]Dept of Methodology and Statistics, Maastricht University, [5]Dept of Internal Medicine and Gastroenterology, Maasland Hospital Sittard, [6]Dept of Internal Medicine and Gastroenterology, Atrium Medical Centre Heerlen, [7]Dept of Gastroenterology, Vie-Curi Medical Centre Venlo, [8]Dept of Gastroenterology, Medisch Spectrum Twente Enschede, the Netherlands

09.10 Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine in a Dutch nationwide study (p. 156)

A.C.W. Vos[1], N. Bakkal[1], R.C. Minnee[2], D.J. de Jong[3], G. Dijkstra[4], P. Stokkers[2], A.A. van Bodegraven[5], M. Pierik[6], C.J. van der Woude[7], B. Oldenburg[8], D.W. Hommes[1], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, [3]Dept of Gastroenterology, Radboud University Medical Center, [4]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, [5]Dept of Gastroenterology and Hepatology, VU University Medical Center, [6]Dept of Gastroenterology, University Hospital Maastricht, [7]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, [8]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht

09.20 Laparoscopic-assisted versus open ileocolic resection for Crohn's Disease: Long term results of a prospective randomized trial (p.157)

E.J. Eshuis[1,2], J.F.M. Slors[1], M.A. Cuesta[3], E.G. Pierik[4], P.C.F. Stokkers[2], M.A. Sprangers[5], W.A. Bemelman[1], [1]Dept of Surgery, Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept of Surgery, VU University Medical Center, Amsterdam, [4]Dept of Surgery, Isala Clinics, Zwolle, [5]Dept of Medical Psychology, Academic Medical Center, Amsterdam, the Netherlands

09.30 Adequately dosed 6-thioguanine is a well tolerated and safe rescue drug in azathioprine or 6-mercaptopurine intolerant IBD patients (p. 158)

D.P. van Asseldonk[1], B. Jharap[1], N.K.H. de Boer[1], A.A. van Bodegraven[1] and C.J. Mulder[1], [1]Dept of Gastroenterology and Hepatology, VU university medical center, Amsterdam, the Netherlands

09.40 Determinants of hyperoxaluria and urolithiasis in Crohn's disease: results of a pilot study (p. 159)

T.E.H. Römkens[1], F.M. Nagengast[1], D.J. de Jong[1], Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, the Netherlands[1]

09.50 High prevalence of fatigue in patients with Inflammatory Bowel Disease: results of a case-control study (p. 160)

M.W.J. van Vugt- van Pinxteren[1], T.E.H. Römkens[1], F.M. Nagengast[1], M.G.H. van Oijen[1], D.J. de Jong[1], University Medical Center St. Radboud Nijmegen, Dept. Gastroenterology and Hepatology[1], the Netherlands

10.00 Visceroperception in Patients with Ulcerative Colitis; role of colorectal mast cells (p. 161)

E.A. van Hoboken[1], A.Y. Thijssen[2], P.P.J. van der Veek[1], D.M.A.E. Jonkers[2], H.W. Verspaget[1], A.A.M. Masclee[2], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Centre, The Netherlands, [2]Division of Gastroenterology and Hepatology, Maastricht University Medical Centre, The Netherlands

10.10 Treatment of refractory Crohn's Disease patients with autologous bone marrow derived Mesenchymal Stem Cells – first results (p. 162)

M. Duijvestein[1], M.H. Verwey[1], H.H. Fidder[1], G.R. van den Brink[1], H. Roelofs[2], J. Zwaginga[2], W.E. Fibbe[2], D.W. Hommes[1], [1]Dept of Gastroenterology and Hepatology and [2]Dept of Immunohematology and Blood Transfusion, Leiden University Medical Center (LUMC), Leiden, the Netherlands

10.20 Genetic Variants in the Region Harbouring IL2/IL21 Associated to Ulcerative Colitis (p. 163)

E.A.M. Festen[1,2], P. Goyette[3], R. Scott[4], V. Annese[5], A. Zhernakova[6], S.R. Brant[7,8], J.H. Cho[9], M.S. Silverberg[10], K.D. Taylor[11], D.J. de Jong[12], P.C. Stokkers[13], D. McGovern[11], O. Palmieri[5], J.P. Achkar[14], R.J. Xavier[15], R.H. Duerr[4,16], M.J. Daly[17,18], C. Wijmenga[2], R.K. Weersma[1] and J.D. Rioux[3], [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands, [2]Dept of Genetics, University Medical Center Groningen and University of Groningen, Groningen, the Netherlands, [3]Laboratory in Genetics and Genomic Medicine of Inflammation, Montreal Heart Institute Université de Montréal, Montreal, Canada, [4]Division of Gastroenterology, Hepatology and Nutrition, Dept of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, USA, [5]UU.OO. Gastroenterologia ed Endoscopia Digestiva, Ospedale "Casa Sollievo della Sofferenza", IRCCS, San Giovanni Rotondo, Italy, [6]Complex Genetics Section, Dept of Medical Genetics, University Medical Center Utrecht, Utrecht, the Netherlands, [7]Harvey M. and Lyn P. Meyerhoff Inflammatory Bowel Disease Center, Dept of Medicine, Johns Hopkins University, Baltimore, USA, [8]Dept of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA, [9]Depts of Medicine and Genetics, Division of Gastroenterology, Inflammatory Bowel Disease (IBD) Center, Yale University, New Haven, USA, [10]Mount Sinai Hospital IBD Centre, University of Toronto, Canada, [11]Medical Genetics Institute and Inflammatory Bowel Disease (IBD) Center, Cedars-Sinai Medical Center, Los Angeles, USA, [12]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, the Netherlands; [13]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands, [14]Center for Inflammatory Bowel Disease, Dept of Gastroenterology & Hepatology, Cleveland Clinic, Cleveland, Ohio, USA, [15]Center for Computational and Integrative Biology and Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, USA, [16]Dept of Human Genetics, Graduate School of Public Health, University of Pittsburgh, USA, [17]Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, USA, [18]Molecular Biology Dept, Massachusetts General Hospital, Harvard Medical School, Boston, USA.

10.30 Koffie/thee in de expositiehal

Nederlandse Vereniging voor Gastroenterologie — Parkzaal

Voorzitters: J.H. Kleibeuker en J.B.M.J. Jansen

Voordrachten in het Nederlands, spreektijd 7 minuten, discussietijd 3 minuten

11.00 Flat colonic neoplasia are left undetected by Fecal Immunochemical Tests (FIT) and will be missed in colorectal cancer screening (p. 164)

F.A. Oort[1], J.S. Terhaar sive Droste[1], R.W.M. van der Hulst[2], H.A. van Heukelem[3], R.J.L.F. Loffeld[4], I.C.E. Wesdorp[5], Q.J.M. Voorham[6], G.A. Meijer[6], C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Slotervaart Hospital, Amsterdam, [4]Internal Medicine, Zaans Medical Center, Zaandam, [5]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [6]Pathology, VU University Medical Center, Amsterdam, the Netherlands

11.10 Randomized trial comparing the test characteristics of immunochemical fecal occult blood test at different cut-off levels to Guaiac-based fecal occult blood test (p. 165)

L. Hol[1], J.A. Wilschut[2], M. van Ballegooijen[2], A.J. van Vuuren[1], H. van der Valk[3], J.C.I.Y. Reijerink[4], A.C.M. van der Togt[5], E.J. Kuipers[1,6], J.D.F. Habbema[2], M.E. van Leerdam[1], [1]Depts of Gastroenterology and Hepatology, [2]Public Health, and [6]Internal Medicine, Erasmus MC, University Medical Centre, Rotterdam, [3]Association of Laboratory Pathology and Cytology (Pathan), Rotterdam, [4]Association of Nation-wide Screening South-west Netherlands, Vlaardingen, [5]Comprehensive Cancer Centre, Rotterdam, the Netherlands

11.20 Advanced neoplasia of the left hemicolon are better detected by FIT than right sided lesions (p. 166)

F.A. Oort[1], R.W.M. van der Hulst[2], J.S. Terhaar sive Droste[1], H.A. van Heukelem[3], R.J.L.F. Loffeld[4], I.C.E. Wesdorp[5], R. Duijkers[1], R.A.M. Ooteman[1], Z.D. Valdehueza[1], M.Q. Wentink[1], V.M.H. Coupe[6], G.A. Meijer[7], C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Slotervaart Hospital, Amsterdam, [4]Internal Medicine, Zaans Medical Center, Zaandam, [5]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [6]Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [7]Pathology, VU University Medical Center, Amsterdam, the Netherlands

11.30 Routine MSI-analysis in Colorectal Cancer patients ≤ 70 years leads to the identification of more patients at high risk for Lynch Syndrome (p. 167)

M.G.F. van Lier[1], A. Wagner[2], W.N.M. Dinjens[3], E.J. Kuipers[1,4], M.E. van Leerdam[1], E.W. Steyerberg[5], Dept of Gastroenterology and Hepatology[1], Dept of Clinical Genetics[2], Dept of Pathology[3], Dept of Internal Medicine[4], Dept of Pubilic Health[5], Erasmus MC, University Medical Center, Rotterdam, the Netherlands

11.40 Screening for colorectal cancer in the Netherlands; acceptance of FOBT and flexible sigmoidoscopy screening (p. 168)

V. de Jonge[1], L. Hol[1], M. van Ballegooijen[2], J.D.F. Habbema[2], M.L. Essink-Bot[2], J. van Vuuren[1], E.J. Kuipers[1], M .E. van Leerdam[1], Dept of Gastroenterology and Hepatology[1] and Public Health[2], Erasmus University Medical Center, Rotterdam, The Netherlands

11.50 Epidemiological and gastric gastric risk in Lynch syndrome families in the Netherlands (p. 169 + p. 170)

L.G. Capelle[1], N.C.T. Van Grieken[2], W.J. Klokman[3], M.J. Bruno[1], H.F.A. Vasen[4,5], E.J. Kuipers[1,6], Depts of [1]Gastroenterology and Hepatology and [6]Internal Medicine, Erasmus MC University Medical Center, Rotterdam, [2]Dept of Pathology, VU University Medical Center, Amsterdam, [3]Dept of Epidemiology, The Netherlands Cancer Institute, Amsterdam, [4]The Netherlands Foundation for the Detection of Hereditary Tumors, [5]Dept of Gastroenterology, Leiden University Medical Centre, Leiden, the Netherlands

12.00 Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicenter cohort study (p. 171)

K.S. Boparai[1], E.M.H. Mathus-Vliegen[1], J.J. Koornstra[2], F. Nagengast[3], M. van Leerdam[4], C.J.M. van Noesel[5], M. Houben[6], A. Cats[7], L. van Hest[8], P. Fockens[1], E. Dekker[1], [1]Depts of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, the Netherlands, [2]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, the Netherlands, [3]Dept of Gastroenterology and Hepatology, Radboud Medical Center, Nijmegen, The Netherlands, [4]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands, [5]Dept of Pathology, Academic Medical Center, University of Amsterdam, the Netherlands, …

[6]Dept of Gastroenterology and Hepatology, Haga Teaching Hospital, The Hague, The Netherlands, [7]Dept of Gastroenterology and Hepatology, Antonie van Leeuwenhoek Hospital, The Netherlands, [8]Dept of Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands

12.10 Stated willingness-to-be-screened for colorectal cancer or not: the participation paradox (p. 172)

L.G.M. van Rossum[1], M.G.H. van Oijen[1], A.L.M. Verbeek[2], R.J.F. Laheij[1], J.B.M.J. Jansen[1] [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [2]Dept of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

12.20 Two samples for immunochemical fecal occult blood tests in screening for colorectal cancer: implementation and participation (p. 173)

L.G.M. van Rossum[1], M.G.H. van Oijen[1], J. Schuurmans[2], A.L.M. Verbeek[3], R.J.F. Laheij[1], J.B.M.J. Jansen[1], [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [2]Dept of Palliative care, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [3]Dept of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

12.30 High Definition Chromoendoscopy for the detection of rectal Aberrant Crypt Foci (p. 174)

G. Delconte[1,3], M.E.I. Schipper[2], F.P. Vleggaar[1], T.Q. Nguyen[2], L. Laghi[3], A. Repici[3], A. Malesci[3], G.J.A. Offerhaus[2], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology and [2]Pathology, University Medical Center Utrecht, The Netherlands, [3]Dept. of Gastroenterology, IRCCS Istituto Clinico Humanitas, University of Milan, Italy

12.40 The role of bone morphogenetic protein signaling and transforming growth factor β signaling and their components in colorectal cancer (p. 175)

R.J. Jacobs[1], L.L. Kodach[1], N.F. De Miranda[2], D.W. Hommes[1], G.R. van den Brink[1], H. Morreau[2], J.C. Hardwick[1], [1]Dept of Gastroenterology & Hepatology and [2]Dept of Pathology, Leiden University Medical Center, Leiden, The Netherlands

12.50 Higher cut off values for FIT in CRC-screening: less colonoscopies, same detection rates for curable cancers (p. 176)

F.A. Oort[1], J.S. Terhaar sive Droste[1], R.W.M. van der Hulst[2], H.A. van Heukelem[3], R.J.L.F. Loffeld[4], I.C.E. Wesdorp[5], I. Ben Larbi[1], S.L. Kanis[1], M. Neerincx[1], M.Räkers[1], V.M.H. Coupe[6], G.A. Meijer[7], C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Slotervaart Hospital, Amsterdam, [4]Internal Medicine, Zaans Medical Center, Zaandam, [5]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [6]Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [7]Pathology, VU University Medical Center, Amsterda, The Netherlands.

13.00 Lunch in de expositiehal

Voorzitters: A.M. Mowat en G. Bouma

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

08.30 Nicotine enhances phagocytosis in macrophages via recruitment of Dynamin-2 to the phagocytic cup (p. 177)

E.P. van der Zanden[1], G.E. Boeckxstaens[1,2], W.J. de Jonge[1], [1]Dept of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, Catholic University Leuven, Leuven, Belgium

08.45 Differential TLR ligation of intestinal epithelial cells drives an inflammatory or regulatory Th1 response in vitro (p. 178)

S. de Kivit[1], E. van Hoffen[2], N. Korthagen[1], J. Garssen[1], L.E.M. Willemsen[1], [1]Pharmacology and Pathophysiology, UIPS, Utrecht University, [2]Dermatology/Allergology, University Medical Center, Utrecht, the Netherlands

09.00 Hepatitis B virus inhibits TLR9-induced plasmacytoid dendritic cell function (p.179)

A.M. Woltman, M.L. Op den Brouw, P.J. Biesta, H.L.A. Janssen, Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, the Netherlands

09.15 The genetically modified Lactococcus lactis OVA modulates T-cells through an antigen-specific effect on dendritic cells (p. 180)

L. Huibregtse[1], H. Braat[2], T.M. van Capel[3], V. Snoeck[4], L. Boon[5], T. van der Poll[1], P. Rottiers[4], S.J.H. van Deventer[6], M.L. Kapsenberg[3] and E.C. de Jong[3], [1]Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept of Cell Biology & Histology, and Dermatology, Academic Medical Center, The Netherlands, [4]Dept for Molecular Biomedical Research, VIB, Ghent, Belgium, [5]Biosceros BV, Utrecht, The Netherlands, [6]Dept of Gastroenterology and Hepatology, Leids Universitair Medisch Centrum,
Leiden, The Netherlands

09.30 The mannose receptor as a putative hepatitis B virus receptor regulating intrahepatic dendritic cell function (p. 181)

M.L. Op den Brouw[1], R.S. Binda[1], T.B.H. Geijtenbeek[2], H.L.A. Janssen[1] and A.M. Woltman[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam,, [2]Dept. of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

09.45 Differences in disease progression of DSS induced colitis in C57BL/6 and BALB/c mice (p. 182)

B.J. Olivier[1], M.J. Greuter[1], M. Knippenberg[1], G. Bouma[2], G. Kraal[1] and R.E. Mebius[1], [1]Dept of Molecular Cell Biology & Immunology and [2]Dept of Gastroenterology, VU University Medical Center, Amsterdam, the Netherlands

Vrijdag 20 maart 2009

10.00 Invited Speaker
Refractory dendritic cells and macrophages in the control of intestinal immune responses
Dr. A.M. Mowat (UK)

10.30 Koffiepauze

DEGH-Meeting **Baroniezaal**

Voorzitters: K. Schoonjans en K.N. Faber

11.00 Invited Speaker
Targeting TGR5 for metabolic diseases
Dr. K. Schoonjans (Switzerland)

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

11.30 Ribavirin is anti-fibrotic in a non-viral rat model for liver fibrosis (p. 183)
R.A Hannivoort, S. Dunning, J. Wallinga, K. van Pelt, M. Buist-Homan, K.N. Faber, H. Moshage, Dept. Gastroenterology and Hepatology, University Medical Center Groningen, the Netherlands

11.45 Altered expression of fibroblast growth factor 15 (FGF15) in acute pancreatitis: potential consequences for bacterial translocation and infection risk (p. 184)
R.M. Nijmeijer[1], L.M.A. Akkermans[1], F.G. Schaap[2], P.L. Jansen[2], J. Terlinde[3], A. Verheem[1], A.B.A. Kroese[1,4], M.G.H. Besselink[1], M. Schipper[5], H.G. Gooszen[1], K. van Erpecum[3], [1]Dept of Surgery, University Medical Center Utrecht, The Netherlands, [2]Dept of Gastroenterology and Hepatology, AMC Liver Center, University of Amsterdam, The Netherlands, [3]Dept of Gastroenterology, University Medical Center Utrecht, The Netherlands, [4]Institute for Risk Assessment Sciences, Utrecht, The Netherlands, [5]Dept of Pathology, University Medical Center Utrecht, The Netherlands

12.00 b-Klotho acts as a chaperone regulating FGFR4 glycosylation and activity (p.185)
V. Triantis[1], E. Saeland[2], N. Bijl[3], R.P. Oude-Elferink[1], P.L.M. Jansen[1], [1]AMC Liver Centre, Amsterdam, [2]Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, [3]Dept of Biochemistry, Academic Medical Center, Amsterdam, the Netherlands

12.15 Experimental steatosis treated with omega 3 fatty acids detected by ^{1}H-magnetic resonance spectroscopy (p. 186)

H.A. Marsman[1], S. Nienhuis[1], J. van Werven[2], A(p.)*.J. Nederveen[2], F.J.W. ten Kate[3], M. Heger[1], J. Stoker[2], T.M. van Gulik[1], Dept of Surgery[1], Radiology[2], and Pathology[3], Academic Medical Center, University of Amsterdam, The Netherlands*

12.30 Vitamin A deficiency strongly aggravates liver damage during obstructive cholestasis; acute vitamin A therapy is the cure (p. 187)

M.O. Hoeke, J. Heegsma, A.U. Rehman, H. Moshage and K.N. Faber, Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, the Netherlands

12.45 Dietary soy phytoestrogens cause infertility in UDP-glucuronyltransferase deficient rats (p. 188)

J. Seppen, AMC Liver Center, Amsterdam, the Netherlands

13.00 **Prijsuitreikingen**

Abstract- en posterprijzen DEGH meeting
Basale junior onderzoeker NVH prijs
Klinische junior onderzoeker NVH prijs

Aansluitend ledenvergadering Sectie Experimentele Gastroenterologie van de NVGE

Vrijdag 20 maart 2009

Sectie Endoscopie Verpleegkundigen en Assistenten **Diezezaal**

Ochtendprogramma

10.30 uur	Opening
10.35 - 11.00 uur	SEVA protocollen.
11.00 - 11.25 uur	Uitkomsten van een onderzoek naar colon voorbereiding
11.25 - 11.45 uur	Achtergrond, diagnostiek en behandeling van diverticulose van het colon.
11.45 - 12.10 uur	Diagnostiek en behandeling van diverticulosis en diverticulitis door radioloog.
12.15 - 13.15 uur	Lunchbuffet in de Kempenhal

Middagprogramma

13.30 -14.15 uur	Ledenvergadering
14.20 -14.40 uur	De rol van vezels bij diverticulose en diverticulitis
14.45 -15.05 uur	Operatie indicaties bij diverticulose en diverticulitis *Prof. dr. J.F. Lange, chirurg, Erasmus Medisch Centrum, Rotterdam.*
15.05	Einde programma, thee/koffie in expositiehal

N.B. Bovenstaand programma kan aan wijzigingen onderhevig zijn

Vereniging Maag Darm Leververpleegkundigen **Auditorium**

09.30 Ontvangst met koffie en thee

10.00 Welkomstwoord
Dhr. W. Goverde, voorzitter VMDLV, UMC St. Radboud Nijmegen

10.15 De somatische gevolgen van alcohol op het spijsverteringskanaal. Met name de lever en alvleesklier/alcoholische hepatitis
Prof. dr. P.L.M. Jansen, maag-darm-leverarts, AMC Amsterdam

10.45 Delier; herkennen en behandelen
Dhr. M. Wouters, consultatief verpleegkundige psychiatrie – Canisius Wilhelmina Ziekenhuis, Nijmegen

11.30 *Koffie/theepauze*

11.45 Ledenvergadering
Dhr. W. Goverde, voorzitter VMDLV, UMC St. Radboud Nijmegen

12.15 Jongeren en alcohol
Opzetten van een poli voor jongeren met een alcoholprobleem
Mw. K. de Groot, preventiewerker bij Tactus Verslavingszorg

12.45 *Lunch*

14.00 Alcohol en voeding
Mw. E. Heijkoop, diëtiste, Medisch Centrum Alkmaar

14.30 Motiverende gespreksvoering bij alcoholgerelateerde gezondheids problemen
Mw. G.C.G. Veenboer, hoofdverpleegkundige en
mw. C. Bakhuyzen, verpleegkundige, AMC Amsterdam

Vrijdag 20 maart 2009

14.50 De introductie van het Jellinekspreekuur in het AMC
Mw. J.A. Jenniskens, medisch maatschappelijk werker AMC Amsterdam

15.10 Verslavingszorg en gedragsverandering
Mw. L. ter Braak, sr. preventiewerker en verpleegkundige, Tactus Verslavingszorg

15.30 Afsluiting met daarna mogelijkheid tot borrelen en netwerken
Dhr. W. Goverde, voorzitter VMDLV, UMC St. Radboud Nijmegen

Theme 1. Metabolism *(Limburg Foyer)*, chairs: K.N. Faber en C.C. Paulusma

Time	*Poster #*	*Title*
12:30	**1**	Characterization of liver-specific *Commd1* knock-out mice *W.I.M. Vonk[1,2], B. van de Sluis[1,2,3], P.V.E. van den Berghe[1], P. de Bie[1,2], C.G.K. Wichers[1], R. Berger[1], C. Wijmenga[2,4], L.W.J. Klomp[1], [1]Dept of Metabolic and Endocrine Diseases, University Medical Center Utrecht, and Netherlands Metabolomics Center, the Netherlands[2] Complex Genetics Section, University Medical Center Utrecht, the Netherlands[3] Dept of Pathology and Laboratory Medicine, University Medical Center Groningen, the Netherlands[4] Dept of Genetics, University Medical Center Groningen, the Netherlands*
12:40	**2**	The bile salt-homeostatic hormone FGF19 is highly expressed in the liver of patients with extrahepatic cholestasis. *F.G. Schaap[1], N.A. van der Gaag[2], D.J. Gouma[2], P.L.M. Jansen[1,3] ,Academic Medical Center, [1]AMC Liver Center, Depts of [2]Surgery and [3]Gastroenterology and Hepatology, Meibergdreef [69-71], [1105] BK Amsterdam, The Netherlands*
12:50	**3**	Hepatic glutamine synthesis is necessary for urea synthesis *Y. He, T.B.M. Hakvoort, J.L.M. Vermeulen, M.P.B. Jansen, D.R. de Waart, C. Kunne, W.H. Lamers, AMC Liver Center, Academic Medical Center, University of Amsterdam, Meibergdreef [69-71], [1105] BK Amsterdam, The Netherlands*
13:00	**4**	Lipid-rich enteral nutrition ameliorates postoperative ileus via activation of cholecystokinin-receptors in rats *T. Lubbers[1], M. Luyer[1,2], J. de Haan[1], M. Hadfoune[1], W. Buurman[1], J. Greve[1,3], [1]Dept of Surgery, Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University Medical Center, Maastricht, the Netherlands, [2]Dept of Surgery, Maasland Hospital, Sittard, the Netherlands, [3]Dept of Surgery, Atrium Medical Center, Heerlen, the Netherlands*
13:10	**5**	The regulation of the intestinal mucin MUC2 expression by short chain fatty acids: implications for epithelial protection *N. Burger-van Paassen[1], A. Vincent[2], P.J. Puiman[1], M. van der Sluis[1], J. Bouma[1], G. Boehm[1,3], J.B. van Goudoever[1], I. van Seuningen[2], and I.B. Renes[1], from Dept of Pediatrics, Div. of Neonatology, Erasmus MC-Sophia, Rotterdam, The Netherlands[1], Inserm, U[837], Centre de Recherche Jean-Pierre Aubert, Lille, France[2] and Danone Research Friedrichsdorf, Germany[3]*

Within this theme another 7 posters (without a presentation) have been selected. You can find these abstracts below:

- **6** The effects of protein restriction during gestation on maternal-fetal cholesterol transport and fetal hepatic cholesterol synthesis in mice

E.M.E. van Straten[1], H. van Meer[1]*, J.F.W. Baller[1], T.H. van Dijk[1], T. Plösch[1], F. Kuipers[1,2], H.J. Verkade[1],* Both authors contributed equally to this work, [1]Dept of Pediatrics, Center for Liver, Digestive and Metabolic Diseases, University Medical Center Groningen, University of Groningen, Groningen, Groningen, Netherlands [2]Dept of Laboratory Medicine, Center for Liver, Digestive and Metabolic Diseases, University Medical Center Groningen, University of Groningen, Groningen, Groningen, Netherlands.*

- **7** Acute biliary pancreatitis is associated with enhanced enterohepatic circulation of bile salts in a rat mode

N.G. Venneman[1], J.J.M. ter Linde[1], L.P. van Minnen[2], A. Verheem[2], L.M.A. Akkermans[2], K.J. van Erpecum[1], [1]Dept of Gastroenterology, UMC Utrecht, Utrecht, The Netherlands [2]Dept of Surgery, UMC Utrecht, Utrecht, The Netherlands

- **8** Luminal exposure to preservation solution improves intestinal graft quality during cold storage of rat intestine.

A.M. Roskott, H.G.D. Leuvenink, G. Snoek, G. Dijkstra, R.J. Ploeg, V.B. Nieuwenhuijs., Dept of Surgery, University Medical Center Groningen, University of Groningen, the Netherlands

- **9** Embolization versus ligation of the portal vein to induce hypertrophy of the future remnant liver in a rabbit model

J.W. van den Esschert[1], W. de Graaf[1], K.P. van Lienden[2], T.M. van Gulik[1], Dept of Surgery[1] and Radiology[2], Academic Medical Center Amsterdam, The Netherlands

- **10** Longitudinal study on the pathomechanisms of fibrogenesis/ cirrhosis and growth and regeneration in copper storage disease

R.P. Favier, B. Spee, T.S.G.A.M. van den Ingh, L.C. Penning, J. Rothuizen.,Dept of Clinical Sciences of Companion Animals, PO Box [80154], [3508] TD Utrecht, The Netherlands

- **11** Mice with humanized liver endothelium

E. El Filali, J. Hiralall, R.P.J. Oude Elferink, J. Seppen, AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands

- **12** Effects of fasting on murine cholesterol homeostasis – transcriptomic and lipid profiling

M. Sokolovic[1,2], C.P.A.A. van Roomen[1], A. Gruber[1], S.S. Scheij[1], A. Sokolovic[2], R. Ottenhoff[1], T.B.M. Hakvoort[2], W.H. Lamers[2], A.K. Groen[1], [1]Dept of Medical Biochemistry and [2]AMC Liver Centre, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Theme 2. Pathology *(Limburg Foyer).* Chairs: L. Fabris en J.P.H. Drenth

Time	*Poster #*	*Title*
12:30	**13**	Clinical and genetic heterogeneity in Immune dysregulation, poly-endocrinopathy, enteropathy X linked (IPEX) syndrome. *N.D. Moes[1,2], B. Begue[1], F. Rieux-Laucat[4], N. Cerf-Bensussan[1], A. Fischer[4], O. Goulet[3], E.H.H.M. Rings[2] and F.M. Ruemmele[1,3]., INSERM U[793], Paris, France [1]Dept of Pediatrics, University Medical Center, Groningen, Holland [2]Dept of Gastroenterology, Necker Enfants Malades Hospital, Paris, France [3]Dept of Immunology, Necker Enfants Malades, Hospital, Paris, France [4]*
12:40	**14**	Biomarker Status at Initial Fluorescence in Situ Hybridization (FISH) on Brush Cytology Specimens Can Predict Long-term Outcome in Barrett's Esophagus Patients with High-Grade Dysplasia *W.M. Westra[2,3], G.A. Prasad[3], K.C. Halling[4], S.M. Brankley[4], E. Barr Fritcher[4], T.N. Oberg[4], J.S. Voss[4], M.B. Campion[4], N.S. Buttar[3], L.M. Wong Kee Song[3], L.S. Lutzke[3], K.T. Dunagan[3], L.S. Borkenhagen[3], A.M. Rygiel[2], K.K. Krishnadath[1], K.K. Wang[3], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Netherlands, [2]Barret Esophagus Unit, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA, [3]Dept of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA, [4]Laboratory of Experimental Gastroenterology, Academic Medical Center, Amsterdam, Netherlands*
12:50	**15**	Higher prevalence of CpG island methylator phenotype-positive (CIMP+) status in advanced adenomas detected using colonoscopy for colorectal cancer (CRC) screening *C. Khalid-de Bakker[1], D. Jonkers[1], K.M. Smits[2], W. Hameeteman[1], A.P. de Bruine[2], R. Stockbrügger[1], M. van Engeland[2], A. Masclee[1] ,[1]Gastroenterology and Hepatology, Maastricht University Medical Centre, Maastricht, The Netherlands, [2]Pathology, Maastricht University Medical Centre, Maastricht, Netherlands*
13:00	**16**	Phylogenetic fingerprinting of the faecal microbiota in IBD-patients using the Human Intestinal Tract (HIT)Chip approach: a twin study *D. Jonkers[1], E.G. Zoetendal[2], M. Romberg[3], M. Hesselink[1], W.M. de Vos[2], A. Masclee[1], M. Pierik[1], Division of Gastroenterology-Hepatology[1], Maastricht University Medical center, Laboratory of Microbiology[2], Wageningen University, The Netherlands, Dept of Internal Medicine[3], Maasland Hospital Sittard, The Netherlands*
13:10	**17**	Keratin 19 expression in hepatocellular carcinoma (HCC) is correlated with postoperative tumour recurrence and metastasis markers. *B. Spee[1,2], A. Durnez[1], S. van der Borght[1], O. Govaerde[1], V.J. Desmet[1], S.S. Thorgeirsson[3], T. Roskams[1], [1]Dept of Morphology and Molecular Pathology, University Hospitals Leuven, Leuven, Belgium, [2]Dept of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, The Netherlands, [3]Laboratory of Experimental Carcinogenesis, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, USA*

Within this theme another 9 posters (without a presentation) have been selected. You can find these abstracts below.

- **18** Identification of new Biomarkers for Colon Cancer using Genomics and Proteomics

M. de Wit[1], C.R. Jimenez[1], B. Carvalho[1], S. Piersma[1], R. Lamerichs[2], G.A. Meijer[1], R.J. Fijneman[1], [1]VU University Medical Center Amsterdam, Netherlands, [2]Philips Research, Eindhoven, Netherlands

- **19** Detection of High-Grade Dysplasia and Esophageal Adenocarcinoma using Endoscopic Mucosal Resection in Combination with Fluorescence In Situ Hybridization.

W.M. Westra[2,3], G.A. Prasad[3], K.C. Halling[4], S.M. Brankley[4], E. Barr Fritcher[4], T.N. Oberg[4], J.S. Voss[4], M.B. Campion[4], N.S. Buttar[3], L.M. Wong Kee Song[3], L.S. Lutzke[3], K.T. Dunagan[3], L.S. Borkenhagen[3], A.M. Rygiel[2], K.K. Krishnadath[1], K.K. Wang[3], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Netherlands, [2]Laboratory of Experimental Gastroenterology, Academic Medical Center, Amsterdam, Netherlands, [3]Barrett Esophagus Unit, Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA, [4]Dept of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA

- **20** The role of the IL-6/STAT3/SOCS3 pathway in ulcerative colitis related carcinogenesis

Y. Li[1], M. Chen[2], J.J. Deuring[1], M.M. Gerrits[3], R. Smits[1], B. Xia[4], C. de Haar[1], E.J. Kuipers[1], C.J. van der Woude[1], [1]Gastroenterology and Hepatology Dept, Erasmus Medical Center, Rotterdam, Netherlands, [2]Geriatric Dept, Zhongnan Hospital, Wuhan, China, [3]Clinic Genetics Dept, Academic Hospital, Maastricht, The Netherlands, [4]Gastroenterology Dept, Zhongnan Hospital, Wuhan, China

- **21** Are microRNA-215 and 199a-5p potentially useful biomarkers in the development of Barrett's esophagus and esophageal adenocarcinoma?

J.W.P.M. van Baal[1], F.P. Vleggaar[1], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands

- **22** Vitamin D receptor gene polymorphisms in the 1c promoter region are associated with the risk for erosive esophagitis, Barrett's esophagus and esophageal cancer

A. van de Winkel[1], L.J.W. van der Laan.[2], L.M.G Moons[1], P.P. Arp[3], J.B.J. van Meurs[3], A.G. Uitterlinden[3], E.J. Kuipers[1], [3]Depts of [1]Gastroenterology & Hepatology, [2]Surgery and [3]Internal Medicine, Erasmus MC - University Medical Center Rotterdam, Rotterdam, Netherlands

- **23** The role of Dlk1 in the pathogenesis of hepatoblastoma: results of Dlk1 liver transgenics

F.A. Falix, I.G. Gaemers, D.C. Aronson, W.H. Lamers, AMC levercentrum (ALC)

- **24** The nuclear receptors FXR and PXR are markers for neoplastic progression in patients with Barrett's esophagus

  A. van de Winkel[1], L.J.W. van der Laan[2], K.P.M. van Zoest[1], L.M.G Moons[1], H. van Dekken[3], E.J. Kuipers[1], Depts of [1]Gastroenterology & Hepatology, [2]Surgery and [3]Pathology, Erasmus MC - University Medical Center Rotterdam, Rotterdam, Netherlands

- **25** Multiple genes on 20q amplicon have a functional role in colorectal cancer progression

  A.H. Sillars-Hardebol, B. Carvalho, M. Tijssen, J.A.M. Beliën, M. de Wit, P. Delis-van Diemen, R.J.A Fijneman and G.A. Meijer, VU University Medical Center, Dept. of Pathology (Tumor Profiling), Amsterdam, The Netherlands

- **26** Verification and Unmasking of Human Esophageal Adenocarcinoma Cell Lines

  J.J. Boonstra[1], R. van Marion[2], D.G. Beer[3], N.K. Altorki[4], J.S. Darnton[5], Y. Shimada[6], H.W. Tilanus[1], W.N.M. Dinjens[2], [1]Surgery and [2]Pathology, Erasmus Medical Center, Rotterdam, Netherlands, [3]Thoracic Tumor Biology Laboratory, University of Michigan, Ann Arbor, USA, [4]Surgery, Cornell University Medical College, New York, USA, [5]Thoracic Surgery, Birmingham Heartlands Hospital, Birmingham, UK, [6]Surgery, University of Toyama, Toyama, Japan

Theme 3. Cell Biology *(Meierij Foyer)*, chairs: G. Hansson en A.A. te Velde

Time	*Poster #*	*Title*
12:30	**27**	Characterization of mutations causing ATP8B1 deficiency and pharmacological restoration of ATP8B1 abundance and cell surface expression

L.M. van der Velden[1],, J.M. Stapelbroek[1],[2],*, E. Krieger[3], P.V.E. van den Berghe[1], R. Berger[1], J.C.M. Holthuis[4], R.H.J. Houwen[2], L.W.J. Klomp[1]# and S.F.J. van de Graaf[1]#, [1]Dept of Metabolic and Endocrine Diseases, UMC Utrecht and Netherlands Metabolomics Centre, Utrecht, The Netherlands, [2]Depts of Paediatric Gastroenterology, UMC Utrecht, Utrecht, The Netherlands, [3]YASARA Biosciences & CMBI Outstation Austria, Graz, Austria, [4]Dept of Membrane Enzymology, Bijvoet Center and Institute of Biomembranes, Utrecht University, The Netherlands *,# Contributed equally*

12:40	**28**	CDC50A, a common interaction partner of several P_4 P-type ATPases, is required for proper localization and expression of ATP8B1 and ATP8A1

L.M. van der Velden[1], A.E.D. van Breevoort[1], J.M. Stapelbroek[3], E.A. van Beurden[1], R.H.J. Houwen[3], P.M. Verhulst[2], J.C.M. Holthuis[2], L.W.J. Klomp[1], [1]Dept of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, the Netherlands [2]Dept of Membrane Enzymology, Bijvoet Center and Institute of Biomembranes, Utrecht University, the Netherlands [3]Dept of Pediatrics, UMC Utrecht, The Netherlands

12:50 **29** The 70 kDa peroxisomal membrane protein is involved in the activetion of rat hepatic stellate cells

J. Woudenberg, F.A.J. van den Heuvel, K.P. Rembacz, S. Dunning, T.E. Woudenberg - Vrenken, M. Buist-Homan, H. Moshage, and K.N. Faber, Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

13:00 **30** Hepatitis-induced accumulation of catalase in the cytosol protects hepatocytes against oxidative stress

A. Pellicoro[1], F.A.J. van den Heuvel[1], S. van der Borght[2], P.L.M. Jansen[3], H. Moshage[1], T.A.D. Roskams[2] and K.N. Faber[1], [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, University of Groningen, The Netherlands, [2]Dept of Pathology, University of Leuven, Leuven, Belgium. [3]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

13:10 **31** Caveolin-1 is enriched in the peroxisomal membrane in rat hepatocytes

J. Woudenberg[1], F.A.J. van den Heuvel[1], K.P. Rembacz[1], T.E. Woudenberg-Vrenken[1], M. Buist-Homan[1], L.E. Deelman[2], R.H. Henning[2], H. Moshage[1] and K.N. Faber[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Within this theme another 8 posters (without a presentation) have been selected. You can find these abstracts below.

- **32** Stable overexpression of pregnane X receptor in hepatoma cell line HepG2: evaluation of a new cell line for bioartificial liver application

G.A.A. Nibourg[1,2], M.T. Huisman[3], T.V. van der Hoeven[1,2], T.M. van Gulik[1], R.A.F.M. Chamuleau[2], R. Hoekstra[1,2], [1]Surgical Laboratory, AMC Amsterdam, [2]AMC Liver Center, Amsterdam, [3]Johnson and Johnson, Beerse, Belgium

- **33** Development of a FRET-based sensor for intracellular FXR ligand detection.

M.V. Golynskiy[1], S.W.C. van Mil[3], E.C.L. Willemsen[3], E.W. Meijer[2], L.W.J. Klomp[3], M. Merkx[1], [1]Dept of Biomedical Engineering and [2]Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, Eindhoven, The Netherlands, [3]Laboratory of Metabolic and Endocrine Diseases and Netherlands Metabolomics Centre, UMC Utrecht, The Netherlands

- **34** Promoter hypermethylation of *PHACTR3*, a potential new biomarker for colorectal cancer detection

L. Bosch[1], M. Neerincx[2], F. Oort[2], S. Mongera[1], A. Masclee[3], D. Jonkers[3], C. Khalid- de Bakker[3], K. Bierau[4], J. Louwagie[4], W. van Criekinge,[4] A. de Bruïne[5], M. van Engeland[5], C. Mulder[2], B. Carvalho[1], G. Meijer[1] ,[1]Dept of Pathology and [2]Gastroenterology, VU University Medical Center, Amsterdam; [3]Dept of Internal Medicine, Divison of Gastroenterology & Hepatology, and [5]Dept of Pathology, Maastricht University Medical Center, Maastricht; [4]OncoMethylome Sciences, SA, Leuven, Belgium

- **35** The phenotypical and functional characteristics of bone marrow derived Mesenchymal Stem Cells from patients with refractory Crohn's Disease

M. Duijvestein[1], M.E. Wildenberg[1], B.B. Wendrich[1], A.C.W. Vos[1], A.P. Verhaar[1], H. Roelofs[2], W. E. Fibbe[2], G.R. van den Brink[1], D.W. Hommes[1] ,[1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center (LUMC), Leiden [2]Dept of Immunohematology and Blood Transfusion, Leiden University Medical Center (LUMC), Leiden

- **36** ATP8B1-depleted intestinal epithelial cells display apical membrane aberrations unrelated to flippase activity

L.M. van der Velden[1,7], P.M. Verhulst[2,7], V. Oorschot[3], E.E. van Faassen[4], J. Klumperman[3], R.H.J. Houwen[5], T. Pomorski[6], J.C.M. Holthuis[2,8], L.W.J. Klomp[1,8], [1]Dept of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, The Netherlands, [2]Dept of Membrane Enzymology, Bijvoet Center and Institute of Biomembranes, Utrecht University, The Netherlands, [3]Cell Microscopy Centre, Dept of Cell Biology, Institute of Biomembranes, University Medical Centre Utrecht, The Netherlands[4]Faculty of Science, Dept of Interface Physics, Utrecht University, The Netherlands, [5]Dept of Pediatrics, UMC Utrecht, The Netherlands, [6]Institute of Biology/ Biophysics, Humboldt University Berlin, Germany[7], These authors contributed equally to this work[8]

- **37** Wnt and Notch signalling pathways are upregulated in activated liver progenitor cell niches in a dog model of highly fibrotic liver disease

B.A. Schotanus[1], L.C. Penning[1], T.A. Roskams[2], S. VanderBorght[2], T.S.G.A.M. van den Ingh[3], J. Rothuizen[1], B. Spee[1,2], [1]Dept of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, The Netherlands, [2]Dept of Morphology and Molecular Pathology, University of Leuven, Leuven, Belgium[3] TCCI Consultancy BV, PO Box 8503, 3508 AA Utrecht, The Netherlands

- **38** Insulin-like growth factor binding protein-5 enhances survival of LX-2 human hepatic stellate cells

A. Sokolovic and P. Bosma, AMC Liver Centre, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

- **39** Expression of bile salt and ATP-binding cassette transporters in human livers with fibrosing cholestatic hepatitis secondary to recurrent hepatitis

CH. Blokzijl[1], S. Vander Borght[2], F. Nevens[3], L. Libbrecht[2], P.L.M. Jansen[3], K.N. Faber[1] and T.A.D. Roskams[2], [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands, [2]Dept of Morphology and Molecular Pathology and [3]Hepatology, University of Leuven, Belgium, [4]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

Theme 4. Immunology *(Meierij Foyer)*, chairs: A.M. Mowat en R. van Tol

Time	*Poster #*	*Title*
12:30	**40**	Acetylcholine enhances macrophage phagocytosis and induces inflamematory anergy via distinct nAChR subunits. *E.P. van der Zanden[1], G.E. Boeckxstaens[1,2], K. Lee[3], W.J. de Jonge[1], [1]Dept. of Gastroenterology, Academical Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, Catholic University Leuven, Leuven, Belgium, [3]Immuno Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline, Stevenage, United Kingdom*
12:40	**41**	CD34-derived myeloid dendritic cell development requires intact PI3K-PKB- mTOR signalling *L. van de Laar[1], M. Buitenhuis[2], H.L.A. Janssen[1], P.J. Coffer[2,3], A.M. Woltman[1], [1]Gastroenterology and Hepatology, Erasmus MC, Rotterdam, , [2]Immunology, UMC Utrecht, Utrecht, The Netherlands, [3]Pediatrics, UMC Utrecht, Utrecht, The Netherlands*
12:50	**42**	Altered phenotype and function of natural killer cells in chronic hepatitis B *E.T.T.L Tjwa, G.W. van Oord, H.L.A. Janssen and A.M. Woltman,Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands*
13:00	**43**	Mast cell induced bacterial translocation in the pathogenesis of postoperative ileus *S.A. Snoek[1], O.I. Stanisor[1], O. Welting[1], C. van 't Veer[2,3], R.M. van den Wijngaard[1], G.E. Boeckxstaens[1,3], W.J. de Jonge[1], [1]Dept of Gastroenterology and Hepatology, AMC, Amsterdam, [2]Center for Infection and Immunity Amsterdam, AMC, Amsterdam, [3]Center for Experimental and Molecular Medicine, AMC, Amsterdam, [4]Dept of Gastroenterology, University Hospitals Leuven, Catholic University of Leuven, Leuven*
13:10	**44**	Innate defense responses in Muc2 deficient mice: an important role for goblet cells *N. Burger-van Paassen[1], J. Bouma[1], A.C.J.M. de Bruijn[1], M. van der Sluis[1], I. van Seuningen[2], J.B. van Goudoever[1], I.B. Renes[1], [1]Pediatrics, division of Neonatology, Erasmus MC-Sophia, Rotterdam, Netherlands,[2] Team [5], Inserm U[837], Centre de Recherche Jean-Pierre Aubert, Lille, France*

Within this theme another 9 posters (without a presentation) have been selected. You can find these abstracts below.

-	**45**	FXR activation represses TNFα-induced NF-κB signalling. *R.M. Gadaleta[1,2,4], K.J. van Erpecum[1], B. Oldenburg[1], M. Spit[2], E. Willemsen[2], W. de Jager[3], L.W.J. Klomp[2], P.D. Siersema[1], A. Moschetta[4], S.W.C. van Mil[2]. ,[1]Dept of Gastroenterology and Hepatology, [2]Laboratory of Metabolic and Endocrine Diseases and Netherlands Metabolomics Centre, [3]Dept of Pediatric Immunology, University Medical Center Utrecht, Utrecht, The Netherlands [4]Laboratory of Lipid Metabolism and Cancer, Consorzio Mario Negri Sud, S.ta Maria Imbaro (Ch), Italy*

- **46** Role of multiple regulatory T cell populations in controlling peripheral blood and liver immunity to human hepatitis C virus infections.

M.A.A. Claassen, R.J. de Knegt, D. Turgut, Z.M.A. Groothuismink, H.L. Janssen, A. Boonstra., Afdeling Maag-, Darm- en Leverziekten, Erasmus MC - Universitair Medisch Centrum Rotterdam

- **48** ATG16L1 and IRGM knock-down results in pro-inflammatory dendritic cells

M.E. Wildenberg, A.C.W. Vos, M. Duijvestein, A.P. Verhaar, G.R. van den Brink and D.W. Hommes, Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

- **49** TGF-β and retinoic acid induced expression of CD38 on T cells reflects mucosal imprinting

M.F. du Pré[1], L.A. van Berkel[1], F. Broere[2], M.N. ter Borg[1], F. Lund[3], G. Kraal[4], E.E.S. Nieuwenhuis[1], J.N. Samsom[1], [1]Dept. of Pediatrics, Erasmus MC – Sophia Children's Hospital, Rotterdam, [2]Div. of Immunology, Institute of Infectious Diseases and Immunology, Utrecht University, Utrecht, [3]Trudeau Institute, Saranac Lake, NY, USA, [4]Dept. of Molecular Cell Biology and Immunology, VUMC, Amsterdam

- **50** T cells primed by TLR-stimulated human plasmacytoid dendritic cells inhibit allogeneic memory T-cell responses

P.P.C Boor[1], H.J. Metselaar[1], S. de Jonge[1], L.J.W. van der Laan[1,2], J. Kwekkeboom[1], Depts of [1]Gastroenterology and Hepatology, and [2]Surgery, Erasmus MC - University Medical Center, Rotterdam, The Netherlands

- **51** Aquaporine 8: a new histological marker for colonic inflammation in Crohn's Disease?

S.C.S. Wolfkamp[1], P.C.F. Stokkers[2], E.W.M. Vogels[2], N.L.H. Bekkali[2], F.J.W. ten Kate[3], A.A. te Velde[1], [1]Center for Experimental Molecular Medicine, Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Pathology Dept, Academic Medical Center, Amsterdam

- **52** Liver-uptake of interleukin-6 in humans during liver resection

S.A.W.G. Dello[1], J.G. Bloemen[1], M.C.G van de Poll[1], J.H.M.B. Stoot[1], M. van den Broek[1], V. Lai Nguyen[1], S.W.M. Olde Damink[1], W.A. Buurman[1], C.H.C. Dejong[1], [1]Dept of Surgery, Maastricht University Medical Center & Nutrim School for Nutrition, Toxicology and Metabolism. Maastricht University, Maastricht, The Netherlands

- **53** Resistance to Toll-like receptors stimulation-induced cell death in peripheral blood monocytes from Crohn's disease patients

A. Leshed, Z. Zelinkova, H.J. Verhoog, E.J. Kuipers, C.J. van der Woude, Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre, Rotterdam, the Netherlands

Theme 5. Therapy *(Meierij Foyer)*, chairs: E.H.H.M. Rings en G. Bouma

Time	*Poster #*	*Title*
12:30	**54**	Coagulation and fibrinolysis in cholestatic patients and the effect of preoperative biliary drainage *J.J. Kloek[1], N.A. van der Gaag[1], M. Heger[1], T.M. van Gulik[1], D.J. Gouma[1], M. Levi[2], Depts of ([1]) Surgery and ([2]) Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands*
12:40	**55**	Effective treatment of Unconjugated Hyperbilirubinemia with the Laxans Polyethylene Glycol in Gunn rats *F.J.C. Cuperus*, A.A. Iemhoff*, R. Havinga*, and H.J. Verkade.*,*Pediatric Gastro-enterology, Dept of Pediatrics, Center for Liver, Digestive, and Metabolic Diseases, University Medical Center Groningen, Groningen, The Netherlands*
12:50	**56**	Radioimmunotherapy improves survival of rats with microscopic liver metastases of colorectal origin *G.M. de Jong, T. Hendriks, W.J.G. Oyen[1], S. Heskamp[1], A. Eek[1], O.C. Boerman[1] and R.P. Bleichrodt ,Radboud University Nijmegen Medical Centre, the Netherlands Depts of Surgery and Nuclear Medicine[1]*
13:00	**57**	Radioimmunotherapy prevents local recurrence of colon cancer in rats *G.M. de Jong, T. Hendriks, W.J.G. Oyen[1], F. Aarts, R.P. Bleichrodt, O.C. Boerman[1], Radboud University Nijmegen Medical Centre, The Netherlands, Depts of Surgery and Nuclear Medicine[1]*
13:10	**58**	Prebiotics and butyrate to improve intestinal anastomotic strength; friend or foe? *J.G. Bloemen[1], M.H.F. Schreinemacher[1], K. Venema[2], M.J.J. Gijbels[3], J. Cleutjens[3], W.A. Buurman[1], N.D. Bouvy[1], C.H.C. Dejong[1], [1]Algemene Heelkunde, Maastricht University Medical Centre, Maastricht, [2]Pathologie, Maastricht University Medical Centre, Maastricht, [3] TI Food & Nutrition, Wageningen*

Within this theme another 5 posters (without a presentation) have been selected. You can find these abstracts below.

-	**59**	Iron supplementation allows rescue of Helicobacter species from bismuth toxicity *J. Stoof[1], A.H.M. van Vliet[2], E.J. Kuipers[1] ,[1]) Dept of Gastroenterology and Hepatology, Erasmus MC - University Medical Center, 's Gravendijkwal [230], [3015] CE Rotterdam, The Netherlands [2]) Institute of Food Research, Norwich NR[4] [7]UA, United Kingdom*
-	**60**	Role of probiotics on intestinal barrier function: effect of *Lactobacillus* GG on mucin MUC2 expression *N. Burger-van Paassen[1], J. Bouma[1], G. Boehm[2], J.B. van Goudoever[1], I. van Seuningen[3], I.B. Renes[1],[1] Dept of Pediatrics, Div. Of Neonatology, Erasmus MC-Sophia, Rotterdam, The Netherlands[2] Danone Research, Friedrichsdorf, Germany[3] Inserm, U[837], Centre de Recherche Jean-Pierre Aubert, Lille, France*

- **61** Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission

H.M. Hamer[1,2], D.M.A.E. Jonkers[1,2], S. Vanhoutvin[1,2], F.J. Troost[1,2], G. Rijkers[3], A. de Bruïne[4], A. Bast[5], K. Venema[1,6], R.J.M. Brummer[1,2], [1]TI Food and Nutrition, Wageningen, The Netherlands, [2]Dept of Internal Medicine, Division of Gastroenterology-Hepatology, Nutrim, Maastricht University Medical Centre, The Netherlands, [3]Medical Microbiology and Immunology, St. Antonius hospital, Nieuwegein, The Netherlands, [4]Dept of Pathology, Maastricht University Medical Centre, The Netherlands, [5]Dept of Pharmacology and Toxicology, Nutrim, Maastricht University Medical Centre, The Netherlands, [6]TNO Quality of Life, Dept of Biosciences, Zeist, the Netherlands

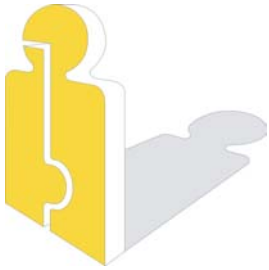
- **62** Systemic administration of lidocaine does not improve liver function after hepatic ischemia-reperfusion injury combined with partial liver resection

W. de Graaf[1], G.M.P. Diepenhorst[1], D. Erdogan[1], M.W. Hollmann[2], T.M. van Gulik[1], [1]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Anaesthesiology, Academic Medical Center, Amsterdam, The Netherlands

- **63** Hepatic effects of flunixin meglumine in endotoxemic rats

A. ACCO[1], T.V. Ávila[1], A.L.B. Pereira[1], A.O. Christoff[1], D. Lugarini[1], J.G. da Siva[1], G.J. Eler[2], A. Bracht[2] , [1]Federal University of Paraná – Curitiba – PR – Brasil, [2]University of Maringá – Maringá – PR - Brazil

Abstracts




Nederlandse
Vereniging voor
Hepatologie


NVGIC
GastroIntestinale
Chirurgie

Losses of chromosome 5q and 14q mark a subset of gastric cancers with good clinical outcome

T.E. Buffart[1], B. Carvalho[1], N.C. Van Grieken[1], W.N. Van Wieringen[2], M. Tijssen[1], E. Klein Kranenbarg[3], H. Grabsch[4], B. Ylstra[1], C.J. Van de Velde[3], G.A. Meijer[1], [1]VU University Medical Center Amsterdam, Amsterdam, Netherlands; [2]Vrije Universiteit, Amsterdam, Netherlands; [3]Leiden University Medical Center, Leiden, Netherlands; [4]Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds, United Kingdom

To improve clinical outcome of gastric cancer patients, most emphasis is on improving therapeutic regimens, including more extensive surgery as well as (neo)adjuvant chemo-therapy. Thepresent study set out to identify, based on genome wide DNA copy number profiling, subgroupsof patients, who are not likely to benefit from intensified therapy. DNA of 206 gastric cancer patients was isolated and analyzed by genomewide array comparative genomic hybridization. DNA copy number profiles were evaluated and correlated to lymph node status and survival. Frequent (>20%) DNA copy number gains were observed on chromosomes 1p, 6p, 7p,7q, 8q, 11q, 12q, 13q, 16p, 16q, 17q, 19p, 19q, 20p, 20q, 21q and 22q, and losses on chromosomes4p, 4q, 6p, 6q, 9p, 13q and 21q. Lymph node negative gastric cancers showed significantly morelosses on chromosomes 5q11.2-q35.1, 10q11.23-q21.3 and 14q32.11-q32.33. In addition, losses on5q11.2-q31.3 and 14q32.11-q32.33 were highly correlated to good clinical outcome, in both lymphnode negative and positive gastric cancer patients. Conclusion: By genome wide DNA copy number profiling we have identified a subgroup of gastriccancers, marked by losses on chromosomes 5q11.2-q31.3 and 14q32.11-q32.33 that have an excellentclinical outcome after surgery alone, and patients with these tumors are unlikely to benefit fromadditional intensified therapies. Possible biological mechanisms might involve loss of heat shockproteins located at these chromosomal regions.

Grading and staging gastritis with the OLGA system: intestinal metaplasia as a reproducible alternative

L.G. Capelle[1], A.C. de Vries[1], J. Haringsma[1], F. ter Borg[2], R. de Vries[3], M. Bruno[1], H. Van Dekken[4], J. Meijer[5], N.C.T. Van Grieken[6], E.J. Kuipers[1, 7],[1]Depts of Gastroenterology and Hepatology, [4]Pathology, and [7]Internal Medicine, Erasmus MC University Medical Center, Rotterdam, [2]Dept of Hepato-gastroenterology, Deventer Hospital, Deventer, [3]Dept of Internal Medicine, University Medical Center, Groningen, [5]Dept of Pathology, Rijnstate Hospital, Arnhem, [6]Dept of Pathology, VU University Medical Center, Amsterdam, the Netherlands

The recently proposed (Operative Link for Gastritis Assessment) OLGA staging system is based on the extent and severity of atrophic gastritis (AG) and provides relevant clinical information regarding gastric cancer risk. However, AG is a difficult histopathological diagnosis of which the interobserver agreement is low. In contrast, intestinal metaplasia (IM) has better defined specific histopathological features and is associated with a much better interobserver agreement. The aim of this study was to evaluate interobserver agreement for AG, IM and dysplasia (DYS) and to assess whether a staging system based on IM instead of AG may be preferred to estimate gastric cancer risk. In a prospective multicenter study, patients with IM and DYS underwent surveillance endoscopy with extensive biopsy sampling. Three expert pathologists graded biopsy specimens according to the updated Sydney classification and the Vienna classification. Interobserver variation for these classifications was analysed by kappa (K) statistics. In the OLGA staging system AG was replaced by IM creating the IM staging system. Both classifications were evaluated for patient distribution and severe pre-malignant gastric lesions by stage. In total, 125 patients (69 men and 56 women) with a mean (± SD) age of 61 ±11.7 years (range 23-81 years) were included in this study. DYS was diagnosed in 7 (6%) patients. For DYS interobserver variability was fair (K=0.4; low grade DYS K=0.2; and high grade DYS K=0.5). The interobserver agreement was moderate for AG (K=0.6), whereas agreement was almost perfect for IM (K=0.9). Overall, 83 (66%) patients were classified in stage I-IV according to the OLGA staging system (stage I n=23; stage II n=29; stage III n=23; stage IV n=8) and 80 (64%) patients were classified in stage I-IV according to the IM staging system (stage I n=24; stage II n=25; stage III n=22; stage IV n=9). Of the dysplasia patients, 5 (71%) patients clustered in stage III-IV in the OLGA system, whereas 6 (86%) patients clustered in III-IV of the IM staging system.

Conclusions: Replacement of AG by IM in the staging and grading of gastritis increases interobserver agreement considerably. Moreover, the correlation with the severity of gastritis remains at least as effective as the OLGA classification. Therefore, the intestinal metaplasia staging may be preferred over the OLGA system for the prediction of gastric cancer risk in patients with pre-malignant gastric lesions.

Changes in overuse and underuse of prophylactic strategies with NSAID treatment over the past decade; further improvement is needed

V.E. Valkhoff[2,1], E.M. van Soest[1], M.C.J.M. Sturkenboom[1,4], E.J. Kuipers[2,3], [1]Medical Informatics, Erasmus Medical Centre, Rotterdam, The Netherlands; [2]Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands; [3]Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands; [4]Epidemiology and Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands

To reduce the risk of gastrointestinal (GI) complications associated with non-steroidal anti-inflammatory drugs (NSAIDs), preventive strategies such as co-prescription of gastroprotective agents (GPAs) are advocated in patients at high risk.
To evaluate trends in use of preventive strategies in naive NSAID users, a population-based cohort study was conducted within the Integrated Primary Care Information database (1996-2006). The study population comprised naive NSAID users > 50 yrs. Considered preventive strategies were:
1) co-prescription of GPAs (H2-receptor antagonists, misoprostol, or proton pump inhibitors), 2) use of a cyclooxygenase-2-specific inhibitor (coxib). Patients who used GPA six months prior NSAID start were excluded. A history of GI bleeding/ulceration, concomitant use of anticoagulants, aspirin or oral corticosteroids and age > 65 yrs were identified as risk factors. Correct utilization was defined either as the use of a preventive strategy in patients with at least one risk factor, or as the absence of a preventive strategy in patients without risk factors. Underuse was defined as the absence of a preventive strategy in patients with at least one risk factor, and overuse as the presence of a preventive strategy in patients without risk factors. The study population comprised 32,660 NSAID users. Correct utilization increased from 52% in 1996 to 62% in 2006 (R^2=0.87, linear trend $p<0.01$). Underutilization decreased from 44% to 22% (R^2=0.97, linear trend $p<0.01$). Overutilization increased from 3.6% tot 15.8% (R^2=0.94, linear trend $p<0.01$). Of all NSAID users, the majority (85%) used non-specific NSAIDs. After the introduction of coxibs, their use increased up till 2004 and comprised 18% of all NSAIDs (rofecoxib: 82%). After the withdrawal of rofecoxib in Sept 2004, the coxib prescription rate decreased to 6.7% in 2006. The decrease in coxib use was not accompanied by an increase in underuse or decrease in correct use of preventive strategies.
Conclusions: Correct use of preventive strategies to reduce the risk of NSAID-associated GI complications has increased over the past ten years, up to 62% in 2006. Over this period, also an increasing trend in overuse was seen. Underuse decreased, but in 2006 still occurred in 22% of patients with risk factors. The withdrawal of rofecoxib in 2004 did not influence the overall trend of increasing correct use.

Underutilization of proton pump inhibitors in short-term NSAID users in a large population in the Netherlands

O.S. van Boxel[1], M.P. Hagenaars[2], A.J.P.M. Smout[1] and P.D. Siersema[1], [1]University Medical Centre Utrecht, the Netherlands[2] Achmea Health Insurance, Leiden, the Netherlands

Introduction: NSAIDs are amongst the most frequently prescribed drugs worldwide. Although adequate gastroprotection is indicated in high-risk patients, underutilization of preventive strategies has been demonstrated in patients receiving NSAIDs on a long-term basis. Thus far, it has not been studied whether this is also true for short-term NSAID users.Aim: To investigate the utilization of PPIs in high-risk short-term NSAID users in a large population in the Netherlands and to assess the association between risk factors and PPI use.Methods: Data were collected from a database of a large Dutch health insurance company covering 2,8 million subjects. Short-term use was defined as an isolated period of NSAID use between 7 to 30 days in 2007. The presence of risk factors for gastrointestinal complications was identified for each subject during the 1-year history period or at the index date. These included age >65 years, history of upper gastrointestinal events, and concurrent use of corticosteroids, aspirin or anticoagulants. Gastroprotective drugs of interest included all available PPIs in the Netherlands, co-prescribed with the NSAID. Logistic regression was performed to determine risk factors associated with PPI use. Results: A total of 155,825 short-term NSAID users were identified. Of these, 116,976 (75.1%) patients had no risk factors and, therefore, no gastroprotection was indicated. However, 37,547 subjects had 1 or 2 risk factors for NSAID-related gastropathy, of whom 21,282 (56.7%) received no PPI prescription. Of the patients with 3 or more risk factors, 448 subjects (34.4%) did not take adequate gastroprotection. In the multivariable analysis, positive predictors for using gastroprotective measures in short-term NSAID use included older age (>65 years) [OR 19.00, CI 17.50-20.63], history of reflux disease [OR 6.49, CI 5.34-7.88], peptic ulcer bleeding [OR 2.20, CI 1.70-2.85] and/or diabetes [OR 1.31, CI 1.27-1.36], concurrent use of selective serotonin reuptake inhibitors [OR 3.87, CI 3.68-4.08] and/or aspirin [OR 2.05, CI 1.96-2.14] and female gender [OR 1.25, CI 1.22-1.27].
Conclusion: although individuals at a higher risk of NSAID-associated ulcer complications have higher odds for receiving a preventive strategy, adequate gastroprotection with PPIs is not provided to more than 50% of NSAID users. Education of physicians and patients on the risks associated with short-term NSAID use and the importance of adherence to the guidelines is indicated.

Premalignant gastric lesions in patients with gastric MALT lymphoma and metachronous gastric carcinoma: a case-control study

C.M. den Hoed[1], L.G. Capelle[1], K. Biermann[3], M.K. Casparie[4], E.J. Kuipers[1,2], Depts of [1]Gastroenterology and Hepatology, [2]Internal Medicine, and [3]Pathology, Erasmus MC University Medical Center, Rotterdam, Netherlands, [4]Foundation PALGA, Utrecht, the Netherlands

Patients with gastric MALT lymphoma (gMALT) have an increased risk of developing gastric carcinoma (GC). Identifying gMALT patients at high GC risk may lead to improved survival and prognosis. The aim of this case-control study was to evaluate whether the premalignant gastric lesions, atrophic gastritis (AG), intestinal metaplasia (IM) and dysplasia (DYS), can be identified in gMALT patients and whether these lesions are more severe in gMALT patients with a subsequent diagnosis of GC. Patients with a first diagnosis of gMALT between 1991 and 2006 were identified in the Dutch nationwide histopathology registry (PALGA). Cases were patients with a diagnosis of gMALT and a subsequent diagnosis of GC. Per case, one to three controls with a diagnosis of gMALT without a subsequent diagnosis of GC were identified, matched for age, sex and follow-up (fu). The histopathology of these cases and controls was retrieved and evaluated by an expert pathologist. AG, IM and DYS were scored according to the updated Sydney classification. In total 7 cases (M/F 2/5; mean age 69.3 yrs, 48-87 yrs; mean fu 4.8 yrs, 1.1-6.1 yrs) and 10 controls (M/F 5/5; mean age 67.7 yrs 46-86 yrs; mean fu 5.9 yrs, 1.2-10 yrs) were included. At gMALT diagnosis, 5 (71%) cases had histological signs of premalignant gastric lesions; AG N=1 (14%), IM N=2 (29%), DYS N= 2 (29%). In the control group, 7 (70%) had histological evidence for premalignant gastric lesions; AG N=1 (10%), IM N=4 (40%), DYS N= 2 (20%) at gMALT diagnosis. At GC diagnosis, 6 (86%) cases showed premalignant lesions in the surrounding gastric mucosa; IM N=3 (43%), DYS N= 3 (43%). In 8 (80%) of the controls premalignant lesions were present at the end of follow up AG N=1 (10%), IM N=4 (40%), DYS N= 3 (30%). All cases (100%) showed progression to GC, whereas 2 (20%) controls showed progression from AG to IM and from IM to DYS and 2 (20%) controls showed regression from AG to normal mucosa. Conclusions: No differences were demonstrated in severity of premalignant gastric lesions of cases and controls at gMALT diagnosis or at end of follow-up. Surprisingly, premalignant gastric lesions were common in both cases and controls. Gastric dysplasia was demonstrated in 24% at gMALT diagnosis and in even more (35%) patients at the end of follow-up. This indicates that endoscopic and histopathologic surveillance with specific attention to the severity of premalignant gastric lesions after diagnosis and treatment of gMALT is highly warranted.

Abdominal Migraine, a new and treatable disorder mimicking functional dyspepsia

M. Bigirwamungu-Bargeman[1], R.H. Geelkerken[2], A.B. Huisman[3], J.J. Kolkman[1], Depts of [1]Gastroenterology, [2]Vascular Surgery and [3]Radiology, Medical Spectrum Twente, Enschede, the Netherlands

Introduction: Non occlusive mesenteric ischemia (NOMI) is characterized by gastrointestinal ischemia despite normal splanchnic vessels. It is often seen in the ICU and OR, and frequently accompanies cardiac failure. In our centre, a referral centre for gastrointestinal ischemia, we use a standard work-up including duplex ultrasound, angiography and gastrointestinal tonometry. In the last 10 years we encountered a subgroup of NOMI patients with unexplained upper abdominal complaints, ischemia on tonometry and normal vessel investigations. In two of these patients vasospasm was noted during angiography, suggesting a 'migraine-like disorder'. Methods: From the cohort of patients analyzed for gastrointestinal ischemia we selected patients with a history suiting splanchnic ischemia, ischemia on tonometry and normal vessels during angiography. When other causes were sufficiently excluded we treated these patients with a sequence of vasodilating drugs. The order was: nitrates, ketanserin, nicorandil and doxazosin. A new drug was started when the complaints remained unchanged after 4-8 weeks or when severe side-effects occurred. A positive response was recorded when the pain severity decreased by >50%.Results: From 1997 to 2008 we analyzed 829 patients. In 333 chronic mesenteric ischemia was found, 150 had asymptomatic vascular stenoses, 278 had normal vessels and no ischemia. In 70 pts ischemia was found with normal vessels; 44 suited our definition of abdominal migraine. Symptomatology included: pain after meals (73%), weight loss (68%) and dyspeptic complaints (30%). Treatment was given to 35 patients (10M/25F, mean age 53 years). A positive response was seen after isosorbide dinitrate in 43%, after ketanserin in 53%, after nicorandil in 43% and after doxazosin in 14%. Side-effects were common and included head-ache, and dizziness. In 63% at least one of these medications resulted in pain reduction >50%. The pain reduction was sustained during follow up of mean 2.5 years (range 0.2-8). Conclusion: By using tonometry we identified patients with GI ischemia, despite normal vessel anatomy. In 63% vasodilating drugs reduced pain, the effect was sustained on follow-up. This condition is probably caused by vasoconstriction in the small vessels, and thus indicate abdominal migraine; further studies are needed to assess the prevalence, mechanisms and optimal treatment.

Short term efficacy of the new D-Weave Niti-S™ stent in malignant gastric outlet obstruction: results of the first European prospective, multicenter study

J.E. van Hooft[1], S.M. Jeurnink[2], M.J. Bruno[1], M. Dijkgraaf[3], P.D. Siersema[2], P. Fockens[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [3]Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, The Netherlands

Introduction: Gastric outlet obstruction (GOO) is a late complication of advanced gastric, periampullary and duodenal malignancies. Palliation of symptoms of obstruction is the primary aim of treatment in these patients. Self-expandable metal stents (SEMS) have emerged as a promising treatment option. Methods: This prospective multicenter study investigates the safety and efficacy of a new enteral stent, the D-Weave Niti-S™ stent (Taewoong Medical, Seoul, Korea), in patients with symptomatic malignant gastro-duodenal obstruction due to incurable malignancy. In case of common bile duct obstruction, biliary drainage with metal stents was achieved prior to stenting. Patient characteristics, GOOSS-score (Gastric Outlet Obstruction Scoring System, a 4-point scoring system from 0 (no oral intake) to 3 (normal diet)), general condition (Body Mass Index (BMI) and WHO performance status), additional therapy (chemotherapy, radiotherapy) and quality of life questionnaires were collected prior to enteral stent placement. Procedure-related data were recorded by the treating physician. Follow-up data were prospectively collected by telephone on a two-weekly basis until patients' death. As this study is descriptive by nature, no formal power calculation could be done. Because follow-up has not yet been fully completed, we now report the changes of the GOOSS-score at 7 and 30 days after stent placement, technical success, time until resuming of oral intake and stent-related complications within 30 days. Results: A total of 52 patients were included (29 males, mean age 65 ± 13 years). All completed 30 days follow-up. The main cause of GOO was pancreatic cancer (31 patients, 60%). Fifty (95%) procedures were technically successful; in 2 patients the guide wire could not be passed across the stricture; one underwent a gastrojejunostomy and one refrained from further treatment. Comparing the mean GOOSS-score prior to stenting with the scores 7 and 30 days after stent placement showed a significant improvement from 0.81 to 2.32 (7 days) and to 2.74 (30 days) (Wilcoxon signed ranks test-two-sided; $p<0.001$). Oral intake was resumed at a mean of 1 day (0-11days) after stent placement. Stent-related complications within 30 days occurred in 5 patients (10%), with tumor ingrowth in 4 and stent migration in 1. Conclusion: This prospective cohort study shows that in patients with non-resectable malignant GOO placement of a D-Weave Niti-S™ enteral stent is safe and provides significant relief of obstructive symptoms in the first 30 days after placement.

Endoscopic visible light spectroscopy: a new minimally invasive technique for the diagnosis of chronic gastrointestinal ischemia

D. van Noord[1], D.A. Benaron[2], P.M.T. Pattynama[3], H.J.M. Verhagen[4], E.J. Kuipers[1], P.B.F. Mensink[1], Depts of Gastroenterology and Hepatology[1], Intervention Radiology[3], Vascular Surgery[4], Erasmus MC - University Medical Center, Rotterdam, The Netherlands, Standford University School of Medicine, Palo Alto, CA, USA[2]

The diagnosis of chronic gastrointestinal ischemia (CGI) remains challenging. Currently, there is no single and simple test with a high sensitivity available for detection of CGI. Visible light spectroscopy (VLS) is a new technique that non-invasively measures actual mucosal capillary hemoglobin oxygen saturations during endoscopy (T-Stat 303 Microvascular Tissue Oximeter, Spectros Corporation, California). This saturation reflects the adequacy of mucosal perfusion and is therefore lowered in CGI. A recent pilot study using VLS in a few CGI patients showed very promising results in detection of mucosal hypoxemia. In this study we evaluated the actual diagnostic value of VLS for detection of ischemia in a large cohort of patients clinically suspected of CGI. Prospectively, consecutive patients referred for evaluation of possible CGI were included. Patients underwent endoscopy-guided VLS next to the standard work-up consisting of a combination of gastrointestinal tonometry (TM) and CT or MR abdominal angiography. VLS measurements were performed at 5 standard locations (distal oesophagus, corpus, antrum, bulbus and duodenum) during upper endoscopy. VLS was performed before start of TM and radiological diagnostics. Mucosal saturation measurements during VLS were compared with the diagnosis CGI and results of TM. In 11 months, 80 patients were included: 30 males, mean age 59 (17 – 86) years. CGI was diagnosed in 58 (73%) patients: 26 single-, 20 multi-vessel disease, and 12 patients with non-occlusive CGI. The VLS mucosal saturations during endoscopy in means ± SD were for CGI and non-CGI patients respectively: 60.2 ± 4.0 and 62.3 ± 5.3 (oesophagus), 62.1 ± 5.6 and 64.9 ± 3.4 (corpus), 63.0 ± 5.4 and 65.6 ± 3.8 (antrum), 58.9 ± 5.2 and 62.6 ± 4.4 (bulbus), 54.4 ± 6.7 and 59.2 ± 4.1 (duodenum), 59.6 ± 3.4 and 62.8 ± 2.3 (overall). The mean saturation in the antrum, bulbus, duodenum and the overall mean saturation were significantly lower in CGI patients as compared to non-CGI patients. Accordingly, low saturation levels measured with VLS correlated significantly with abnormal TM results ($p<0.0001$). No differences were found comparing saturations in single- or multivessel disease CGI patients.
Conclusions: VLS measurement of mucosal oxygenation during gastroduodenoscopy is a very promising technique for detection of actual mucosal hypoxemia (i.e. ischemia) in patients suspected for CGI. The technique is easy to perform and shows excellent correlation with TM.

Evaluation of molecular changes in sporadic duodenal adenomas

D. Ramsoekh[1], M. Theeuwes[1], W. van Veelen[1], R. Smits[1], W.N.M. Dinjens[2], E. Dekker[3], K. Boparai[3], E.J. Kuipers[1] and M.E. van Leerdam[1], Depts. of [1]Gastroenterology and Hepatology and [2]Molecular Pathology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [3]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

Background: The duodenal adenomas as seen in familial adenomatous polyposis (FAP) are likely to develop through the classical adenoma-carcinoma pathway as they exhibit mutations in the APC gene, KRAS mutations, p53 dysfunction, and loss of E-cadherin expression. However, it is unknown whether sporadic duodenal adenomas also develop into duodenal carcinoma through the classical adenoma carcinoma sequence. Limited data suggest that sporadic adenomas show similar molecular features as colorectal adenomas, harboring *APC* and *KRAS* mutations. Therefore, the aim of the present study was to evaluate the molecular changes of sporadic duodenal adenomas. Methods: Tissue samples of 64 sporadic duodenal adenomas were available from the pathology archives of two academic hospitals. Tissue samples of patients with duodenal carcinoma or patients with FAP were excluded. None of the patients belonged to a known Lynch syndrome family. DNA was extracted from paraffin sections of the adenoma and analyzed for the presence of microsatellite instability. Also, mutation analysis using polymerase chain reaction followed by direct-sequencing was performed. The mutation analysis included mutational hotspots of the Wnt signaling pathway (APC, β-catenin), the MAP kinase pathway (KRAS and BRAF) and the del1100c mutation within the CHK2 gene.Results: Two (3%) of the 64 adenomas showed a high level of MSI (MSI-H). APC mutation analysis was possible in 52 adenomas and revealed a mutation in thirteen (24%), including seven duodenal adenomas with a recurrent 4684insA (K1555fsX1557) mutation. KRAS mutation analysis was possible in 52 adenomas and revealed one (2%) mutation (34GGT>TGT (G12C)). β-catenin mutation analysis was possible in 48 adenomas and revealed one (2%) mutation (121ACC>GCC(T41A)). BRAF (58 adenomas) and CHK2 (53 adenomas) mutation analysis did not reveal any mutation. Conclusions: In our cohort of sporadic duodenal adenomas the frequency of Wnt signaling pathway abnormalities is low, most adenomas are microsatellite stable and the number of MAP kinase pathway abnormalities is negligible. In addition, CHK2 mutations seem not to be present in sporadic duodenal adenomas. These findings suggest that a proportion of sporadic duodenal adenomas develop via the same mechanisms (the adenoma-carcinoma sequence) as colorectal adenomas, but it is possible that other molecular changes may also underlie the development of sporadic duodenal adenomas.

MMP-14/MT1-MMP mediates endoglin shedding in colorectal cancer

L.J.A.C. Hawinkels[1,2], P. Kuiper[1], H.W. Verspaget[1], R. Hanemaaijer[3], P. ten Dijke[2], C.F.M. Sier[1], Depts of Gastroenterology-Hepatology[1] and Molecular Cell Biology and Centre for Biomedical Genetics[2], Leiden University Medical Center, TNO Quality of Life BioSciences[3], Leiden, the Netherlands

Endoglin (CD105) is a trans-membrane co-receptor for Transforming Growth Factor-β and is highly expressed on angiogenic endothelial cells with a crucial role in angiogenesis. A soluble form of endoglin has been detected in the circulation, which is thought to pose anti-angiogenic properties by scavenging of circulating angiogenic factors. Increased endoglin levels are reported in pregnant women suffering from pre-eclampsia, but the few reports on soluble endoglin in cancer patients are contradictory. We examined the endoglin shedding mechanism in association with the soluble endoglin levels in blood of colorectal cancer patients. Immunohistochemical analysis of colorectal cancer specimens revealed high endoglin expression in angiogenic endothelial cells. Interestingly, low expression of endoglin on the blood vessels in cancer tissue was accompanied by high expression of MMP-14. In the circulation of these patients (n=23) soluble endoglin levels were decreased compared to healthy controls, although not statistically significant. The endoglin shedding mechanism was evaluated in vitro using HUVEC endothelial cells which secreted high levels of soluble endoglin into the medium. This could be inhibited by addition of broad-spectrum MMP inhibitors, but not by specific serine- or cystein-protease inhibitors, or by specific inhibitors for MMP of the gelatinase or stromelysin subclasses, indicating that membrane-type MMPs are the primary protease candidates. Therefore we examined co-transfection of endoglin with MMP-14 (MT1-MMP), the most abundant membrane-type MMP, in COS cells. Co-expression of endoglin and membrane bound MMP-14 lead to strongly increased soluble endoglin levels, whereas cells co-transfected with a MMP-14 mutant, lacking the trans-membrane domain, did not increase soluble endoglin. This indicates that MMP-14 membrane localization was required for efficient endoglin shedding. Knockdown of MMP-14 by siRNA in endothelial cells confirmed that endoglin shedding was strongly reduced upon reduction of MMP-14 expression.
In conclusion, this study shows, for the first time, that MMP-14 is capable of mediating endoglin shedding from endothelial cells. These data indicate that reduction of endothelial MMP-14 expression could result in decreased soluble endoglin levels and therefore enhanced angiogenic potential of these cells during colorectal cancer angiogenesis.

Depletion of the colonic epithelial precursor cell compartment upon conditional activation of the Hedgehog pathway

W.A. van Dop[1,2], A. Uhmann[3], M. Wijgerde[4], E. Sleddens-Linkels[4], G.J. Offerhaus[5], G.E. Boeckxstaens[1], M.A. van den Bergh Weerman[1], D.W. Hommes[2], J.C. Hardwick[2], H. Hahn[3], G.R. van den Brink[1,2] ,[1]AMC, Amsterdam, The Netherlands, [2]UMC Leiden, Leiden, The Netherlands, [3]University of Göttingen, Göttingen, Germany, [4]Erasmus UMC, Rotterdam, The Netherlands, [5]UMC Utrecht, Utrecht, The Netherlands

Hedgehogs (Hh) are expressed throughout the epithelium of the gastrointestinal tract. The study on the role of Hh signaling in the adult gut has been hampered by the embryological phenotype of Hh mutant mice. Here we examined the role of Hh signaling in the maintenance of homeostasis of the adult colonic epithelial layer. We conditionally inactivated the Hh receptor Patched1 (Ptch1) in adult mice. Inactivation of Ptch1 leads to loss of inhibition of the Hh signaling receptor Smoothened and constitutive activation of the Hh pathway. To study the effect of Hh on the colonic epithelium we examined the colons of adult tamoxifen-treated Ptch1$^{flox/flox}$-Rosa26CreERT2 mice and control mice. We performed in situ hybridization for Hh, Gli1, Ptch1 and Bone Morphogenetic Proteins (BMPs). The phenotype of Ptch1 mutant mice was examined using routine histological techniques, electron microscopy and immunohistochemical analysis of cellular proliferation, differentiation markers and Wnt signaling activity. Indian Hedgehog (Ihh) but not Sonic Hedgehog (Shh) was expressed in the colonic epithelium. Expression of Hh signaling targets Ptch1 and Gli1 was restricted to the mesenchyme. Constitutive activation of Hh signaling in the mesenchyme resulted in colonic crypt hypoplasia. A reduction in the number of proliferating precursor cells was observed with premature development into the enterocyte lineage and inhibition of Wnt signaling. Mesenchymal activation of Hh signaling resulted in the induction of mesenchymal Bmp7 expression and a reciprocal induction of Bmp signaling in the epithelium.
Conclusions: Our results show that Ihh signals from the epithelium to the mesenchyme in the adult colon. Conditional deletion of the Hh receptor Ptch1 results in colonic crypt hypoplasia, inhibition of Wnt signaling and depletion of the colonic precursor cell compartment. Our results provide the first genetic evidence that Hh signaling acts as a negative feedback loop from the differentiated cells via the mesenchyme to the colonic epithelial precursor cell compartment.

Optimization of aav liver-directed gene therapy for the treatment of crigler-najjar syndrome

P. Miranda, L. ten Bloemendaal, C. Kunne, S. Duijst, P. Bosma , AMC Liver Center, Amsterdam, The Netherlands

The aim of this project is to develop adeno-associated virus (AAV) liver-directed gene therapy for the treatment of Crigler-Najjar syndrome (CN), severe unconjugated hyperbilirubinemia, caused by deficiency of the hepatic UDP glucuronosyltransferase (UGT1A1). To allow clinical application of this therapy the vector must be optimized. In this study we evaluated the efficiency of single-stranded (ss) and double stranded or self-complementary (sc) AAV-1 vectors and studied the effects of transient immune suppressive therapy. In addition we investigated the preferential administration route and identify the optimal AAV serotype. ss and sc AAV vectors expressing human UGT1A1 driven by a liver-specific promoter were injected in the portal or tail vein of Gunn rats, the animal model for CN syndrome. The efficacy of the treatment was assessed by measuring bilirubin levels in serum and bile. The immunosuppressive regimen consisted of daily subcutaneous injections with 10 mg/kg mycophenolate mofetil (MMF).Upon portal vein administration, switching from ssAAV1 to scAAV1 allowed a 10-fold reduction of the therapeutic dose, from $2{,}5x10^{12}$gc/kg to $3x10^{11}$gc/kg. While in females a dose of $2{,}5x10^{12}$gc/kg ssAAV-1 did not result in a significant correction, a dose of $3x10^{11}$gc/kg scAAV resulted in 80% reduction of serum bilirubin levels. Although, transient immune suppression with MMF reduced the anti-AAV antibody response, it also lowered the ssAAV- mediated correction of the hyperbilirubinemia. Importantly, liver transduction by scAAV was not impaired by MMF treatment. When comparing different administration routes our results showed that the portal vein injection provides a more efficient liver transduction than peripheral vein injection and between the different AAV serotypes tested, AAV8 seems to be the optimal serotype for this therapy. Conclusions: Our data shows that portal vein administration of scAAV8 seems the best approach of liver directed gene therapy for CN syndrome.

Tissue repair induces cancer in p53 and Rb deficient livers

M.J.M. Toussaint[1], R.B. Matondo[1], S. Pandit[1], P.C.J. Tooten[1], R. Kisjes[1], T. Roskams[2] and A. de Bruin[1] ,[1]Dept of Pathobiology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands and Dept of Morphology and Molecular Pathology, University of Leuven, Belgium

Hepatocellular carcinomas are often associated with mutations of the tumor suppressor genes p53 and Retinoblastoma (Rb). To determine whether mutations of p53 and Rb can cause liver cancer, we deleted both genes specifically in the liver of mice. Interestingly, simultaneously ablation of p53 and Rb in the liver was insufficient to induce liver cancer, indicating that besides inactivating these tumor suppressors other factors are required for cancer initiation. We therefore performed two subsequent partial hepatectomies to induce liver regeneration in these mice. Undifferentiated hepatocellular carcinomas in p53/Rb deficient livers were observed with high incidence (>60%) 4-5 weeks after the second hepatectomy. Strikingly, all tumours occurred at the same anatomic location, namely within the remaining liver stump of the first hepatectomy. Some tumours metastasize to regional lymph nodes and surrounding tissues and histologically the neoplastic cells resembled oval cells, the progenitor cells of hepatocytes and bile duct cells. Surrounding non neoplastic liver regions show marked oval cell proliferation particularly adjacent to the portal triads. Expression analysis of tumour tissue revealed increase expression of alpha-fetoprotein, an oval cell marker, as well as the transcription factor E2F1, a downstream partner of Rb, which is often upregulated in human hepato-cellular carcinomas. Our findings demonstrate that livers deficient of p53 and Rb induces oval cell proliferation and undifferentiated hepatocellular carcinomas upon partial hepatectomy.

Endoscopic mucosal resection appears equally effective, but is associated with less morbidity than transanal endoscopic microsurgery for the treatment of large rectal adenomas

F.J.C. van den Broek[1], J. van Schooten[1], W.A. Bemelman[2], E.J.R. de Graaf[3], P. Fockens[1], E. Dekker[1], for the TREND-study group, Depts. of [1]Gastroenterology and Hepatology, and [2]Surgery, Academic Medical Center Amsterdam, [3]Dept. of Surgery, IJsselland Hospital Cappelle a/d IJssel, The Netherlands

Large rectal adenomas are currently being treated by either transanal endoscopic microsurgery (TEM) or piecemeal endoscopic mucosal resection (EMR). EMR is likely to be associated with lower morbidity, although this potential advantage may become irrelevant if these treatments are not equally effective. We conducted a retrospective study to compare the safety and effectiveness of TEM vs. EMR for the treatment of large rectal adenomas. Data were collected from patients with a preoperative diagnosis of a large rectal adenoma (>2cm) who underwent TEM or EMR in 8 Dutch hospitals from January 2004-December 2007. Patient and procedure related characteristics, as well as complications and recurrences were registered. Since EMR may require several attempts to achieve complete removal of adenomas, two recurrence rates were defined: early and late recurrences (including and not including remnant adenomas successfully re-treated during the first control endoscopy). In total, 248 patients were treated by TEM and 51 by EMR (144 male; mean 67 yrs). With respect to sex and age, there were no differences between TEM and EMR; however, adenomas treated by EMR were located higher in the rectum (mean 9.4 vs. 6.7cm ab ano) and were smaller in size (median 30 vs. 40mm; $p<0.001$). Histological evaluation of the resection specimen revealed unexpected invasive cancer in 11.3% after TEM and 3.9% after EMR ($p=0.278$). Intra-operative peritoneal entrance occurred in 29 TEM procedures (12%) and in none of the EMR procedures ($p=0.007$). Any postoperative complication occurred in 69 patients (28%; major 8.5%) after TEM and in 5 patients (9.8%; major 0%) after EMR ($p=0.007$). Complications needing operative intervention occurred in 16 (6.5%) patients after TEM versus no patients after EMR ($p=0.083$). The median in-hospital stay after TEM was 4 days versus 0 days after EMR ($p<0.001$).The mean time of follow-up was 13 months (0-48); 56 patients (19%) did not have follow-up (yet). During the first control endoscopy, remnant adenoma tissue was found in 6/205 (2.9%) TEM- and 6/38 (16%) EMR-patients ($p=0.006$). After removal of remnant adenomas during the first control endoscopy once-only, late recurrence rates of TEM and EMR were 9.3% and 10.5% ($p=0.766$). Conclusion: EMR appears equally effective, but associated with less morbidity than TEM for the treatment of large rectal adenomas. However, adenomas treated by EMR were slightly smaller and the retrospective nature of this study likely has introduced selection bias. A prospective randomized comparison seems imperative to determine which technique is more cost-effective.

Intestinal barrier function in patients undergoing open or laparoscopic (sub)total colectomy: a randomized trial

M.S. Vlug[1], G.M.P. Diepenhorst[2], P.J. van Koperen[1], J.F. Slors[1], M.A. Boermeester[1], W.A. Bemelman[1], [1]Dept of Surgery, Academic Medical Center, [2]Dept of Surgery, Surgical Laboratory, Academic Medical Center, University of Amsterdam, The Netherlands

To determine whether the type of approach, open or laparoscopic, and order of devascularisation in laparoscopic colectomy, affects intestinal barrier function. Bacterial translocation (BT) may occur after abdominal surgery. Intestinal ischemia impairs the intestinal barrier function and therefore enhances intestinal permeability and BT. Total colectomies are performed both open and laparoscopically. In open surgery devascularisation is performed after mobilization of the bowel, whereas the medial laparoscopic approach commences with left-sided or right-sided devascularisation. It is unknown whether the order of devascularisation influences the intestinal barrier function.Elective colectomy patients were included from April 2006 to July 2008. After informed consent, laparoscopically scheduled patients were randomized to start with left or right-sided devascularisation. To assess the intestinal barrier function polyethylene glycol recovery (PEG; measuring the intestinal permeability) and intestinal fatty acid binding protein (I-FABP; marker of mucosal ischemia) were measured in urine pre-operatively and at post-operative days 1, 3 and 7. Mesenteric lymph nodes were harvested after specimen retrieval to assess expression of inflammatory mediator-related genes using Multiplex Ligation Probe Amplification (MLPA). Twenty-two patients were randomized to start laparoscopic devascularisation left or right-sided. Eighteen patients undergoing open colectomy served as controls. Time course of PEG and I-FABP was not significantly different between surgical techniques. Only in the right-sided group I-FABP was significantly higher at day 1 and 3 compared to pre-operative levels ($p=0.006$ and $p=0.000$), whereas in the left-sided group there was no increase compared to baseline. MLPLA showed no difference between the two approaches for relevant inflammatory mediated-related genes. Post-operative morbidity was not significantly different between surgical techniques. There was no difference between length of time of surgery between laparoscopic starting left or right-sided. Starting laparoscopic devascularisation at the right-side can lead to more intestinal mucosal ischemia, although this is not clinically relevant.

DNA copy number changes predict clinical outcome in Stage II Colon cancer

R.P.M. Brosens[1], T. Buffart[2], A.F. Engel[3], M.A. Cuesta[1], G.A. Meijer[2], [1]Dept of Surgery, VU University Medical Centre, Amsterdam, The Netherlands [2]Dept of Pathology, VU University Medical Centre, Amsterdam, The Netherlands, [3]Dept of Surgery, Zaans Medical Centre, Zaandam, The Netherlands

Background: 20-30% of Stage II colon cancer will relapse and patients will die of their disease. Benefit of postoperative chemotherapy or surgery only for stage II tumours is still not demonstrated. Traditional histopathologic features have failed to predict prognosis accurately in Stage II colon cancer. More objective markers for classifying stage II colon cancer are needed. DNA copy numbers changes are one way to alter gene function and can be used to identify markers for prognosis. However, the correlation between DNA copy number changes and prognosis in stage II colon cancer is still not clear. Aim: To identify chromosomal aberrations that can predict relapse of tumour in patients with Stage II colon cancer. Methods: Clinicopathological data of 40 Stage II colon cancer patients were obtained and DNA isolated from formaldehyde fixed, paraffin embedded colon cancer tissue and normal colon mucosa of these patients. DNA copy number changes were analyzed with 44K oligonucleotide micro-array based comparative genomic hybridisation (aCGH).Regions of different DNA copy number changes were constructed. Wilcoxon rank-sum test with correction for false positive results was used to analyze differences between Stage II Colon cancer patients with and without relapse of tumour. Log rank test was used for survival analysis. Results: Mean follow-up was 72 months. Sixteen patients (40%) relapsed and died of their disease. No differences in clinicopathological characteristics between patients with and without relapse were seen.Patients with relapse exhibited more losses of chromosome 4p15, 4q22, 4q24, 4q28.3, 4q31.3, 4q32, 4q34, 4q35 and 5q32 (false discovery rate < 0.10, P-value <0.007). One chromosomal region, 4q28.3, showed the strongest correlation with relapse (fdr =0.07, P=0.0006). Overall and disease free survival was significant worse for patients with loss of 4q28.3. (Log rank test 0.000 and 0.002 respectively).
Conclusion: Losses of 4p15, 4q22, 4q24, 4q28.3, 4q31.3, 4q32, 4q34, 4q35 and 5q32 predict worse prognosis in Stage II Colon cancer patients. Loss of 4q28.3 was most significant for worse prognosis. Genes located on 4q28, could be candidate tumour suppressor genes and markers for worse prognosis in Stage II colon cancer.

Stroma production and downregulation of SMAD4 correlates with worse survival for stage I-II colon cancer patients

W.E. Mesker[1], G.J. Liefers[1], J. Morreau[2], R.A.E.M. Tollenaar[1], [1]Dept of Surgery[2] Dept of Pathology Leiden University Medical Center (LUMC), Leiden, The Netherlands

Background: Recent models on metastatic invasion focus on the tumor-"host" interface, in particular the role of the stromal tissue. The biological meaning of the stromal compartments are thought to be part of the process of wound healing, but there is also strong emphasis that CAF's (cancer-associated fibroblasts) are important promotors for tumor growth and progression. Assuming these models are correct we anticipated that changes in the proportion of stroma in the primary tumor could reflect progression. We therefore investigated if the amount of intra-tumor stroma could be applied as a candidate marker to identify patients for adjuvant therapy. Methods: In a first study we have investigated the proportion of intra-tumor stroma, on heamatoxylin-eosin (H&E) stained histological sections in a set of 122 patients (stage I-III) and distinguished between patients with a high amount of stroma (stroma-high) and patients with less stroma (stroma-low). The second study is based on stage I-II patients only, a subgroup of patients who might benefit from adjuvant therapy. We have analyzed 135 stage I-II colon cancer patients for the proportion of tumor related stroma and for TGFβ-R2, SMAD4 and β-catenin, markers involved in pathways related to stromal production and epithelial-to-mesenchymal transition (EMT). Results: The first study showed five-year survival rates for stroma-high versus stroma-low of respectively for OS: 15.2% and 73.0% and for DFS: 12.1% and 67.4% (OS $p<0.0001$, HZ 3.73; DFS $p<0.0001$, HZ 4.18). In a multivariate Cox regression analysis, the amount of stroma remained an independent variable when adjusted for either stage or for tumor status and lymph-node status (OS: $p<0.001$, OS: $p<0.001$). For the second study of 136 analyzed patients 35 (25.7%) patients were stroma-high and 101 (74.3%) stroma-low. Significant differences in survival were observed between the two groups, with stroma-high patients showing poor survival (OS $p<0.0001$, HZ 2.59; DFS $p=0.0002$, HZ 2.31). A high-risk group was identified with stroma-high and SMAD4 loss (OS $p=0.008$, HZ 7.98, CI 4.12-15.44, DFS $p=0.005$, HZ 6.57, CI 3.43-12.56); 12 of 14 (85.7%) patients died within 3 years. In a logistic-regression analysis a high proportion of stroma and SMAD4 loss were strongly related (HZ 5.42, CI 2.13-13.82, $p<0.001$).
Conclusions: Conventional haematoxylin-eosin stained tumor slides contain more prognostic information than previously fathomed. This can be unleashed by assessing the tumor-stroma ratio. The combination of analyzing the tumor-stroma ratio and staining for SMAD4 results in an independent parameter for confident prediction of clinical outcome.

Long-term symptomatic and anatomical outcome of laparoscopic para-oesophageal hiatal herniation repair

E.J.B. Furnée[1], W.A. Draaisma[2], H.G. Gooszen[1], G. Stapper[3], I.A.M.J. Broeders[2], Dept of Surgery[1], University Medical Centre Utrecht, The Netherlands Dept of Surgery[2], Meander Medical Centre, Amersfoort, The Netherlands Departement of Radiology[3], University Medical Centre Utrecht, The Netherlands

Surgical repair of minimal invasive para-oesophageal hiatal herniation (PHH) is accompanied with less complications, less postoperative pain and shorter hospital stay compared to the conventional approach. Long-term durability of the repair performed by the laparoscopic approach, however, is uncertain. This study aimed to assess the long-term symptomatic and anatomical outcome of laparoscopic large PHH repair. Between January 2000 and December 2007, 70 patients (49 females, mean age ± SD 60.6 ± 10.9 years) undergoing laparoscopic repair of large PHH were studied. Pre-, intra- and postoperative data were prospectively documented. In September 2008, patients were requested for symptomatic and anatomical follow-up, by standardised questionnaires and barium oesophagogram, respectively. Logistic regression analysis was performed to identify predictors of outcome.Intra-operative complications occurred during 14 repairs (20.0%) and in nine patients (12.9%) conversion to laparotomy was required. Thirteen patients (18.6%) had postoperative complications with one postoperative death (1.4%). Mean duration of operation was 134.7 ± 34.7 minutes and hospital stay was 7.6 ± 7.6 days. After a mean follow-up of 45.6 ± 23.8 months, 65 patients (92.9%) were available for symptomatic and 60 (85.7%) for radiological follow-up. Symptomatic outcome was successful in 58 patients (89.2%) and gastro-oesophageal anatomy was intact on barium oesophagogram in 42 patients (70.0%). Symptomatic and anatomical outcome were not significantly correlated (r=-0.015, p=.908). The addition of an antireflux procedure, performed in 37 patients (52.8%), was the only significant predictor of unfavourable anatomical outcome in the univariable analysis (odds ratio 0.413, 95% confidence interval 0.130-1.308, p=.125).
Conclusions: In this prospective study, long-term symptomatic outcome of surgical repair of large PHH was favourable in 89% of patients and 70% had successful anatomical repair. Symptomatic and objective outcome showed no correlation. The addition of an antireflux procedure did unfavourably influence the anatomical outcome.

A multi-center randomized efficacy study of the EndoBarrier for pre-surgical weight loss in bariatric surgery

R. Schouten[1], MD, C. Rijs[3], MD, N.D. Bouvy[1], MD PhD, W. Hameeteman[2], MD PhD, G.H. Koek[2], MD PhD, I. Jansen[3], J.W.M. Greve[1], MD PhD, [1]Dept of General Surgery, University Hospital Maastricht, [2]Dept of Gastroenterology and Hepatology, University Hospital Maastricht, [3]Dept of Surgery, Rijnstate Hospital, Arnhem, The Netherlands

Background: The endoscopically placed duodenal jejunal bypass sleeve (DJBS) or EndoBarrier™ has been designed to achieve weight loss in morbidly obese patients. We report on the first European experience with this device. Methods: A multi-center, randomized clinical trial was performed. Forty-one patients were included and 30 underwent sleeve implantation. Eleven patients served as a diet control group. All patients followed the same low-calorie diet during the study period. The purpose of the study was to determine the safety and efficacy of the device. Results: 26 devices were successfully implanted. In 4 patients implantation could not be achieved. Four devices were explanted prior to the initial protocol date because of migration (1), dislocation of the anchor (1), gastro-intestinal obstruction (1) and continuous epigastric pain (1). The remaining patients all completed the study. Mean procedure time was 33 minutes (range: 9 – 62 minutes) for a successful implantation and 15 minutes (range: 4 – 120 minutes) for explantation. There were no procedure related adverse events. During the study period 26 patients (100%) had at least one adverse event, mainly abdominal pain and nausea during the first week after implantation. Initial mean body mass index (BMI, kg/m²) was 48.9 and 47.4 kg/m² for the device and control patients, respectively. Mean excess weight loss (EWL) after 3 months was 18.9 % for device patients versus 6.9 % for control patients ($p<0.002$). Absolute change in BMI at 3 months was 4.4 and 1.7 k/m², respectively. Diabetes mellitus was present at baseline in 8 patients of the device group and improved in 7 patients during the study period (lower glucose levels, HbA1c and insulin dosages).
Conclusion: The EndoBarrier™ is a feasible and safe noninvasive device with excellent short-term weight loss results. The device also has a significant positive effect on diabetes mellitus. Long term randomized and sham studies for weight loss and treatment of diabetes are necessary to determine the role of the device in the treatment of morbid obesity.

Intrathoracic manifestations of cervical anastomotic leaks: transhiatal vs. transthoracic oesophagectomy

M. van Heijl MD[1], A.K.S. van Wijngaarden[1], S.M. Lagarde MD, PhD[1], O.R.C. Busch MD, PhD[1], J.J.B. van Lanschot MD, PhD[2], M.I. van Berge Henegouwen MD, PhD[1], [1]Department of Surgery, Academic Medical Centre, Amsterdam, Netherlands, [2]Department of Surgery, Erasmus Medical Centre, Rotterdam, Netherlands

A cervical anastomosis is required for reconstruction after transhiatal oesophagectomy and seems to reduce the intrathoracic consequences of anastomotic leakage. It is questioned whether a cervical anastomosis after transthoracic oesophagectomy harbours this advantage too. In the present study, we investigated incidence and risk factors of intrathoracic manifestations after cervical anastomotic leakage in a prospectively collected consecutive series of patients with potentially curable oesophageal carcinoma. The aim of the present study is to investigate whether intrathoracic manifestations of cervical anastomotic leakage are encountered more frequently after transthoracic oesophagectomy compared with transhiatal oesophagectomy. From 1993 to 2007, all patients in the prospective database undergoing transhiatal or transthoracic oesophagectomy with a cervical anastomosis were included. All patients developing either radiological or clinical signs of anastomotic leakage were evaluated. Occurrence and outcome of intrathoracic manifestations after cervical anastomotic leakage were compared after transhiatal and transthoracic oesophagectomy. Multivariate logistic regression analysis was used to identify potential risk factors for intrathoracic manifestations including age, body mass index, tumour histology, use of neoadjuvant therapy and surgical approach. In the study period, 847 patients underwent potentially curative oesophagectomy. 79/516 (15%) patients developed anastomotic leakage after transhiatal oesophagectomy versus 50/331 (15%) patients after transthoracic oesophagectomy (p=N.S.) However, significantly (p=0.041) more intrathoracic manifestations of cervical anastomotic leakage were seen after transthoracic oesophagectomy than after transhiatal oesophagectomy, 22/50 (44%) versus 21/79 (27%). Total hospital stay (p<0.001), ICU stay (p<0.001) and mortality (p=0.035) were significantly higher in patients with intrathoracic manifestations compared to patients without intrathoracic manifestations of cervical leakage. Transthoracic approach was the only independent predictive factor for development of intrathoracic manifestations in patients with cervical leakage (p=0.014, Odds Ratio 2.859).
Conclusion: Intrathoracic manifestations of cervical anastomotic leakage after oesophagectomy result in longer hospital stay and higher mortality. Intrathoracic manifestations occur significantly more after a transthoracic approach than after a transhiatal approach.

Risk factors for development and persistency of benign cervical anastomotic strictures after oesophagectomy

M. van Heijl MD[1], J.A.H. Gooszen[1], P. Fockens MD, PhD[2], O.R.C. Busch MD, PhD[1], J.J.B. van Lanschot MD, PhD[3], M.I. van Berge Henegouwen MD, PhD[1], [1]Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands, [2]Department of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands, [3]Department of Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

Benign strictures develop frequently when cervical anastomosis is performed after oesophagectomy, causing debilitating symptoms and poor quality of life. The aim of the present study is to investigate risk factors for development and persistency of strictures in a large series of patients. From 1996 to 2006, all patients in the prospective database undergoing transhiatal or transthoracic oesophagectomy with a cervical anastomosis were included. Standard of care was a cervical hand sewn end to end oesophagogastric anastomosis. Stricture was defined as dysphagia requiring endoscopic dilatation of the anastomosis. Patients were evaluated on a number of risk factors: surgical approach, age, sex, Body Mass Index (BMI), smoking, cardiovascular disease, diabetes, spirometry, neoadjuvant therapy and anastomotic leakage. Prediction of stricture was assessed using univariate logistic regression analysis. Significantly predictive factors were analysed in a multivariate regression model. To evaluate risk factors for increased persistence of strictures the mean number of dilatations was compared between patients with and without risk factor. Finally we investigated whether early development of a stricture is associated with persistency of a stricture. In the study period, a total of 607 patients underwent potentially curative oesophagectomy, with an in-hospital mortality of 3.1%. During follow-up, 242 (39.9%) patients developed a stricture after a median time interval of 71 days. Cardiovascular disease ($p<0.001$), diabetes ($p<0.001$), BMI ($p=0.023$), gastric tube compared with colonic segment ($p=0.036$) and anastomotic leakage ($p<0.001$) were predictive for development of stricture. Cardiovascular disease ($p=0.001$) and anastomotic leakage ($p=0.001$) proved to be predictive for stricture in multivariate analysis. Mean number of dilatations was higher in patients with anastomotic leakage compared to patients without leakage (10.1 vs 6.6; $p=0.001$). Patients developing stricture within 90 days of surgery require more dilatations (8.4 vs 5.6; $p=0.002$). Benign stricture rate after oesophagectomy with cervical anastomosis is high. Cardiovascular disease and postoperative anastomotic leakage are independent predictors for development of benign anastomotic stricture. Anastomotic leakage is associated with a more persistent stricture, requiring more dilatations. Patients who develop stricture early in the postoperative course show more persistent strictures requiring more dilatations.

Mortality rates for gastric cancer surgery in the Southwest of The Netherlands

B.P.L. Wijnhoven[1], C. Schroten[2], P.D. de Rooij[3], R.A.M. Damhuis[2], [1]Erasmus MC, Dept of Surgery, Rotterdam, The Netherlands, [2]Comprehensive Cancer Centre IKR, Rotterdam, The Netherlands, [3]Maasstad Ziekenhuis, Dept of Surgery, Rotterdam, The Netherlands

Surgery for benign andmalignant conditions of the stomach was an important domain of general surgicalpractise in the 60's, 70's and 80's. The number of gastric operations hasdeclined sharp in more recent decades. This is caused by the introduction ofeffective medical treatment for ulcer disease and the declining incidence ofgastric cancer. Hence, it is difficult for younger surgeons to becomeproficient in gastric surgery. We evaluated mortality rates for gastric cancersurgery in the Southwest of the Netherlands. Patients who underwent a partialor total gastrectomy for invasive gastric cancer in the Southwest of theNetherlands (Comprehensive Cancer Centre; 16 hospitals) were identified fromthe cancer registry. Lymphomas, GIST tumours and tumours of thegastroesophageal junction were excluded. Postoperative mortality was defined asdeath within 30 days after the operation. The covariates age, sex, type ofoperation, hospital, number of removed lymph nodes and tumour stage wereincluded in the analysis. Univariate analysis was performed with chi-squaretest and multivariate logistic regression was applied. Some 1918 patients wereincluded and154 (8.0%) died within 30 days after the operation. Between theyears 1989 and 2006 the number of gastric resections declined from 161 to 61per annum. The most important prognostic factor for mortality was age (75-84years: 11%, 85+: 27%. Other prognostic factors were tumour stage (pT4: 18%, pM1: 18%) and gastrectomy with en-bloc resection of a neighbouring organ (17%). There was no significant difference in mortality between the participating hospitals (p=0.52). Moreover, hospital volume was not correlated with mortality (p=0.25).
Conclusions: The number of gastrectomiesfor gastric cancer has declined in the Southwest of the Netherlands and isassociated with high mortality rates. Especially in elderly patients and inpatients with advanced tumour stage, the operative risk needs to carefullyassessed and balanced against the chance of achieving long-term survival.

Fast intestinal barrier recovery following ischemia/reperfusion damage in the human gut: myosin light chain kinase mediated closure of the villus tip

G. Thuijls[1], J. Grootjans[1], J.P.M. Derikx[1], F. Heyers[1], R. Matthijsen[1], E. Heineman[1], R.M. van Dam[1], C.H.C. Dejong[1], W.A. Buurman[1] ,[1]Dept of Surgery, Maastricht University Medical Centre and Nutrition and Toxicology Research Institute Maastricht (NUTRIM),The Netherlands

In a recently developed human model of intestinal ischemia reperfusion (I-IR) a rapid reversal of intestinal damage by shedding of injured enterocytes and villus tip closure was described. Here we investigated the putative involvement of myosin light chain kinase (MLCK) mediated actin contraction in villus tip closure. During surgery, an isolated part of the jejunum scheduled to be removed was subjected to 30 min ischemia and subsequent reperfusion. Immunohistochemistry was used to study the localization of MLCK, phosphorylated-MLC (pMLC), filamentous actin and claudin-3. Protein levels of MLCK, pMLC and claudin-3 were semi-quantitatively analyzed using western blot. Intestinal claudin-3 production was determined by qPCR. After 30 min ischemia sub-epithelial spaces were noted as retractions of the basal membrane. A 30 min reperfusion period resulted in disintegration of epithelial lining at the villus tip, with epithelial cell damage and loss of claudin-3. Both MLCK and pMLC increased following ischemia and were distributed around the disrupted villus tips after 30 min of reperfusion (MLCK; 918±430 versus 641±338 INT, $P<0.01$). After 60 min reperfusion complete barrier recovery was observed.
This study shows fast gut barrier recovery following I-IR damage in the human gut after myosin light chain kinase mediated closure of the villus tip.

Laparoscopic cholecystectomy for acute cholecystitis for laparoscopic surgeons only?

K. Kortram, D. Boerma, M.J. Wiezer, P.M.N.Y.H. Go, B. van Ramshorst, St. Antonius Ziekenhuis Nieuwegein, the Netherlands

In general surgical care there is an increasing demand for differentiation. Within the field of gastro-intestinal surgery, laparoscopic expertise has increased enormously. Aim of this study was to evaluate the consequences of this development on the outcome of a still considered 'general surgical procedure' like the laparoscopic cholecystectomy (LC). Data were collected of 818 consecutive patients who underwent LC between 2002 and 2006. In 566 patients the operation was performed by or under supervision of a staff surgeon, in 252 by residents. Surgeons were divided into 'laparoscopically oriented' (LS), > 60 laparoscopic procedures/year, and not-laparoscopically oriented (NLS). Residents were counted as NLS. LC were divided into elective surgery for cholelithiasis and acute surgery for cholecystitis. Duration of surgery, conversion rate, postoperative complications and hospital stay were compared between surgeons and indications. 492 Patients were operated or supervised by LS, 326 by NLS. Patient characteristics were comparable in the two groups. Since NLS performed LC mainly when they were on call, acute cholecystitis was more often the indication for surgery: 14.7% vs 9.4% for LS. In case of acute LC for cholecystitis, duration of surgery was 50 (15-210) minutes for LS vs 65 (30-180) for NLS ($p<0.002$). Conversion rate was high in the NLS group: one out of three patients (32.4%) ended up with an open cholecystectomy vs 4.4% in the LS group ($p<0.005$). Complications were mainly intraabdominal abcess, wound infection, bleeding and cardiopulmonary and corresponded in both groups (17% vs 4%, $p=0.1$). Median hospital stay did not differ significantly between surgeons. Complications were not significantly different after converted vs laparoscopic cholecystectomie, nor was median hospital stay (five vs four days, $p=0.4$). For elective LC there were no significant differences in the outcome parameters. Patients with acute cholecystitis have a better chance of undergoing a successful LC when the operation is performed by a LS. Conversion results in a large incision with a higher risk of wound infections, longer postoperative recovery time and less satisfying cosmetic result. The surgical profession will have to take stand whether or not LC for acute cholecystitis should be the primary domain of the laparoscopic surgeon.

Quality of life and pancreatic function after resection of pancreatic cysts

N.A. van der Gaag[1], O. Berkhemer[1], O.R.C. Busch[1], T.M. van Gulik[1], D.J. Gouma[1], [1]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

Radical resection is the accepted treatment for (pre)malignant cysts, but preoperative differentiation with benign lesions is sometimes difficult. Evaluation of death due to recurrence, but in particular long term quality of life (QoL) and pancreatic function after resection is scarcely reported, which were the aims of the present study. Records of 108 patients that underwent various surgical procedures between Jan/1992-June/2007 for a pancreatic cystic lesion (pathology proven serous cystic, mucinous cystic [MCN], intraductal papillary mucinous [IPMN] and solid pseudopapillary neoplasia) were reviewed. Last follow-up was collected. Participating living patients received generic (SF-36, QLQ-C30) and pancreatic (PAN26) QoL questionnaires at home. Pancreatic function tests were performed [endocrine: HbA1c, fasting glucose; exocrine: faeces elastase] during a prospectively scheduled visit. Death due to recurrence occurred in 11 (10%) patients (6 IPMN, 5 MCN) at a median of 13 months. Two died in-hospital due to complications, 7 due to other causes. Sixty-five of 88 (74%) living patients agreed to participate; female gender was 69%, mean age 61 years. Median follow-up was 59 (IQR 44-108) months. Thirty-one (48%) patients had undergone pancreatoduodenectomy, 26 (40%) tail resection, 4 (6%) central and 4 (6%) total pancreatectomy. Study population characteristics were not significantly different from non-participants. Reported global health status (QLQ-C30) was 83 (median; IQR 67-92) (max. possible: 100). Physical and mental QoL scores including all subdomains (SF36) were not different from a healthy reference population, except for a lower vitality score (61 vs 69, P <.05). In none of the 14 pancreatic symptom scales (PAN 26) median scores were above 50 (50-100: moderate/severe complaints). Endocrine insufficiency occurred in 24 (40%) of 60 patients available for analysis; 19 were already diagnosed but only 5 appeared to be adequately treated (HbA1c <6%). Exocrine insufficiency was present in 32 (59%) of 54 available patients.

Conclusions: Death due to recurrence after resection of a pancreatic cyst was 10% in the present series and occurred after a median of 13 months. After resection some deterioration of pancreatic function occurs, for which recognition and medical treatment should be improved. Patients report excellent long term QoL scores, equal to healthy individuals, which might lower the threshold to surgery in case differentiation between a benign and (pre)malignant lesion cannot be established in advance.

In-hospital mortality decreased significantly after regionalization of pancreatic surgery in the south-east of The Netherlands

S.W. Nienhuijs[1], H.J.T. Rutten[1], E.J.T. Luiten[2], O.J. Repelaer van Driel[3], P.H.M. Reemst[3], V.E.P.P. Lemmens[4], I.H.J.T. de Hingh[1], [1]Dept of Surgery, Catharina Hospital, Eindhoven, [2]Dept of Surgery, St. Anna Hospital, Geldrop, [3]Dept of Surgery, Maxima Medical Center, Veldhoven, [4]Comprehensive Cancer Centre South, Eindhoven Cancer Registry, Eindhoven, The Netherlands

In the south of The Netherlands, surgery for pancreatic and peri-ampullary cancer used to be performed in low-volume hospitals (<5 resections/year). In 2005, the Comprehensive Cancer Centre South (CCCS) reported the clearly unsatisfying results of this practice. This stimulated the regionalization of pancreatic surgery by 3 collaborating surgical units into one non-academic teaching hospital. As the impact on surgical outcome of such an initiative has not been reported yet, the results are reviewed. All patients in the regionalized cohort group (Oct 05-Dec 08) operated with curative intent for a (peri-)pancreatic tumor were followed prospectively. Their outcome was compared to the reported CCCS cohort group (Jan 95-Dec 00). Since the regionalization the number of annually treated patients increased from 10 to 41, making a total of 90 patients. The in-hospital mortality rate was 3.3% (3/90). Almost one-third (n=29) of the tumours was peroperatively deemed locally advanced or metastasised and a palliative procedure was performed. In 61 patients (68%) a resection was performed. Their outcomes were a mortality rate of 4.9%, complication rate of 48% and re-intervention rate of 23%. These results were lower than the previously reported ones (24% ($p<0.001$), 72% and 38% respectively.
Conclusion: After regionalization of pancreatic surgery in the south-east of The Netherlands the in-hospital mortality decreased significantly from an unacceptable 24% in 2000 to 4.9% in 2008. These data underline the recommendations of various experts advocating that centralisation of pancreatic surgery improves the standard of care.

Incomplete colonoscopy: significant findings in a mixed referral population during follow up

M. Neerincx[1], J.S. Terhaar sive Droste[1], M. Räkers[1], J.F.W.M. Bartelsman[2], R.J. Loffeld[3], H.A.R.E. Tuynman[4], C.J.J. Mulder[1], R.W.M. van der Hulst[5], Dept. of Gastroenterology and Hepatology[1], VU University Medical Center, Amsterdam, Dept. of Gastroenterology and Hepatology[2], Academic Medical Center, Amsterdam, Dept. of Internal Medicine[3], Zaans Medical Center, Zaandam, Dept. of Gastroenterology and Hepatology[4], Medical Center Alkmaar, Alkmaar, Dept. of Gastroenterology and Hepatology[5], Kennemer Gasthuis, Haarlem, The Netherlands

In literature in 87-98% of colonoscopies, caecal intubation is inadequate. However, the magnitude of missed significant lesions in the unobserved part of the colon remains unknown and the efforts made by physicians to visualize the remaining part of the colon are still elusive.The aim of this project was to evaluate 1) the reasons for colonoscopic failure, 2) the diagnostic yield after a second investigation of the large bowel and 3) the highest diagnostic accuracy adjusted for the various procedures.In a population-based cohort study in the Amsterdam area, data of all colonoscopies performed during a three months period were analyzed to identify incomplete colonoscopies. Incompleteness was defined as inability to intubate the caecum. Secondary examinations to visualize the unobserved part of the colon were assessed until 18 months after the index colonoscopy. Follow up examinations included: repeated colonoscopy, CT colonography, barium enema, CT abdomen and surgical interventions involving the colorectum. Of 3149 procedures, 289 were incomplete (9.2%). Incomplete colonoscopy was predominant in females (OR 1.39; 95% CI: 1.09-1.79) and in procedures without conscious sedation (OR 2.65; 95% CI: 2.02-3.47). Reasons for failure included dolichocolon (19%), discomfort (13%), obstructing tumour (13%), suspected adhesions (13%), stenosis/diverticulosis (13%), insufficient preparation (12%) and severe inflammation (2%). Follow up examinations were performed in 55% of the patients. The remaining 45% consisted mainly of patients with IBS related complaints (14%), rectal blood loss (9%) and patients with full visualization of the colon < 1 year before (10%). With follow up examination, colorectal carcinoma was diagnosed in 16 patients (6%), advanced adenoma in 3 patients (1%) and other polyps in 6 patients (2%). In total 25 neoplastic lesions were found in 22 patients. In 23 patients (8%), other colon pathology was diagnosed (i.e. diverticulosis, inflammatory bowel disease, fistula). Neoplasia was predominantly found with repeated colonoscopy or surgical intervention.In conclusion, in 22 of 289 patients (8%) neoplasia was found that was missed by incomplete colonoscopy. Surgical intervention and repeated colonoscopy resulted in the highest secondary diagnostic yield. Therefore, in a mixed referral population incomplete colonoscopy should be followed by either a repeated colonoscopy/additional imaging and if necessary surgical intervention.

High Cumulative Risk of Intussusceptions in patients with Peutz-Jeghers Syndrome

M.G.F. van Lier[1], A. Wagner[2], A.M. Westerman[3], J.H.P. Wilson[3], F.W.M. de Rooij[3], E.J. Kuipers[1,3], M.E. van Leerdam[1], Dept of Gastroenterology and Hepatology[1], Dept of Clinical Genetics[2] and Dept of Internal Medicine[3], Erasmus MC, University Medical Center, Rotterdam, the Netherlands

Peutz-Jeghers Syndrome (PJS) is an inherited disorder characterized by gastrointestinal hamartomas and mucocutaneous pigmentation. A germline mutation in the STK11 gene can be found in 70% of clinically affected patients. The hamartomas are mainly located in the small bowel and may cause intussusceptions. Since balloon-enteroscopy (BE) enables endoscopic removal of small bowel polyps, we assessed genotype-phenotype correlations and the risk and onset of intussusception. Patients diagnosed with PJS based on clinical diagnostic criteria or proven STK11 mutation were included in this prospective cohort study (1995 - Nov 2008). Clinical data including sex, date of birth and death, diagnosis of PJS, STK11 mutation status, family history and diagnosis of intussusception were obtained by interview and chart-review. Genotype-phenotype correlations were evaluated. The cumulative risk of intussusception was calculated by Kaplan-Meier analyses. Forty-four PJS patients (57% males) were included out of 18 PJS families; 32 patients still alive had a median age of 44 years (range 10-74 yrs) and 12 patients had deceased at a median age of 45 years (range 11-73 yrs). A germline STK11 mutation had been detected in 32 patients (73%). Thirty-four patients (77%) had a history of one or more episodes of intussusception (range 1-6) due to small bowel polyps (one malignant degenerated polyp). The median age at which the first intussusception had occurred was 13,5 years (range 3-50 yrs). Surgery was required in 33 patients (75%), whereas in 1 case the invagination resolved spontaneously. There was no significant difference in intussusception incidence according to sex (p=0,15) or mutation-status (p=0,70). Kaplan Meier analyses showed that intussusception had occurred in 50% of the cohort at a median age of 16 years (95% CI 11-21), increasing to 75% (95% CI 62-88) at the age of 35 yrs. The 10-year probability of intussusception was 25% (95% CI 12-38).
Conclusion: PJS patients carry a high cumulative risk of intussusception (50% at 16 yrs) caused by small bowel hamartomas. The incidence of intussusception is not influenced by STK11 mutation status. These findings support the approach of enteroscopic surveillance with timely removal of small bowel hamartomas. The effect of this approach on the incidence of intussusception (as well as malignant degeneration) remains to be established and weighted against the burden and complication risk of the intervention.

Is colonoscopy screening mandatory for post-LTx recipients?

J. Sint Nicolaas[1], S.W.A. Tjon[1], H.J. Metselaar[1], E.J. Kuipers[1], R.A. de Man[1], M.E. van Leerdam[1], [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

Introduction: Liver transplantation (LTx) is being performed in a steadily increasing number of patients. Several malignancies are reported more often after LTx. In a Dutch LTx cohort an increased risk of colorectal cancer (CRC) was found compared to the general population (RR 12,5). However, other reports suggest that the overall incidence of CRC after LTx does not differ from the general population. Aim & methods: The aim of our study was to evaluate the observed rate of CRC in a post-LTx cohort and compare these data with the general population. All medical records of LTx patients with a follow up of at least 3 months were used. Patients were excluded if CRC was diagnosed before LTx. PSC patients were evaluated separately because of the known increased risk of CRC. Incidence rate of the general Dutch population were retrieved from the Dutch Comprehensive Cancer Centre. Results: 394 Patients (227 men (58%)) were included in the period 1986-2007. Colonoscopy or barium enema combined with sigmoidoscopy pre-LTx was performed in 89% of all patients with sub-acute or chronic liver failure. In patients with acute liver failure a bowel investigation was performed in only 48%. Median follow up after LTx was 5,1 years (range: 0,25-20 yrs). The mean age of the patients still alive was 52 years (SD 13 yrs). Overall mortality rate was 20,6% (81 deaths). The mean age of death among the non-survivals was 51 years (SD 13 yrs). During follow up, 72 patients (18%) developed one or more malignancies, including 24 patients with skin malignancies (6,1%) and 18 patients with lymphatic malignancies (3,6%). In total, 4 patients were diagnosed with CRC (1%). Two PSC patients developed CRC at 41 and 37 years while being under surveillance colonoscopy. Two other patients developed CRC at 65 and 55 years of age, respectively 17 and 1 year after LTx. None of these two patients had a bowel investigation prior to LTx. The expected CRC incidence using the general Dutch population was 2.72 per 2353 person-years, compared to 4 observed cases (2 PSC cases) per 2353 person-years.
Conclusion: This study shows that malignancies occur often, but suggests that the incidence of CRC was not increased in a large cohort of LTx patients compared to the incidence in the general Dutch population. Based on our data it seems not reasonable to advise a different CRC screening or surveillance program for LTx patients.

The burden of colonoscopy: gastroenterologists' ability to assess patients' most important issues of concern

M.J. Denters[1], M. Deutekom[2], H.H.F. Derkx[3], E. Dekker[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of Social Medicine, Academic Medical Center, Amsterdam, [3]Dept of Pediatrics, Academic Medical Center, Amsterdam, The Netherlands

Apart from surveillance of high-risk groups, mass-screening programs for colorectal cancer are being implemented throughout the western world. The effectiveness of these programs depends on the willingness of patients to undergo a colonoscopy. Therefore it is important to minimize the burden associated with the colonscopic procedure. To achieve this, insight into factors that contribute to this burden is essential. To assess gastroenterologists' (GE) ability to rate the most important issues on the burden of colonoscopy. An item list consisting of 55 items-of-concern was developed using patient focus groups. Both consecutive patients undergoing colonoscopy and GEs were asked to rate the importance of each item on a five-point scale. GEs were instructed to rate the importance from a patient perspective. 50 patients (50% male, mean age 52±15.9 years) and 35 GEs (68% male, mean age 44±0.9years) completed the list. Of the top 10 most important items identified by patients, 5 items were also present in the top 10 by GEs (respect, personal approach, results of colonoscopy directly after the procedure, information on the colonoscopy and the need for the procedure). Of the remaining 5 items, GEs rated opportunity to participate in choice for sedation and information on risks and complications significantly lower than patients (respectively 4.06 vs 4.52 (p=0.044) and 3.97 vs 4.38 (p=0.030)). Two items appearing in the GEs' top 10 were rated significantly lower by patients (pain experienced during colonoscopy and performance of the colonoscopy by one's own GE (respectively 4.12 vs 4.71 (p=0.012) and 3.12 vs 4.17 (p=0.03)). Conclusions: GEs correctly identified half of the top 10 items most important to patients. However, GEs overestimated the role of the patients' own doctor and the importance of pain. In contrast, they underestimated the importance of providing information on the risks of colonoscopies and involving the patient in the decision-making process.

In conclusion, although GEs showed to have some insight into the patient burden of colonoscopy, they were wrong on several important items. In an effort to achieve high attendance rates for colonoscopy in both screening and surveillance programs, a change in attitude among GEs is required, shifting attention from their own beliefs to involving the patient in the exploration and reduction of the burden of colonoscopy.

First population-based study on the incidence and prognosis of patients suffering from synchronous peritoneal carcinomatosis of colorectal origin

Y.L.B. Klaver[1], V.E.P.P. Lemmens[2], V.J. Verwaal[3], H.J.T. Rutten[1], J.W. Coebergh[2], I.H.J.T. de Hingh[1], [1]Dept of Surgery, Catharina Hospital, Eindhoven, [2]Dept of Research, Comprehensive Cancer Centre South, Eindhoven Cancer Registry, [3]Dept of Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Approximately one fourth of patients diagnosed with colorectal cancer (CRC) present with disseminated disease. A large number of these patients is affected by peritoneal carcinomatosis (PC). For a long time, this was considered to be an untreatable condition. However, new treatment modalities like HIPEC seem to be effective in selected patients. These developments request baseline data on the incidence and prognosis of PC. Currently these data are not available. The aim of this population-based study is to provide data on the incidence and prognosis of PC related to relevant patient and tumour characteristics, and to evaluate predictors for the development of synchronous PC. Between 1995 and 2006, 14,929 cases of primary CRC were diagnosed. Information on patient and tumour characteristics was registered by one of the cancer registry centres. The independent influence of relevant patient and tumour characteristics on the risk of presenting with PC was analyzed by means of a multivariable logistic regression analysis. Median survival in weeks was calculated by site of metastasis. In total, 718 patients with CRC were diagnosed with synchronous PC. From these patients, 399 patients had at least 1 metastasis elsewhere at time of diagnosis. In patients diagnosed with T3 and T4 colon tumors, PC was the single site of metastasis in 1.8% and 6% of patients, respectively. In patients with rectal carcinomas, these percentages were 0.4% and 6% respectively. The risk of synchronous PC among patients with CRC was significantly increased in case of an advanced T and N stage, a poor differentiation grade, and a right-sided localisation of the primary tumour.
Median survival of patients with PC as single site of metastasis was only 34 weeks. In patients with at least 1 additional metastasis on another location, median survival decreased to 22 weeks.
Concluding, 4.8% of patients diagnosed with primary CRC present with synchronous PC. This is associated with a poor survival of less than 34 weeks. In 44% of these cases, PC is the only site of metastasis. This group of patients may potentially benefit from treatment with HIPEC, which has shown to improve survival in selected patients. This is the first study providing reliable, population-based data on incidence and prognosis of peritoneal carcinomatosis from colorectal origin from a large group of patients.

Population based survival of patients suffering from peritoneal carcinomatosis does not improve over time despite increasing usage of palliative chemotherapy

Y.L.B. Klaver[1], G.J. Creemers[2], V.E.P.P. Lemmens[3], S.W. Nienhuijs[1], I.H.J.T. de Hingh[1], [1]Dept of Surgery, Catharina Hospital, Eindhoven, [2]Dept of Internal Medicine, Catharina Hospital, Eindhoven, [3]Dept of Research, Comprehensive Cancer Centre South, Eindhoven Cancer Registry, The Netherlands

Several trials have shown that treatment with palliative chemotherapy improves median survival of patients suffering from metastasised colorectal cancer. It is not clear however whether these results also apply to patients suffering from peritoneal carcinomatosis (PC). This is caused by the fact that PC cannot be detected on imaging studies and therefore these patients are usually not included in randomised trials. In order to investigate the effectiveness of chemotherapy in unselected patients with PC we analysed population-based survival data of patients who presented with synchronous PC at diagnosis. All patients diagnosed with PC of colorectal origin from 1995 to 2006 in the registration area of the Eindhoven Cancer Registry were included. Date of diagnosis was divided into two periods (1995-2000 and 2001-2006) according to the availability of chemotherapy for metastatic colon cancer. We assessed overall survival according to period. Follow-up was complete until December 31st, 2007. In total 811 patients with synchronous PC were diagnosed. Chemotherapy use gradually increased over time from 16% in 1995 to 42% in 2006 ($p<0.01$) for all ages. Chemotherapy usage was higher in patients aged <70 years (n=397), increasing from 25% in 1995 to 64% in 2006 ($p<0.01$). Median survival for patients diagnosed with PC only in 1995–2000 was 35 weeks [95% confidence interval (CI) 26-41], while patients diagnosed in 2001-2006 had a median survival of 30 weeks (95% CI 17-42). Median survival for patients diagnosed with PC with other metastases in 1995– 2000 was 20 weeks [95% CI 15-27], while patients diagnosed in 2001-2006 had a median survival of 24 weeks (95% CI 19-29). To compare these figures with median survival for unselected patients with synchronous metastases restricted to the liver: this increased in the same area and time frame from 34 weeks [95% CI 29-39] to 51 weeks [95% CI 43-57].
Conclusion: Despite the increasing usage of palliative chemotherapy and the availability of more potent agents in recent years the population based survival of patients with PC has not improved. These data suggest that palliative chemotherapy is not very effective in these patients. Treatment by Hyperthermic Intraperitoneal Chemotherapy (HIPEC), which has shown promising results in selected patients, may provide an interesting alternative.

Endoscopically removed malignant colorectal polyps with uncertain histological radicality: surgery or endoscopic follow-up?

L. van Nunspeet[1], J.W. Arends[2], F. ter Borg[1], E.J. Kuipers[3] Depts. of Gastroenterology[1] and Pathology[2], Deventer Ziekenhuis, Deventer, [3]Dept of Gastroenterology, Erasmus Medical Centre, Rotterdam, The Netherlands

Adenomatous polyps may harbour adenocarcinoma. Additional surgical resection is recommended when radicality can not be ascertained, i.e. malignant cells are within 2 mm of the resection margin. Pathological judgement is hampered, however, by cauterisation effects or fragmentation of the specimen. Taking biopsies from the luminal scar is another way to investigate the radicality of the endoscopic resection (ER). It has been shown, that when these biopsies are negative, the association between histological irradicality and lymph node metastasis is absent.The aim of this study was to analyse the safety of endoscopic follow-up (FU) in patients with ER of submucosal (T1) or intra-mucosal (IM) adenocarcinomas, when radicality can not be guaranteed histologically but biopsies of the scar show no residual malignancy.Patients with ER of T1/IM adenocarcinoma were retrospectively identified using pathology reports from 1999 to 2008. Data were obtained using clinical, colonoscopic and pathological records. Cases with metastatic disease or requiring surgery for adenocarcinoma elsewhere in the colon were excluded.Thirty-nine patients met our selection criteria. Surgical resection was preferred by 3 patients; no tumour was found in the resection specimen. Endoscopic FU with biopsies of the scar was undertaken in 36 patients. During FU, a lesion suitable for ER (T1 carcinoma in a polyp, carcinoma in situ, IM lesion) was found in the scar of 3 patients after 2, 3 and 7 years. After ER, the remaining scar was free of malignancy again. Nevertheless, one patient preferred additional surgery: no tumour was found.One patient underwent surgery for a small but endoscopically unresectable adenocarcinoma of the scar, after 11 months of FU. It turned out to be a T2N1 tumour. There is no recurrence at this moment, 7 years later. One very old patient with severe cardio-pulmonary comorbidity was lost to FU. The remaining 33 patients are still included in our FU program without recurrence of adenocarcinoma. Up to now, 20 patients have been followed for more than 2 years; 14 of them have undergone a colonoscopy after more than 2 years (median 4.8 years). Our data suggest that endoscopic FU of endoscopically resected T1/IM adenocarcinomas is safe when biopsies from the scar show no malignancy. None of the patients that preferred operation had residual tumour. Prospective evaluation of this strategy is warranted.

Inter-observer variation in the histological diagnosis of polyps in colorectal cancer screening

P.G. van Putten[1], L. Hol[1], H. van Dekken[2], J.H. van Krieken[3], M. van Ballegooijen[4], M.E. van Leerdam[1] and E.J. Kuipers[1,5], [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [2]Dept of Pathology, St. Lucas Andreas Hospital, Amsterdam, [3]Dept of Pathology, University Nijmegen Medical Center, Nijmegen, [4]Dept of Public Health, Erasmus University Medical Center, Rotterdam, [5]Dept of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

Background: Colorectal cancer (CRC) screening has been shown to be effective in reducing CRC incidence and mortality. Histopathological identification of colorectal lesions plays a crucial role in patient management and surveillance. However, concern has been expressed about the reproducibility of the histological interpretation of colorectal polyps. Aim: To determine the interobserver variation in the histological diagnosis of colorectal polyps detected in a CRC screening program. Methods: 299 polyps were randomly selected from a population-based CRC screening program (CORERO study) from the Netherlands. Polyps were first evaluated by a general (184 polyps) or expert gastrointestinal (115 polyps) pathologist. The polyps were then blindly re- evaluated by one of two expert gastrointestinal pathologists. Histopathological specimens were identified according to current guidelines. Conditional agreement was reported and inter-observer agreement was determined by using Cohen κ statistics. Results: In 286/299 polyps (96%) agreement for the non-adenomatous or adenomatous nature of polyps was obtained, corresponding with a very good kappa off 0.89. There was consensus for 73 non-adenomatous and 213 adenomatous polyps. Differentiating adenomatous polyps in non-advanced and advanced adenomas (>25% villous component or high grade dysplasia) obtained consensus in 181/213 adenomas (85%), including 147 non- advanced adenomas and 34 advanced adenomas. Interobserver agreement for non-advanced versus advanced adenoma was substantial with kappa 0.62. Categorising adenomas in tubular versus >25% villous component obtained consensus in 180/211 (85%) with kappa 0,57. Agreement for low or high grade dysplasia was found in 204/213 (96%) with kappa 0.55. Overall consensus for categorising polyps in non-adenoma or adenoma, histological type and grade of dysplasia was obtained in 242/299 polyps (81%). For the adenomatous or non-adenomatous nature, both general and expert pathologists, and expert pathologists showed very good agreement (kappa 0.90 and 0.86, respectively). Categorizing adenomas in advanced and non-advanced adenomas showed substantial agreement between general and expert pathologists, and between expert pathologists (kappa 0.60 and 0.64, respectively). Conclusion: Pathologists demonstrated very good interobserver agreement in the differentiation between non-adenomatous and adenomatous colorectal polyps in a CRC screening program. However, agreement was only substantial for categorizing adenomas in non-advanced and advanced adenomas. Inter-observer variability was not different between general and expert pathologists, and between expert pathologists.

A Gly82Ser polymorphism of RAGE is not associated with gastric or colorectal cancer in a Western population

E. Hoff, J.J. van der Reijden, A.A. Dihal, H.W. Verspaget, D.W. Hommes, G.R. van den Brink, Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands

Introduction: In recent years it has become evident that activation of the innate immune system plays an important role in cancer development. The receptor for advanced glycosylation endproducts (RAGE) is a pattern recognition receptor that activates the innate immune system in response to proteins such as HMGB1 and S100 proteins. These ligands and RAGE itself are up regulated in colon carcinomas. Animal experiments have shown that Rage null mice are protected against tumorigenesis, suggesting that RAGE signaling may also be important in cancer development. The G82S polymorphism is a functional single nucleotide polymorphism at codon 82 of RAGE which alters the ligand binding domain and enhances its function. This polymorphism has been linked to gastric cancer in a Chinese population (Clin Cancer Res. 2008; 14:3627). We investigated whether this polymorphism is linked to gastric and colon cancer in a Western population. Methods: DNA was isolated from blood or tissue of 235 patients with colorectal cancer, 75 patients with gastric cancer and 165 healthy volunteers. A PCR was performed, the 397 bp PCR product was digested by the restriction enzyme Alu1. The digestion resulted in two fragments in the wild-type Gly82 allele, three fragments in the variant Ser82 allele and four fragments in patients carrying both of these alleles. Results: We found a prevalence of the 7/165 (4%) of the heterozygous G82S genotype in the healthy volunteers. No carriers of the homozygous 82Ser/Ser genotype were found in our western population. There was no difference in prevalence of the heterozygous genotype between the group of gastric carcinoma patients, 3/75 (4%) and controls. In the colorectal cancer patient group we found a non-significant higher frequency of the heterozygous genotype, 14/235 (6%) compared to our controls.
Conclusion: The prevalence of the gly82ser polymorphism (4% heterozygous) is significantly lower in a Western population compared to that reported in the Chinese population (44%). We found a slightly higher prevalence of the 82Ser allele in patients with colorectal carcinomas, but, possibly because of the low prevalence of this mutant allele, we could not identify this genotype as a risk factor for gastric or colorectal cancer.

Early or delayed laparoscopic cholecystectomy after endoscopic sphincterotomy for common bile duct stones: A prospective randomized multi-centre trial

J.S.K. Reinders[1], A. Goud[1], R. Timmer[2], Ph.M. Kruijt[3], B.J.M. Witteman[4], N. Smakman[5], R. Breumelhof[6], S.C. Donkervoort[7], J.M. Jansen[8], B. van Ramshorst[1], D. Boerma[7].,Depts of Surgery[1] and Gastroenterology[2], St. Antonius Hospital Nieuwegein, Depts of Surgery[3] and Gastroenterology[4], Hospital Gelderse Vallei, Ede, Depts of Surgery[5] and Gastroenterology[6], Diakonessenhuis, Utrecht, Depts of Surgery[7] and Gastroenterology[8], Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Patients with combined choledochocystolithiasis generally undergo endoscopic sphincterotomy (ES) followed by laparoscopic cholecystectomie (LC). The timing of the operation, remains a matter of debate. Nowadays patients are being scheduled for surgery, for practical reasons, between 6 and 8 weeks after ES. Conversion rate of elective LC after ES is high (up to 25%). The timing of surgery may influence these figures. During the waiting period, recurrent biliary events may occur, further compromising the clinical course of the patient. In a prospective, randomized, multicenter trial patients with combined choledochocystolithiases, who underwent successful endoscopic retrograde cholangiography (ERC) with ES, were randomised between LC within 72 hours after ES, or LC after 6-8 weeks. Based on an expected difference in conversion rate of 25% versus 5% 96 patients were randomised. Conversion rate, duration and difficulty of surgery, postoperative morbidity and hospital stay were scored. Postoperative pain was and perfomance status were measured until 14 days after surgery. Analysis was based on an Intention-to-treat principle. 49 patients were allocated for early LC, and 47 patients for 'delayed' LC. Both groups were comparable in age, sex, and co-morbidity. Surprisingly, there was no difference between both groups in conversion rate (4% in early group vs 8% in late group), nor was there any difference in operating time and/or difficulty. Postoperative morbidity and hospital stay were comparable. Consequently, postoperative pain and functional impairment were also the same. However, during the waiting period for LC at least 12 of the 47 patients (25%) in the delayed group developed recurrent biliary events, versus 0 patients in the early group (p=0.00, LR=18.9). Nine patients (19%) suffered from recurrent biliary colics and 3 patients (6%) developed a cholecystitis for which they needed emergency surgery. This is the first prospective randomized trial that addresses the issue of timing of LC after ES in patients with combined choledochocystolithiasis. The expected difference in conversion rate was not found. On the other hand, early LC, i.e. within 72 hours after ES, appeared to be safe. Most importantly recurrent biliary events, seen in almost every fourth patient in the delayed group, were being avoided by early LC. Thus, for the patient's well being, as well as for imaginable socioeconomic reasons, LC should be performed as soon as possible after ES.

Are hyperplastic polyps precursors of colorectal cancer? A long-term, retrospective study

M. Bouwens[1], E. Rondagh[1], B. Winkens[2], A. Driessen[3], A. De Bruine[3], A. Masclee[1], S. Sanduleanu[1], Dept of Gastroenterology and Hepatology[1], Dept of Methodology and Statistics[2], Dept of Pathology[3], Maastricht University Medical Center, Maastricht, the Netherlands

Traditionally, hyperplastic polyps of the colon were considered to be innocent lesions, with no malignant potential. However, the recently discovered alternative serrated pathway to colorectal cancer (CRC) suggests that at least some of these polyps are potential precursors for CRC. The aims of this study were i) to investigate the relation between hyperplastic polyps and the development of CRC and ii) to analyze the predictors for colorectal cancer in patients with hyperplastic polyps. Patients were retrospectively selected using a national pathology database (PALGA). Between 1991-1998, 943 hyperplastic polyps were detected in 568 patients undergoing diagnostic colonoscopy at our university hospital. Endoscopical data regarding number, size and location of the polyps at the index-colonoscopy were recorded. Endpoints were CRC, last colonoscopy or death. Outcome data were available using the registration database of the Regional Comprehensive Cancer Center. Kaplan-Meyer analysis was used to calculate the risk of CRC in patients with hyperplastic polyps. Results: A total of 568 patients were included (mean (SEM) age: 60 (±1) years, 57% males), 410 patients with hyperplastic polyps only and 158 patients with hyperplastic polyps and also adenomas. Prevalence of CRC was 3.5% during a median follow-up period of 11 years (20 CRC cases), in line with prevalence of CRC in the general Dutch population. CRCs tended to be more frequently located in the right colon compared to the left colon (2.5% versus 1.1%, p=0.074). Multivariate analysis showed that presence of multiple hyperplastic polyps (hazard ratio 2.7, 95% CI 1.1 – 6.9; p=0.043), as well as presence of large (> 5 mm) hyperplastic polyps in the right colon (hazard ratio 7.8, 95% CI 3.0 – 20.5 p < 0.0001) were independent risk factors for the development of CRC. The concomitant presence of adenomas was not an additional risk factor for the development of CRC.
Conclusion: Patients with large, right-sided hyperplastic polyps have nearly 8-fold increased risk for development of colorectal cancer. These data reinforce the potential role of the serrated pathway in the pathogenesis of CRC. As surveillance of patients with high-risk hyperplastic polyps remains controversial, development of guidelines is indicated.

Adult human liver contains residential mesenchymal stem cells which mobilize during liver transplantation and contribute to immunomodulation and hepatic regeneration

Q. Pan[1], S.M.G. Fouraschen[2], F.S.F. Aerts-Kaya[3], M.M.A. Verstegen[3], A. van der Sloot[2], R. Smits[1], J. Kwekkeboom[1], H. Metselaar[1], H.W. Tilanus[2], G. Wagemaker[3], H.L.A. Janssen[1] and L.J.W. van der Laan[2], Depts of [1]Gastroenterology & Hepatology; [2]Surgery and [3]Hematology, Erasmus MC - University Medical Center Rotterdam, The Netherlands

Mesenchymal stem cells (MSC) have multi-lineage differentiation capacity and play an important role in responses to tissue injury by promoting regeneration and dampening inflammatory by their immunomodulatory properties. Though present in human fetal liver, it is unknown whether MSC are resident in adult human liver and can respond to transplantation-associated injury. The aim of this study is to investigate the presence of MSC in human liver and demonstrate their mobilization, engraftment, differentiation and anti-proliferative potential in liver transplantation. Liver tissue samples (n=13) and perfused graft preservation fluids (perfusates, n=15) were collected for MSC isolation at the time of liver transplantation. Characterization of cultured liver and bone marrow (BM) MSC was determined by adipocyte and osteocyte differentiation, gene expression profiles, suppressive effects on T cell proliferation, hepatic differentiation and cell transplantation in immunodeficient NOD/SCID mice. Liver tissue samples as well as perfusates contained a small (<0.1%) but consistent population of cells expressing MSC markers CD90, CD105 and CD166. These cells rapidly expanded upon culturing, could be subcultured for at least 15 passages and showed distinctive fibroblast-like morphology. Cells displayed a characteristic MSC phenotype that is highly positive for CD90, CD105, CD166, and negative for CD34, CD45, HLA-DR. Liver MSC effectively differentiated into adipocyte, osteoblasts and hepatocyte lineages. Hepatic-differentiated MSC gained the ability to support hepatitis C virus replication, a characteristic property of hepatocytes. In vivo, in a CCL4 liver injury model both liver and BM MSC showed hepatic differentiation as demonstrated by albumin immunostaining and RT-PCR (n=5). Importantly, MSC could be retrieved and rapidly expanded from the mice liver even at four weeks after engraftment, indicating their self-renewal capacity. Undifferentiated MSC possessed potent immunosuppressive capacity, shown by significant inhibition of allogenic or mitogenic stimulated T cell proliferation in vitro (92% average inhibition at MSC:T-cell ratio 1:4, $p<0.001$).
Conclusions: Multipotent MSC are present in adult human liver tissue and mobilize from the liver graft at time of transplantation. Immunomodulation, hepatic differentiation and self-renew capacity of liver MSC suggest that they may contribute to injury responses as well as allo-immune regulation after liver transplantation.

Genetic and mucosal expression analysis shows important roles for JAK2 and MST1 in the pathogenesis of ulcerative colitis and identifies more susceptibility loci

E.A.M. Festen[1,2], P.C. Stokkers[3], M.C. Wapenaar[2], C.C. van Diemen[2], A.A. van Bodegraven[4], M. Bruinenberg[2], H.M. Boezen[5], J.B.A. Crusius[6], D.W. Hommes[7], C.J. van der Woude[8], T. Balschun[9], H.W. Verspaget[7], S. Schreiber[9], D.J. de Jong[10], A. Franke[9], K.N. Faber[1], G. Dijkstra[1], C. Wijmenga[2], and R.K. Weersma[1],*, [1]Dept of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, [2]Dept of Genetics, University Medical Centre Groningen and University of Groningen, Groningen, the Netherlands, [3]Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, the Netherlands, [4]Dept of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, the Netherlands, [5]Dept of Epidemiology, University Medical Centre Groningen and University of Groningen, Groningen, the Netherlands, [6]Dept of Immunogenetics, VU University Medical Centre, Amsterdam, the Netherlands, [7]Dept of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, the Netherlands, [8]Dept of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, the Netherlands, [9]Institute for Clinical Molecular Biology, Christian Albrechts- University, Kiel, Germany, [10]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.*
**These authors contributed equally to this work.*

Genetic susceptibility is known to make a major contribution to the pathogenesis of ulcerative colitis (UC). Recently three studies, including a genome-wide association study (GWAS), reported novel UC risk loci. The top-20 SNPs from the UC-GWAS and eight SNPs from two additional studies were genotyped in 561 UC cases and 728 controls and were replicated in 894 UC cases and 1174 controls from the Netherlands. A combined analysis for all patients (n=1455) and controls (n=1902) was performed. We determined mRNA expression of the associated genes in inflamed and non-inflamed mucosa of untreated UC patients and healthy controls. Cumulative risk models were constructed with the associated risk alleles. We found 12 SNPs tagging ten loci, including HLA-DRA, IL10, IL23R, JAK2, S100Z, ARPC2, ECM1 and MST1, to be associated with UC. We identified GAS7 and 10q26, flagged by the UC-GWAS, as novel UC loci. No association with disease localisation or severity was found. Several genes, including JAK2, were differentially expressed in inflamed UC mucosa. MST1 had a lower expression in untreated non-inflamed mucosa of UC patients compared to healthy controls. Individuals carrying 11 or more risk alleles have an OR of 8.2 (CI 3.0-22.8) for UC susceptibility.
Conclusions: We confirmed the association of multiple loci with UC in the Dutch population and found evidence for association of GAS7 and 10q26. Genetic and mRNA expression analysis shows important roles for JAK2 and MST1. Cholinergic co-stimulation, either through the vagus nerve or through chemical substances, such as nicotine, exert their anti-inflammatory effect partly through JAK2-signalling. The protective effect of smoking to ulcerative colitis could be explained by the role of JAK2 in disease pathogenesis. The protein encoded by *MST-1* is able to suppresses cell-mediated immune responses by downregulating interleukin 12 production and thus inhibiting the activation of macrophages. Our expression data imply that UC patients have an impaired function of *MST-1* making them less able to down-regulate an initial innate immune response. Finally, the genetic models show that multiple risk loci in an individual increase the risk for developing UC: someone with eight risk alleles has an almost four times higher risk for ulcerative colitis than someone with two risk alleles. This suggests that genetics may eventually become useful in disease prediction.

Preservation of intestinal integrity precedes anti-inflammatory actions of lipid-rich enteral nutrition

J. de Haan[1], G. Thuijls[1], T. Lubbers[1], M. Hadfoune[1], J.P.M. Derikx[1, 3], M.D. Luyer[1,3], W.A. Buurman[1], J.W.M. Greve[2,1], [1]Surgery, Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University Medical Center, Maastricht; [2]Surgery, Atrium Medical Center, Heerlen; [3]Surgery, Maaslandziekenhuis, Sittard, the Netherlands

Intestinal integrity loss as a result of splanchnic hypoperfusion is considered crucial in the development of inflammatory complications following surgery and trauma. Previously, we demonstrated that the inflammatory response is preceded by intestinal cell damage. Enteral lipid-rich nutrition was identified as a potent physiological activator of the cholinergic anti-inflammatory pathway. Here, the effects of lipid-rich nutrition are investigated on splanchnic perfusion and intestinal integrity directly following hemorrhagic shock before systemic inflammation develops. Shock in rats was induced by extracting 30-40% of circulating volume. Rats were fasted or received a lipid-rich (containing 30% phospholipids) or a control low-lipid nutrition at 18 hours (3ml), 2 hours (0.75ml) and 45 minutes (0.75ml) before shock. Following shock, rats were sacrificed at 30, 60 and 90 minutes (each group n=6). Splanchnic perfusion at 15 minutes after shock as studied with Laser Doppler was not affected by pre-feeding, however between 15 and 90 minutes following shock lipid-rich treated animals showed enhanced recovery of perfusion (22.9±2.5% vs fasting: 6.9±4.0% increase; $p<0.05$). Gut permeability to horse radish peroxidase (HRP) was significantly reduced at 30 minutes and later timepoints by lipid-rich nutrition (30 minutes: 264±46 vs low-lipid: 487±50; $p<0.05$ and fasted: 738±35 ng/ml; $p<0.01$). In line, at 30 minutes bacterial translocation was decreased in lipid-rich fed animals (11±1 vs. low-lipid: 18±2; $p<0.05$ and fasted: 35±3 CFU/g tissue; $p<0.01$). Circulating ileal lipid binding protein (ILBP) was measured as a marker of enterocyte damage. Whereas plasma levels of ILBP were hardly detectable at 30 minutes, at 60 minutes post-shock lipid-rich animals showed significantly reduced concentrations compared with fasted animals (5.1±1.4 vs 11.4±5.1 ng/ml; $p<0.05$). In accordance with previous studies, plasma concentrations of TNFα, an early marker of systemic inflammation, were strongly reduced by lipid-rich feeding compared to low-lipid and fasted groups first at 90 minutes post-shock ($p<0.05$).
In conclusion, this study shows that enteral lipid-rich nutrition preserves gut barrier function as early as 30 minutes after hemorrhagic shock and improves splanchnic perfusion before systemic inflammation develops. The mechanism that underlies the protective actions of lipid-rich feeding on immediate intestinal integrity loss following shock is subject of further studies.

Central venous catheter related complications and experienced problems in HPN dependent patients

G. Huisman-de Waal[1], L. Schoonhoven[1], G. Wanten[2] , J. Jansen[2], H. Sauerwein[3], T. van Achterberg[1], [1]IQ Healthcare, Nursing Science, [2]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, [3]Dept of Endocrinology and Metabolism, University Medical Centre Amsterdam, the Netherlands

More than 35 years after its introduction, venous access (VA)-related complications remain the most important drawback of home parenteral nutrition (HPN) treatment. In addition to these complications, HPN patients also experience significant psychosocial problems in daily life, mainly comprising depression, social impairment and fatigue. The aim of the present retrospective analysis is to present an overview of VA-related complications in the population of patients on HPN in the Netherlands and to assess whether these adversities are related to the experienced psychosocial problems and quality of life (QoL). Information on VA-related complications was collected retrospectively from the medical records of all 110 adult patients who had been on HPN for more than 3 months in The Netherlands in 2006. In addition, a survey was performed in 75 amenable patients of this group to characterize the experienced psychosocial problems and assess their association with VA-related complications. HPN was administered over a central venous catheter (Hickman/Broviac catheter or Porth-a-cath) or an arteriovenous fistula (shunt). The majority of patients (76%) had already been confronted with infectious VA complications, with on average 3.5 ± 4.3 infections (range 0 to 20, 1.08 ± 1.3/ VA yr). VA occlusions had occurred on average 1.85 ± 3.2 times per patient (range 0 to 17, 0.27± 0.5 / VA yr). Other complications, such as exit site infections or dysfunction of the catheter occurred 1.1 ± 1.7 times per patient (range 0 to 7, 0.24 ± 0.6/ catheter yr). There were no significant differences between the two included HPN centers. In addition, our analysis showed a significant relation between the rate of VA-related complications, and psychosocial complaints, in the form of depression (r=.295, p=.011), fatigue (r=.304, p=.009), social impairment (r=.342, p=.003), and QoL (r=-.381, p=.001).
Conclusion: Vascular access-related complications remain the major drawback of HPN treatment and are experienced by the vast majority of HPN patients in the Netherlands. Our consistent finding is that these access-related complications significantly influence QoL and confer depression, social impairment, and fatigue in a rate-dependent manner. Taken together, our findings underscore the need for preventive strategies in this respect.

Effects of corticosteroids on bone metabolism in patient with active Crohn's disease

D.J. de Jong[1], C.G.J. Sweep[2], A.R.M.M. Hermus[3], R. Greinwald[4], R. Mohrbacher[4], A.H.J. Naber[5], Depts of [1]Gastroenterology and Hepatology, [2]Chemical endocrinology, [3]Endocrinology, Radboud University Nijmegen Medical Centre, Nijmegen, [4]Dept of Research and Development, Dr. Falk Pharma Gmbh, Freiburg, [5]Dept of Gastroenterology, Tergooi Hospital Hilversum, the Netherlands

The etiology of osteoporosis in Crohn's disease is multifactorial. Factors such as malabsorbtion, systemic inflammation and the use of corticosteroids all may play a role. Aim of the present study is to determine predictive factors for changes in bone metabolism in patients treated with corticosteroids. In a prospective randomized controlled trial, 27 Crohn's disease patients were treated with either prednisone (40 mg with tapering to 10 mg) or high dose budesonide (18 mg) as induction therapy. At baseline and after 2 months data were obtained concerning bone metabolism (dual energy X-ray absorptiometry, alkaline phosphatase, serum osteocalcin, pro- and telopeptide of type 1 collagen (P1CP and 1-CTP)), disease activity (CDAI, ESR, ex-vivo production of cytokines, serum albumen), the pituitary-adrenal axis (serum cortisol, 24-hr urinary cortisol excretion, ACTH) and parathyroid hormone (PTH). These potentially predictive factors for changes in bone metabolism were analyzed by multivariate analysis. In 8 weeks, CDAI decreased significantly from 259 ± 58 to 122 ± 84 in the budesonide group and from 267 ± 71 to 174 ± 110 in the prednisone group. Overall, the change in bone mineral density was -2.0 ± 3.6% in the femoral neck (p 0.01) and +0.03 ± 4.9% in the lumbosacral spine (NS). This was accompanied by a non-significant 18.6 ± 39.7% decrease in serum osteocalcin (p=0.06). Changes in P1CP and 1-CTP were not significant. Multivariate analysis showed baseline PTH as the only independent predictor for change in femoral BMD at a significance level of 0.1. For the change in lumbar spine BMD, baseline PTH, change in PTH, serum albumen and serum alkaline phosphatase were independent predictors.
Conclusion: During 8 weeks treatment of active Crohn's disease with corticosteroids, a significant decrease in BMD occurs in the femoral neck, but not in the lumbar spine. Changes in serum osteocalcin, 1-CTP and P1CP levels were not significant. Changes in disease activity and adrenal axis were no independent predictors for bone loss, while baseline PTH level do seem to play an independent role.

Detection of Tropheryma whipplei DNA in intestinal biopsy specimens with a novel real-time PCR

M.E. Grasman[1], A.M. Pettersson[2], A.G. Koek[2], C.J. Mulder[1], P.H.M. Savelkoul[2], A.A. van Bodegraven[1], [1]Dept of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, [2]Dept of Medical Microbiology and Infection Control, VU University Medical Centre, Amsterdam, the Netherlands

Introduction: Whipple's disease (WD) is a rare, multisystemic infectious disease caused by the bacterium Tropheryma whipplei (Tw). Periodic acid Schiff (PAS) stain is usually performed to diagnose the disease. PCR is currently used to confirm the presence of Tw DNA. However, conventional PCR is not specific, whereas real-time PCR (rtPCR) based on the 16S rRNA gene is insensitive since only one copy of the gene is present in Tw genome. Recently, we developed a novel, more sensitive and specific rtPCR to detect the presence of Tw DNA. Aims: To determine prevalence of Tw in duodenal and colonic biopsy specimens with rtPCR in a random population of patients undergoing routine gastroscopy or colonoscopy. Materials and methods: Mucosal biopsy specimens from the duodenum or sigmoid were harvested from subsequent patients undergoing upper or lower endoscopy. Most frequent indications for gastroscopy were dyspepsia, pyrosis, and follow-up of celiac disease. Common indications for colonoscopy were colorectal cancer screening and surveillance, and abdominal pain. Specimens were analyzed by rtPCR targeting an exclusive, repetitive sequence which is seven times present in the Tw genome. Results: In total, 48 duodenal and 90 colonic mucosal biopsy specimens of 118 patients were analyzed. Of these patients, 40% were men, mean age 54y (range 18-84y). Normal appearance of duodenal and colonic mucosa was found in 87% and 83%, respectively. Main abnormalities found in the duodenum were signs of celiac disease (CD). Abnormalities of colonic specimens included signs of IBD and pseudomelanosis coli. Of the duodenal and colonic specimens 2.1% and 6.7% were positive in the Tw rtPCR, respectively (mean age 43y, male/female: 2/5). One showed CD at microscopy, whereas all others were normal. In another patient, signs and symptoms of WD were recorded namely arthralgia, weight loss and peripheral neuropathy. The Cycle threshold-value of the PCR was considerably lower in this patient, consistent with a high load of Tw DNA.
Discussion/Conclusion: With a novel rtPCR, Tw DNA is present in duodenal or colonic biopsy specimens in a proportion of patients without signs or symptoms of WD. Therefore, additional factors, other than merely the presence of Tw, play a role in development of disease. Initiation of antibiotic therapy against Tw may not exclusively depend on positive PCR findings, but should also be based on PAS stain and signs and symptoms of WD. Clinical significant WD appears to be associated with a higher Tw load.

Ten-year Outcome of Laparoscopic and Conventional Nissen Fundoplication: Randomized Clinical Trial

J.A.J.L. Broeders[1], H.G. Rijnhart – de Jong[1], W.A. Draaisma[1], A.J. Bredenoord[3], A.J.P.M. Smout[2], H.G. Gooszen[1], Gastro-enterologische onderzoeksgroep van het Universitair Medisch Centrum Utrecht Afdeling Heelkunde[1] en Maag-Darm-Leverziekten[2] Afdeling Maag-Darm-Leverziekten, St. Antonius Ziekenhuis, Nieuwegein[3], The Netherlands

Laparoscopic Nissen fundoplication (LNF) has replaced conventional Nissen fundoplication (CNF) as surgical treatment of choice for PPI-refractory gastro-oesophageal reflux disease (GORD). Decisions are based on early results but long-term results of randomised clinical trials (RCTs) are lacking. This study aimed to compare ten-year outcome of a multicentre RCT on LNF and CNF. From 1997 to 1999, 177 PPI-refractory GORD patients were randomised to undergo LNF or CNF. The ten-year results of surgery on reflux symptoms, general state of health (GsH), quality of life (QoL), PPI use and reoperation rates, are described. A total of 133 patients participated in this ten-year follow-up study: 70 patients after LNF and 63 patients after CNF. General GORD symptoms were relieved in 92.2% and 89.8% after LNF and CNF, respectively. At ten years, heartburn and dysphagia grades were similar, but more patients had relief of regurgitation after LNF (98.4 vs 90.2%; P=0.048). The percentage of patients using PPIs increased similarly with time in both groups to 19.4% for LNF and 24.0% for CNF. Twice as many patients underwent reoperation after CNF (12 (17.1%) for LNF vs 21 (33.3%) for CNF; P=0.031), including a higher number of cicatricial hernia corrections after CNF (1 vs 7; P=0.019). Mean interval between operation and reintervention was longer after CNF (13.9 vs 47.1 months; P=0.004). GsH improved in a higher percentage after LNF compared to CNF (81.3 vs 64.0%; P=0.034). QoL was higher after LNF than after CNF as well (VAS-score: 62.6 vs 57.0; P=0.246). The percentage of patients that would not have chosen surgery again in retrospect, was slightly higher after CNF (7.8 vs 18.0%; P=0.100). High resolution manometry and 24-h pH-impedance monitoring are currently being performed in patients using daily PPIs at ten years (10 LNF, 10 CNF) and will be presented at the meeting in case of acceptance.
Conclusions: Long-term effectiveness of laparoscopic and conventional Nissen fundoplication is comparable in terms of reduction of GORD symptoms and PPI use. CNF carries a higher risk for surgical reintervention compared to LNF. Improvement of general health, quality of life and patient satisfaction are higher after LNF. Consequently, this RCT on long-term results of antireflux surgery supports the use of LNF as the procedure of choice for PPI-refractory GORD.

Audit on the Dutch 2001 guideline for the use of sedation during gastrointestinal endoscopy

R.W.F. ter Steege[1], P. Fockens[2], S. van den Hazel[3], J.J. Kolkman[1], [1]Gastroenterology, Medical Spectrum Twente, Enschede, the Netherlands, [2]Gastroenterology and hepatology, Academic Medical Centre, Amsterdam, [3]Gastroenterology Slingeland Hospital, Doetinchem, the Netherlands

In 2001, the Dutch society of Gastroenterology developed a guideline to improve the quality and safety of sedation during GI endoscopic procedures. The main advices were: Pulse oxymetry during and after sedation in all patients, and blood pressure monitoring when using a combination of sedative drugs. We performed a nationwide audit on this guideline. An online questionnaire was sent to all gastroenterologists in the Netherlands. The questions concerned the use of sedation, the type of monitoring during and after sedation, and the number of serious complications related to sedation. Data were analyzed per hospital. Sixty-three of the 75 hospitals returned the questionnaire (response 87%). In these hospitals, 155,790 gastroscopies, 123,037 colonoscopies, 14,532 ERCP's and 7,430 EUS were performed. ERCP and EUS were always performed with sedation, mean 81% of the colonoscopies and mean 15% of the gastroscopies. Midazolam was used in all hospitals, fentanyl in 76%. All patients are monitored during sedation by dedicated personnel. Pulse oxymetry is always used in 95.2% and in 4.8% on indication only. Blood pressure monitoring is always used in 20%, on indication in 42%; in 38% no blood pressure is monitored. During recovery, 80% is monitored by dedicated personnel. Pulse oxymetry is used in 60%, and blood pressure measurement in 20%. In 31/63 of the hospitals, less than 0.1% of the endoscopies had to be preliminary ended due to a sedation related event. 25/63 hospitals estimated this percentage at 0.1-1%, 7/63 hospitals at >1%. Three deaths were reported, all caused by cardio respiratory arrest (mortality 1/110,000). Fifteen serious sedation related complications were reported (complication rate 1/22,500). Eleven complications were due to apnea or serious hypoventilation. There was one case of myocardial infarction, one case of epileptic seizure and four cases of cerebral vascular accident.
Conclusions: The guideline on sedation during endoscopy has been well implemented. Pulse oxymetry and personal observation during endoscopy is standard. Monitoring during recovery is less rigidly implemented. Mortality and complication rates are low but may be underestimated due to the retrospective nature of this audit.

Pre-procedural screening of patients undergoing gastrointestinal endoscopy; the current status in the Netherlands

R.W.F. ter Steege[1], P. Fockens[2], S. van den Hazel[3], J.J. Kolkman[1], [1]Gastroenterology, Medical Spectrum Twente, Enschede, the Netherlands, [2]Gastroenterology and hepatology, Academic Medical Centre, Amsterdam, [3]Gastroenterology Slingeland Hospital, Doetinchem, the Netherlands

In 2001, the Dutch Society of Gastroenterology developed and implemented a guideline with emphasis on safety monitoring during GI-procedures. It had no formal recommendations on pre-sedation screening. A new guideline is being developed focused on 1) screening the patient before using sedative drugs during GI-endoscopy (pre-procedural screening) and 2) exact registration of procedural sedation and complications. In this study we report on the current policy of pre-procedural screening and registration in the Netherlands. An online questionnaire was sent to all gastroenterologists in the Netherlands. The questions concerned, apart from monitoring policy and complication rates, the practice on pre-procedural screening and the current registration policy towards endoscopic procedures, procedural sedation and complications. Data were analyzed per hospital. Sixty-three of the 75 hospitals returned the questionnaire (response 87%). In these 63 hospitals, 300,790 endoscopies were performed in 2007, of which procedural sedation was used in mean 145,130 (48%) (estimated range 119,115-171,145, 40-56%). Monitoring during sedation was performed in 100%, after sedation in more than 80%. A registration database on procedural sedation was used 20%. Twenty-two percent has a systematical registration for endoscopies being preliminary aborted due to sedation related complications. In 27 hospitals (43%) no pre-procedural screening is done at all. In 17 hospitals (27%) all patients are screened, in the remaining 30% screening is performed in a selection of patients. The timing of screening varied from separate consultations (23 hospitals) to immediately before the procedure (13 hospitals). If pre-procedural screening is done (n=36), this is performed by protocol in 56%. Two hospitals use a questionnaire for pre-procedural screening, which is given to the endoscopist just before the start of the procedure.
Conclusions: In this audit, mean 48% of GI endoscopies were performed under sedation. Pre-procedural screening practices vary widely, with less than half of patients are screened before the procedure, and a standard protocol in a minority. A registration of all sedation procedures and sedation-related events is used in only 20%.

Preoperative biliary drainage versus direct operation for pancreatic tumors causing obstructive jaundice (DROP-Trial)

N.A. van der Gaag[1], E.A. Rauws[2], C.H. van Eijck[3], M.J. Bruno[4], E. van der Harst[5], J.J. Gerritsen[6], J.W. Greve[7], M.F. Gerhards[8], I.H. de Hingh[9], J.H. Klinkenbijl[10], C.Y. Nio[11], S.M. de Castro[1], O.R. Busch[1], T.M. van Gulik[1], P.M. Bossuyt[12], D.J. Gouma[1], [1]Surgery, Academic Medical Center, Amsterdam, [2]Gastroenterology, Academic Medical Center, Amsterdam, [3]Surgery, Erasmus Medical Center, Rotterdam, [4]Gastroenterology, Erasmus Medical Center, Rotterdam, [5]Surgery, Maasstad Hospital, Rotterdam, [6]Surgery, Medisch Spectrum Twente, Enschede, [7]Surgery, University Hospital Maastricht, Maastricht, [8]Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, [9]Surgery, Catharina Hospital, Eindhoven, [10]Surgery, Rijnstaete Hospital, Arnhem,[11]Radiology, Academic Medical Center, Amsterdam, [12]Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, The Netherlands

Preoperative biliary drainage (PBD) was introduced to improve postoperative outcome in patients with obstructive jaundice due to a pancreatic head tumor, but the benefit of its routine application is questioned. We conducted a multicenter, randomized, controlled trial to compare a 'PBD-strategy' with endoscopic retrograde cholangiography (ERC) with an 'early-surgery' strategy. Patients with obstructive jaundice, bilirubin level 40-250 µmol, due to a suspected pancreatic head tumor were randomly assigned to a (standard) PBD-strategy with PBD for 4-6 weeks followed by surgery or to an early surgery strategy with surgical treatment without PBD within one week. Overall complications was the primary endpoint, defined as the composite of complications related to PBD and surgery with 90 days follow-up. Analyses were by intention to treat.Two hundred-two patients underwent randomization: 96 to early surgery, 106 to PBD. Six patients were excluded for analysis. Overall complications occurred in 38 (40%) patients in the early surgery group and in 76 (75%) patients in the PBD group (relative risk 0.55, 95% CI 0.41-0.71). PBD-related complications occurred in 2 (2%) patients in the early surgery group and in 48 (47%) patients in the PBD group (relative risk 0.05, 95% CI 0.01-0.18) and surgery related complications in 36 (38%) of early surgery patients and in 48 (47%) of PBD patients (relative risk 0.81, 95% CI 0.59-1.13). Mortality and hospital stay were not significantly different between groups.
Conclusions: Routine PBD in patients with obstructive jaundice undergoing surgery for a suspected pancreatic head tumor results in high overall morbidity due to PBD procedure related complications, while surgical outcome is equal to an early surgery strategy without PBD. PBD should not be performed routinely.

Bacterial translocation in patients undergoing pancreatic surgery and the influence of prophylactic use of probiotics and selective decontamination of the digestive tract in a randomized placebo-controlled trial

G.M.P. Diepenhorst[1], O. van Ruler[2], M.G.H. Besselink[3], H.C. van Santvoort[3], P.R. Wijnandts[4], D.J. Gouma[2], H.G. Gooszen[3], M.A. Boermeester[2], [1]Dept of Surgery (Surgical Laboratory), Academic Medical Center, and Dept of Immunopathology, Sanquin Research, Amsterdam, [2]Dept of Surgery, Academic Medical Center, Amsterdam, and Dutch Acute Pancreatitis Study Group, Utrecht,[3]Depts of Surgery, University Medical Center Utrecht and Dutch Acute Pancreatitis Study Group, Utrecht, [4]Dept of Anaesthesiology, Academic Medical Center, The Netherlands

Objective: We aimed to assess bacterial translocation (BT) and the subsequent local inflammatory response in patients undergoing major abdominal surgery. Moreover, the effect on peri-operative gut barrier function of the administration of probiotics and selective decontamination of the digestive tract (SDD) was compared to standard treatment. Background: BT describes the passage of gastrointestinal microbiota across the intestinal mucosal barrier to local mesenteric lymph nodes (MLNs) and ultimately to other organs. The process is suggested to play a major role in the development of postoperative infections in patients undergoing major abdominal surgery. However, its exact mechanism and clinical significance remain to be established. Methods: This randomized controlled multicenter trial included 30 consecutive patients planned for elective pylorus preserving pancreatico-duodenectomy receiving peri-operative probiotics, SDD or standard treatment. To assess intestinal barrier function, Intestinal Fatty Acid Binding Protein (I-FABP) and polyethylene glycol (PEG) recovery in urine were measured peri-operatively. Peroperative BT was assessed by real-time polymerase chain reaction (q-PCR) and Multiplex ligation-dependent probe amplification (MLPA) in mesenteric lymph nodes (MLNs) harvested early (baseline control) and late during the operation. Results: When combining all treatment groups, bacterial DNA was detected in 18 out of 27 of late MLNs as compared to 13 out of 23 of control MLNs by PCR. Probiotics and SDD showed no significant effect on the number of positive MLNs. MLPA analysis indicated a significant per-operative increase in expression of 12/30 inflammatory mediator-related genes ($P<0.05$), whereas none of the genes demonstrated a decrease in expression levels. Intestinal permeability was unaffected by surgery as well as by probiotics and SDD as compared to standard treatment. Mucosal damage in patients receiving the SDD regime was significantly affected by surgery when compared to the other groups.
Conclusion: This study suggests that BT and its subsequent inflammatory response after major elective abdominal surgery may be part of physiological antigen-sampling processes of the gut-associated lymphoid tissue. Administration of probiotics and SDD did not alter the prevalence of BT or intestinal permeability, and seem unlikely candidates for prophylactic clinical use in this setting.

Prevalence of pancreatic cysts in individuals undergoing preventive medical examination by Magnetic Resonance Imaging (MRI)

K. de Jong[1], C.Y. Nio[2], J. Hermans[3], M.G. Dijkgraaf[4], D.J. Gouma[5], C.H.J. van Eijck[6], E. van Heel[7], G. Klaß[8], P. Fockens[1], M.J. Bruno[9], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of Radiology, Academic Medical Center, Amsterdam, [3]Dept of Radiology, Erasmus Medical Center, Rotterdam, [4]Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, [5]Dept of Surgery, Academic Medical Center, Amsterdam, [6]Dept of Surgery, Erasmus Medical Center, Rotterdam, [7]Prescan Nederland, Hengelo, [8]Dept of Radiology, Mathias Spital Hospital, Rheine, Germany, [9]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

The true prevalence of pancreatic cysts (PCs) in the general population is unknown. Asymptomatic PCs are diagnosed with increasing frequency due to a more wide spread use of diagnostic advanced cross-sectional imaging and the increased frequency at which individuals undergo preventive medical examinations. PC(s) may be identified as a coincidental finding with subsequent clinical management dilemmas. We investigated the prevalence of PCs in individuals undergoing screenings MRI performed at their own initiative and cost. This study includes 3000 consecutive persons who underwent an abdominal MRI (non-secretin) as part of a preventive medical examination (Prescan, Rheine, Germany) between 3-2007 and 9-2008. MRI reports and application forms were retrospectively reviewed. Primary endpoint was PC prevalence. Secondary endpoints were: age-, gender distribution, PC characteristics, presence of liver- or kidney cysts, presence of abdominal complaints, and previous pancreatic disease. Until the end of 11-2008, 1761 persons (M=1119) with a mean age of 51 years (SD, 11.0; range, 21-86) have been investigated. PCs were reported in 38 persons, representing a prevalence of 2.2 per 100 persons (95% CI, 1.6-3.0). Mean age of individuals with PC(s) was 60 years (SD, 9.6). No difference in prevalence by sex was found (p=0.960). PC sizes ranged from 2 to 54mm (median, 9mm; ≥30mm, n=2, 5.3%). 8% of PCs were multilocular. 36.8% of PCs were located in the tail. Communication with pancreatic duct was reported in 10%. PC presence correlated with increasing age, no PCs were identified <40 years, and prevalence of PCs from 70-80 years was 8.1% (95% CI, 3.5-17.5). No other pancreatic MRI abnormalities were reported in any of the 1761 persons. Liver or kidney cyst(s) were present in 39% and 47% of cases with PCs as opposed to 25% and 35% in those without PCs (p=0.042; p=0.122). 5.3% of individuals with PC(s) had reported abdominal complaints as opposed to 7.6% of those without PC(s) (p = 0.589). None of the individuals with PC(s) had pancreatic disease in their medical history.
Conclusion: In individuals undergoing preventive medical examination with MRI, the prevalence of PCs was 2.2%. Of these PCs, 5.3% were ≥30 mm, 8% were multilocular and in 10% of cases may represent side-branch IPMN. Cyst presence correlated with increasing age, no difference of prevalence by sex was found. Abdominal complaints did not correlate with PC presence.

Genetic variants of Myosin IXB and Pard3 predispose to acute pancreatitis

R.M. Nijmeijer[1], H.C. van Santvoort[1], A. Zhernakova[2], M.G.H. Besselink[1], M.C. Wapenaar[3], M.A. Boermeester[4], H.G. Gooszen[1], L.M.A. Akkermans[1], C. Wijmenga[2,3], on behalf of the Dutch Pancreatitis Study Group, [1]Dept of Surgery, University Medical Center Utrecht, The Netherlands; [2]Complex Genetics Section, Dept of Medical Genetics, University Medical Center Utrecht, The Netherlands; [3]Dept of Genetics, University Medical Center Groningen and University of Groningen, The Netherlands; [4]Dept of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Acute pancreatitis (AP) runs a severe clinical course in around 20% of all patients. This is characterized by complications, such as pancreatic necrosis, (multiple) organ failure and secondary infections due to bacterial translocation from the patient's own gut. It is hypothesized that impairment of the mucosal barrier plays an important pathophysiological role in these complications. Myosin IXB (*MYO9B*), encoding an unconventional myosin molecule with a Rho GTPase-activating protein (RhoGAP) in its tail, is thought to be involved in remodeling of the cytoskeleton and tight junction assembly. We hypothesized that *MYO9B* plays a role in gastrointestinal and pancreatic permeability. Common genetic variation of *MYO9B* and 2 tight junction adaptor genes (*PARD3* and *MAGI2*) has been associated with susceptibility to both celiac disease (CD) and inflammatory bowel disease (IBD), inflammatory conditions in which impairment of the mucosal barrier also plays a role. We investigated *MYO9B*, *PARD3* and *MAGI2* for association with AP and with complications of the disease.We selected 5 tagging SNPs from the 35-kb 3' region of *MYO9B* and 5 SNPs in *PARD3* and *MAGI2*. These SNPs were studied in 374 both mild and severe AP patients (278 mild and 96 severe AP patients) and controls (n = 1624 for *MYO9B*; n = 929 for *PARD3* and *MAGI2*). To explore a potential relation with disease phenotypes, we analyzed the genes for association with course of AP (severe vs. mild disease), mortality due to AP, infectious complications, infection of pancreatic necrosis and organ failure. Common variants of *MYO9B* are associated with susceptibility to AP (most associated SNP, rs1545620; P=0.000012, OR 1.44, 95% CI 1.22-1.70). The same *MYO9B* alleles as reported for CD and IBD showed association. Two variants of *PARD3* are also associated with susceptibility to AP (most associated SNP, rs4379776; P=0.0014, OR 1.34, 95% CI 1.12-1.61). No association with *MAGI2* was found. Subgroup analyses showed no significant association of *MYO9B* or either of the two tight junction adaptor genes with complications of AP. Genetic variants of *MYO9B* and *PARD3* predispose to AP. The most associated SNP of *MYO9B*, located on exon 20 and giving rise to an amino acid change (Ala1011Ser) was previously shown to be the most associated SNP with IBD. These findings may point to shared mechanisms underlying mucosal barrier impairment in different diseases of the gastrointestinal tract.

A mouse model of Juvenile Polyposis shows that Colorectal Cancer can arise due to a landscaper defect (MLDS project 04-06)

L.A.A. Brosens[1], W.A. van Hattem[1,2], W.W.J. de Leng[1], F.M. Morsink[1], G.J.A. Offerhaus[1,2] , [1]Dept of Pathology, University Medical Center, Utrecht, [2]Dept of Pathology, Academic Medical Center, Amsterdam, the Netherlands

The hereditary gastrointestinal polyposis syndromes are instrumental for clarifying the molecular pathways of colorectal cancer (CRC). Of the gastrointestinal polyposis syndromes juvenile polyposis (JP) is one of the well known hamartomatous polyposis syndromes and may serve as a proof of principle that CRC can arise due to landscaper defects. JP is an autosomal dominant hereditary disorder characterized by multiple gastrointestinal hamartomatous polyps, most frequently in the colorectum. The polyps in JP are non-neoplastic and typical features are abundant stroma, crypt distortion and inflammation. However, neoplastic change of the epithelium and dysplasia can also be found in juvenile polyps and JP is associated with an increased risk for gastrointestinal cancer that is ill-defined. Our first aim was therefore to define the magnitude of risk for gastrointestinal cancer in JP. By person-year analysis a high relative (RR 34) and absolute risk (life-time risk 38.7%) of CRC in JP were found. No other GI tumors were found in our cohort.Germline mutation of *SMAD4* or *BMPR1A* is found in 30-40% of patients. Therefore alternative ways of inactivation, such as germline deletion, of these genes may exist. Using MLPA it was shown that germline deletion of *SMAD4* or *BMPR1A* causes JP in about 15% of JP patients. By combining sequencing and MLPA, a germline defect in *SMAD4* or *BMPR1A* was found in almost 50% of JP patients.Because 50% of JP patients remain without genetic diagnosis other genes predisposing to JP may exist. Therefore, it was investigated whether *TGFBRII* germline mutation can cause JP. No pathogenic germline mutations or deletions were found in this gene and it is concluded that *TGFBRII* is unlikely to be a JP susceptibility gene.Prevention of polyp and neoplasia development in JP using chemoprevention may be helpful in treatment of JP. To investigate the potential value of chemoprevention by COX-2 inhibition, expression of COX-2 was measured in JP and sporadic juvenile polyps. Increased levels of COX-2 were found in JP polyps compared to sporadic juvenile polyps, suggesting that chemoprevention using COX-2 inhibition can be beneficial in JP.
Conclusions: A well defined risk profile for colorectal cancer for patients with JP is provided that will facilitate surveillance strategies. Also, germline deletion of *SMAD4* and *BMPR1A* was identified as a cause of JP and the *TGFBRII* gene was excluded as a JP susceptibility gene. Increased COX-2 levels in JP suggest that chemoprevention by COX-2 inhibition can be beneficial in JP.

Reduced responsiveness of the steatotic liver to FGF19 (MLDS-project 05-03)

P.J. Jansen[1], K. van den Oever[1], W. Patsch[2], P.L.M. Jansen[1,3], F,G. Schaap[1], Academic Medical Center, [1]AMC Liver Center, [3]Dept of Gastroenterology and Hepatology, Amsterdam, The Netherlands, [2]Dept of Laboratory Medicine, Paracelsus Medical University, Salzburg, Austria

Reclamation of bile salts in the terminal ileum results in activation of the bile salt receptor FXR and as a consequence transcriptional induction of Fibroblast Growth Factor 19 (FGF19). Secretion of FGF19 in the portal circulation and subsequent binding of FGF19 to the hepatocytic receptor FGFR4 results in repression of bile salt synthesis. Apart from its established role in bile salt homeostasis, FGF19 has been implicated in regulation of lipid metabolism. The effect of FGF19 on hepatic lipid metabolism was explored in mice with and without steatosis. Adenoviral gene transfer was used to moderately elevate plasma FGF19 in chow-fed mice. As expected, this resulted in repression of *Cyp7a1* mRNA, indicative for lowered bile salt synthesis. *Fas* (Fatty Acid Synthase, involved in lipid synthesis) and *Acc2* (acetyl-CoA carboxylase 2, a negative regulator of fatty acid oxidation) were identified as novel FGF19-repressed genes. The inferred involvement of FGF19 in regulating cellular lipid content was studied in mice fed a high-fat diet (HFD). Short-term (4 days) plasma overexpression of FGF19, however, had no effect on hepatic triglyceride content in these steatotic mice. Interestingly, FGF19 failed to repress both *Cyp7a1* and *Acc2* in the liver of steatotic mice. Hepatic *Fgfr4* mRNA levels were identical in chow- and HFD-fed mice. Reduced FGF19 responsiveness in steatotic liver was further suggested by the observation that higher doses of intravenously administered FGF19 protein were required to reach a similar level of *Cyp7a1* repression in mice fed a HFD in comparison with chow-fed animals. To complement these studies, we analyzed plasma FGF19 and hepatic transcript levels in human subjects with varying degrees of hepatic steatosis. Although a tendency towards somewhat lowered levels was observed in subjects with severe steatosis, fasted plasma FGF19 levels were not different in subjects without, and with moderate and severe steatosis. Nonetheless, hepatic CYP7A1 mRNA levels were elevated in subjects with severe steatosis. Hepatic FGFR4 mRNA levels were not different in the groups.
Conclusions: In the animal experiments, *Fas* and *Acc2* were identified as new targets of FGF19 implicating FGF19 in the regulation of hepatic lipid homeostasis. The combined findings from animal experiments and studies in human subjects, indicate that the steatotic liver shows reduced responsiveness to FGF19. Disturbed intracellular FGF19 signaling may underlie this phenomenon.

The position of the acid pocket as risk factor to have acid reflux during a TLESR

H. Beaumont[1], R.J. Bennink[2], J.W. Jong[2], G.E. Boeckxstaens[1,3], Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands[1], Dept of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands[2], Dept of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium[3]

Gastroesophageal reflux occurs twice as much during transient lower esophageal sphincter relaxations (TLESR) in GERD patients compared to healthy volunteers (HV). However, the mechanisms underlying this difference remain unclear. The aim of this study was to evaluate the hypothesis that the position of the postprandial acid pocket is an important factor determining the risk to have acid reflux during a TLESR. 10 HV (22-53, 7M) without a hiatal hernia (HH) and 22 GERD patients (19-66, 12M, 12 patients with HH<3cm (s-HH), 10 patients with a HH³3cm (l-HH)) were studied. During upper endoscopy, the squamocolumnar junction and diaphragmatic impression were marked with a radio-labelled clip. To visualize the acid pocket, 99mTc-pertechnetate was injected iv and scintigraphic images were acquired up to 2hrs postprandial in 15s frames. Concurrently, combined manometry/impedance and pH metry (2cm above the LES) were performed to record TLESRs and reflux. The rate of TLESRs and the % associated with reflux (acid and non-acid) was comparable between the groups (HV: 12.5 (7.8-16.8)/subject with 88.0±4.7% reflux; s-HH: 11.0 (9.0-12.0) with 89.8±3.1% reflux; l-HH: 11.0 (8.0-13.0) with 92.1±3.2% reflux). Acid reflux occurred significantly more frequent during a TLESR in GERD patients compared to HV (HV: 3%, s-HH: 43%, l-HH: 64%). Immediately before a TLESR, the acid pocket was more frequently located within the hiatus or above the diaphragm in GERD patients compared to HV (HV: 22%, s-HH: 55%, l-HH: 76%). Acid reflux during a TLESR was significantly more frequent when the acid pocket extended into the hiatal opening or was located above the diaphragm in all three groups (HV: 7% vs 74%; s-HH: 21% vs 72%; l-HH: 20% vs 85% of TLESRs, p<0.001). In a multivariate analysis, the presence of a HH (OR 5.26) and the supradiaphragmatic position of the acid pocket (OR 5.33) were identified as major independent risk factors for acid reflux to occur. We showed that the acid pocket is more frequently located above the diaphragm in GERD patients, especially in patients with a large HH. Extension of the acid pocket into the hiatus or above the diaphragm is associated with an increased risk to have acid reflux during a TLESR, also in HV. Our findings suggest that the increased number of TLESRs associated with acid reflux in GERD patients compared to HV results from different dynamics (position) of the acid pocket due to the presence of a HH.

Speech therapy in patients with excessive supragastric belching

G.J.M. Hemmink[1], L. ten Cate[2], A.J. Bredenoord[1,3], R. Timmer[1], B.L.A.M. Weusten[1], A.J.P.M. Smout[3], [1]Dept of Gastroenterology, Sint Antonius Hospital, Nieuwegein, the Netherlands, [2]Practice for Speech and Voice Therapy, L. ten Cate, Utrecht, [3]Gastrointestinal Research Center, University Medical Center, Utrecht, the Netherlands

In patients with excessive belching as presenting symptom, supragastric belches are identified as the cause of their symptoms rather than excessive air swallowing. Supragastric belching is characterized by a rapid influx of air into the oesophagus, due to either the generation of a negative intrathoracic pressure ('air-sucking') or a pharyngeal contraction ('air-pushing'), immediately followed by rapid air expulsion. The frequency of these supragastric belches is influenced by attention and distraction, suggesting a behavioral disorder, and speech therapy may be of benefit in these patients. In 17 consecutive patients with isolated excessive belching, stationary combined impedance monitoring and high-resolution manometry was performed to assess the number and mechanism of supragastric belches during a 30-minute pre-prandial and 1-hr postprandial phase. Patients with supragastric belches were referred to a speech language therapist who was familiar with the concept of supragastric belching. The speech therapy was focused on awareness of the mechanism and on the self-induced nature of the belching disorder, on normalizing breathing pattern and regaining control by breathing and speech exercises. At the beginning and the end of the speech therapy patients filled in a VAS scale regarding the severity of their symptoms. With impedance monitoring supragastric belches were identified with a frequency of 32 (10-68)/h preprandially and 41 (29-184)/h postprandially (p=0.18). Air-sucking was the underlying mechanism of belching in 14 patients, air-pushing in 2, and a combination of both mechanisms in 1. Twelve patients were referred to the speech therapist, as 5 patients were not able or willing to comply with repetitive treatments. Three patients are still being treated, and 9 patients completed treatment by the speech therapist in 10 (5-10) sessions. Overall, median VAS severity scores decreased significantly after treatment from 398 (214-551) mm to 194 (50-409) mm (p=0.04). Five of the 9 patients reported major symptom reduction: 73 (51-96) %. In two patients, symptom reduction was modest (symptom reduction: 9 (6-14) %). In 1 patient the VAS scores increased after treatment.
Conclusion: Speech therapy performed by a well-informed therapist leads to a significant symptom reduction in the majority of patients with excessive supragastric belching.

Characterization of gastro-esophageal motor function following esophageal atresia repair

M.P. van Wijk[1], F.M.C. Knüppe[1], T.I. Omari[2], D.C. Aronson[3], J.A. Deurloo[3], M.A. Benninga[1], [1]Paediatric Gastroenterology and Nutrition, Emma Children's Hospital / Academic Medical Centre , Amsterdam, Netherlands, [2]Centre for Paediatric and Adolescent Gastroenterology, Children, Youth and Women's Health Services, Adelaide, SA, Australia, [3]Amsterdam Centre for Paediatric Surgery, AMC / VUmc, Amsterdam, the Netherlands

In adults born with esophageal atresia (EA), manometry studies show marked abnormalities in esophageal motility. However, few data are present in children and no combined impedance/manometry studies are available. Our aim was to characterize esophageal function in these patients. A random selection from a cohort born with EA between 1989 and 2008 was invited to participate. All patients were intubated with an age appropriate combined multichannel intraluminal impedance (MII) and water perfused 6-7 channel manometric sleeve catheter. They were given 5 liquid and 5 viscous bolus in both upright and supine position. Manometry and MII data were compared to normative values (Nguyen 2005). Ten patients (7 male; median age:5 (1-17)yr) were included. One and 2 patients had normal (≥ 70% peristaltic) motility during liquid and viscous swallows respectively. All patients with normal motility had normal clearance. Of those patients with abnormal motility, 33.3% and 12.5% had normal clearance during liquid and viscous bolus swallows respectively. Two patients had mean lower esophageal sphincter (LES) baseline pressure <6 mmHg and two patients had incomplete LES relaxations in more than 10% of swallows. A median number of 17 (5-20) bolus per patient could be analyzed. Of a total of 153 swallows, 40 showed normal peristalsis. Mean LES resting pressure preceding a swallow was 14±11 mmHg and LES relaxation was complete (nadir<3mmHg) in 110(72%) swallows. In 54(48%) swallows associated with abnormal motility, normal peristalsis was observed in the proximal part of the esophagus, which did not propagate distally. Other abnormalities included synchronous contractions (20%), generalized failure (16%), and focal failure (12%). A total of 38(34%) contractions were hypotensive, of which 3 were otherwise normal. MII analysis (bolus clearance time) showed normal clearance of bolus in 77(50%) swallows. Clearance of liquid bolus was significantly more often effective compared to viscous (46/77(60%) vs 31/76(41%), p<0.05). Normal motility caused normal clearance in 33/40(83%) swallows. Normal clearance was present in 44/113(39%) swallows with abnormal motility patterns. Conclusions: Despite EA and its surgical repair, some pediatric patients have normal motility patterns and normal bolus clearance. Although some patients have effective clearance with abnormal motility, the majority have abnormal motility and delayed bolus clearance. LES resting pressure and relaxation is normal in most patients.

Non-invasive measurement of early postprandial volume and accommodation-response in health and functional dyspepsia using Magnetic Resonance Imaging

J.J.L. Haans[1], I.M. de Zwart[2], A. de Roos[2], A.A.M. Masclee[1], [1]Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [2]Dept of Radiology, Leiden University Medical Center, Leiden, The Netherlands

Background: Impaired accommodationis considered to be one of the pathophysiological mechanisms in functionaldyspepsia. Several studies using the invasive barostat technique have foundimpaired accommodation in response to a meal in up to 40% of patients withfunctional dyspepsia. Magnetic Resonance Imaging is a non-invasive technique tomeasure volume changes in response to a meal. Methods: Measurements wereperformed in 21 healthy subjects (HS) and 18 patients with functional dyspepsia (FD). MRI was used to obtain data prior to and up to 30 minutes after intake ofa labeled 200 ml liquid meal (300 kcal). Intragastric air and intragastric mealvolumes were obtained using volume scans. Total volume (intragastric air pluscontents), accommodation volume (mean total volume over 30 min minus fastingtotal volume) and accommodation ratio (accommodation volume divided by fastingtotal volume) were calculated. All data are provided as mean±SD. Results: HS and FD (endoscopynegative) did not differ significantly in age, gender or BMI. Fasting totalvolume did not differ significantly between both groups, 39±24 and 45±16 ml forHS and FD resp. Immediately after meal intake total volume increased to 304±51and 315±63 ml for HS and FD resp. Accommodation volume did not differsignificantly between both groups, 270±38 and 278±46 ml for HS and FD resp. The lower range of normal (mean-2SD) for accommodation volume was 194 ml in HS. None of the patients with functional dyspepsia had an accommodation volumelower than 194 ml. Accommodation ratio did not differ significantly between both groups, 11±7 en 8±2 for HS and FD resp. After meal intake (0-15 min) an increase in intragastric contents, apart from the meal, was observed in both groups, 18±33 and 11±44 ml for HS and FD resp., onlysignificant in HS ($p<0.05$). Hereafter (15-30 min) a significant decrease inintragastric contents was observed in both groups, -31±32 and -23±24 ml for HS and FD resp. ($p<0.05$).
Conclusions: Using MRI we did not observe a difference involume response to a liquid meal between healthy subjects and patients withfunctional dyspepsia, nor did we observe a difference in accommodationresponse. These results are in contrast to various barostat studies. After mealintake intragastric contents increased most likely due to gastric secretion. Only in healthy subjects this increase was significant, that might reflectimpairment in gastric secretion in patients with functional dyspepsia.

CRH-receptor antagonism prevents the development of stress-induced visceral hypersensitivity but fails to affect established hypersensitivity

O.I. Stanisor[1], S.A. van Diest[1], O. Welting[1], W.J. de Jonge[1], G.E. Boeckxstaens[1,2], R.M. van den Wijngaard[1], Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands[1], Dept of Gastroenterology, University Hospital Gasthuisberg, Catholic University of Leuven, Leuven, Belgium[2]

Introduction: CRH1-receptor antagonists administered before application of stress prevent mast cell degranulation, barrier dysfunction and the subsequent development of visceral hypersensitivity in animal models. To what extent these agents can reverse stress-induced sustained visceral hypersensitivity remains unclear, but is clearly of great importance in view of the ongoing clinical studies evaluating these antagonists as potential new treatment for irritable bowel patients. Therefore, we evaluated whether the non-selective peripheral CRH-receptor antagonist α-helical CRH (9-41) not only prevents but also reverses established stress-induced (mast-cell dependent) hypersensitivity (HS) to colorectal distension (CRD) in the maternal separation (MS) model for rats. Methods: The receptor-antagonist was administered (A) immediately before water avoidance (WA) to evaluate its efficacy to prevent the development of stress-induced HS, and (B) 15 days after WA to evaluate whether established HS could be reversed. The latter was compared with post-WA administration of the mast cell stabilizer doxantrazole. The visceromotor response to CRD (1, 1½, 2ml) was measured pre- and post-WA and expressed as area-under-curve (AUC, volume-vs-response, significant difference when $P<0.05$: Wilcoxon). As an indirect measure for barrier function we quantified mucosal expression (stripped colonic mucosa) of the tight junction protein occludin (over actin) by Western blotting. Results: Pre-WA administration of α-helical-CRH prevented the occurrence of visceral hypersensitivity (68±4 vs 71±4, ns) whereas vehicle alone was ineffective (70±5 vs 112±10, P=0.008). Established WA-induced hypersensitivity (70±3 vs 98±8, P=0.011) could not be reversed by α-helical-CRH treatment at day 15 post WA (98±8 vs 100±5, ns). In contrast, WA-induced hypersensitivity was revered by post-WA doxantrazole treatment (101±6 vs 80±6, P=0.012) where vehicle treated rats remained hypersensitive. Compared to vehicle alone occludin/actin pixel density was higher when rats were pre-treated with α-helical CRH (P=0.01, Mann-Whitney), no differences were observed in case of post-WA treatment.
Conclusion: Our results confirm that the receptor antagonist α-helical-CRH (9-41) potently prevents the development of visceral hypersensitivity and barrier dysfunction when administered before the stressor. In contrast, established visceral hypersensitivity was not affected by the receptor antagonist, but was reversed by mast cell stabilization. Our results question the use of CRH-receptor antagonists in the treatment of existing visceral hypersensitivity.

Rectal butyrate administration dose-dependently lowers visceral sensitivity in healthy humans

*S. Vanhoutvin[1,2] *, F. Troost[1,2], P. Lindsey[3], T. Kilkens[2], H. Hamer[1,2], D. Jonkers[1,2], K. Venema[1,4], R.J. Brummer[1,2,5], [1]TIFood and Nutrition, Wageningen, The Netherlands, [2]Maastricht University, Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht, The Netherlands, [3]Maastricht University, Dept of Population Genetics, Genomics and Bioinformatics, Maastricht, The Netherlands, [4]TNO Quality of Life, Dept of Biosciences, Zeist, The Netherlands, [5]Örebro University, School of Health and Medical Sciences, Örebro, Sweden *s.vanhoutvin@intmed.unimaas.nl*

Fermentation of dietary fibers in the colon results in the production of short chain fatty acids, mainly acetate, propionate and butyrate. Previous studies have shown positive effects of butyrate on oxidative stress, inflammation and apoptosis. Rat studies, however, showed that butyrate increases both visceral pain and inflammation [1]. The aim of this study was to determine theeffects of rectally administered, physiologically achievable concentrations ofbutyrate on visceral perception and sensitivity in healthy volunteers. 11 healthy volunteers (3 males and 8 females) participated in this randomised double blind, placebo controlled crossover study. The study consisted of three periods of one week in which thevolunteers self-administered rectal enemas once daily prior to sleeping. Each enema contained 60ml of either 100mM or 50mM butyrate solution, or placebo (saline), respectively. The enemas were made isotonic with sodium chloride at apH of 7. The test weeks were interspaced by a wash-out period of two weeks.Visceral perception was measured at the start and the end of each test week using a semi-random barostat protocol for rectal balloon distensions. Pain and discomfort were measured using visual analogue scales and urge was measured ona 6-point scale. Butyrate significantly affected visceral perception in a dose-dependent way compared to placebo. Butyrate treatment resulted in a significant dose-dependent reduction of pain, urge and discomfort throughout the entire pressure range of the protocol. The effects of 100 mM butyrateon all parameters differed significantly from those of 50 mM butyrate. At apressure of 4 mmHg, 50 mM and 100 mM butyrate concentration resulted in a reduction of pain scores of 23,9% and 42,1% respectively and the discomfort scores decreased with 44,2% and 69% after the 50 mM and 100 mM butyrate intervention, respectively. At a pressure of 67 mmHg, 50 and 100 mM of butyrate decreased the painscores by 23,8% and 42% respectively and discomfort scores decreased by 1,9% and 5,2%, respectively. Intra luminal administration of butyrateinto the distal colon at physiologically achievable concentrations dose-dependently decreases visceral sensitivity in healthy volunteers.

[1] Tarrerias et al. Short-chain fatty acid enemas fail to decrease colonic hypersensitivity and inflammation in TNBS-induced colonic inflammation in rats.Pain. 2002 100:91-7.

Does the presence of a hiatal hernia affects the efficacy of the reflux inhibitor baclofen?

H. Beaumont[1], G.E.E. Boeckxstaens[1,2] Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands[1], Dept of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium[2]

Reflux inhibitors like the $GABA_B$ receptor agonist baclofen, block transient lower esophageal sphincter relaxations (TLESRs) and are proposed as add-on therapy in patients with PPI resistant symptoms. However, as other mechanisms of gastroesophageal reflux become more important in the presence of a hiatal hernia (HH), the efficacy of reflux inhibitors to reduce acid and non-acid reflux may be hampered. Therefore, we compared the effect of baclofen on gastroesophageal reflux during PPI treatment in patients with no HH and those with a large HH. 27 GERD patients on PPI were included in the study (15M, median age 54) of which 16 had no HH (–HH, 8M, median age 54) and 11 had a large HH ≥ 3 cm (+HH, 7M, median age 58). During PPI treatment, the effect of baclofen (3x20mg) on acid and non-acid reflux was evaluated in a randomized, double-blind, placebo controlled cross-over study. Reflux was measured during 24 hrs using combined esophageal impedance and pH metry, with the pH electrode 5cm above the proximal margin of the LES. HH size measured 3.6±0.3cm in +HH patients. After placebo, a total of 694 and 1157 reflux episodes were recorded in –HH and +HH patients, respectively. Baclofen significantly reduced the total amount of reflux episodes with 32% in –HH patients (from 56 (43-66)/patient to 40 (27-50)/patient, $p<0.01$) and with 43% in +HH patients (from 95 (87-141)/patient to 69 (32-74)/patient, $p=0.003$). This decrease was mainly due to reduction of non-acid reflux episodes in both –HH patients (from 45 (17-59)/patient to 29 (22-35)/patient, $p<0.03$) and +HH patients (from 79 (54-121)/patient to 38 (39-61)/patient, $p=0.003$). Furthermore, baclofen significantly reduced the rate of reflux episodes extending into the proximal esophagus in both –HH (placebo: 182 (9 (6-16)/patient); baclofen: 119 (6 (2-12)/patient), $p<0.05$) and +HH patients (placebo: 246 (21 (5-40)/patient); baclofen: 116 (15 (2-19)/patient), $p=0.005$). Acid exposure time was in the normal range in both groups during placebo and was not significantly changed by baclofen. Somnolence was most commonly reported as side effect after baclofen. All side effects were of mild to moderate intensity. This study demonstrates that baclofen is also effective in reducing PPI resistant reflux, particularly non-acid reflux, in GERD patients with a large HH. These findings further strengthen the therapeutic potential for reflux inhibitors as add-on therapy in GERD patients with incomplete response to acid suppression.

Colonic manometry in children with defecation disorders: should we measure for 24 hours?*

O. Liem[1,2], R. Burgers[1,2], F. Connor[3], M. Benninga[2], S. Reddy[4], H. Mousa[1], C. Di Lorenzo[1], [1]Nationwide Children's Hospital, Columbus, OH, USA, [2]Emma Children's Hospital, Amsterdam Medical Center, Amsterdam, Netherlands, [3]Royal Children's Hospital, Brisbane, QL, Australia, [4]Sriram Motility Clinic, Hyderabad, India

Colonic manometry is a diagnostic test frequently used in the evaluation of children with defecation disorders unresponsive to medical and behavioral management. The standard protocol in pediatrics consists of a study that lasts approximately 4 hours. Given the wide physiologic variations in colonic motility throughout the day, longer observation might detect clinically relevant information. Our aim was to determine whether prolonged colonic motility measurement results in treatment modifications in children with defecation disorders. A water perfused and a solid state colonic catheter with recording sites positioned at the same level were simultaneously placed using colonoscopy in 13 children (6 boys, median age 9 yrs, range 3-16 yrs) presenting with severe defecation disorders. The tip of the catheters was placed in the cecum in 11 patients and in the transverse colon in two. First, a "standard test" was performed with at least 1 hr fasting, 1 hr postprandial and 1 hr post-bisacodyl provocation recording. After this portion of the test was completed, recordings continued until the next day using the solid state, ambulatory technique. Colonic manometry was performed in 10 children with intractable constipation, in one child with fecal incontinence and in two children with symptoms of pseudo-obstruction. Based on the short duration recordings, normal motility in the entire colon was found in 6/13 children. In 3/13 children normal motility was only found in the proximal segment with abnormalities limited to the dilated distal colon. Other patients showed low amplitude contractions (n=2) consistent with myopathy and colonic inertia with lack of contractions throughout the entire colon (n=2). The 24-hours recording results mostly agreed with the short recordings but revealed more information in 2 patients. In one patient with normal motility in the standard short recording, an excessive frequency of HAPCs was noted in the prolonged study, possibly contributing to the fecal incontinence. In another patient, standard recordings showed colonic activity only in the most proximal part of the colon but the 24 hour study showed normal motility over a larger portion of the colon. These findings did not, however, change treatment recommendations.

Conclusion: Prolonged colonic measurement provides more information regarding colonic motor function and allows detection of motor events missed by the standard short manometry study with provocation. Further studies are necessary to evaluate the clinical relevance of this information.

Muscularis mucosae of the rectum in children with Hirschsprung's disease & functional constipation *

N. Bekkali[1], M.M. Tabbers[1], J.C.H. Wilde[2], M.W.N. Oomen[2], M.A. Benninga[1], F.J.W. ten Kate[3], [1]Dept of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre, Amsterdam, the Netherlands, [2]Dept of Paediatric surgery, Emma Children's Hospital, Academic Medical Centre, Amsterdam, the Netherlands, [3]Dept of Pathology, Academic Medical Centre, Amsterdam, the Netherlands*

Withholding behavior is the major cause of constipation in children. This (un)conscious contraction of the pelvic floor muscles and consequent fecal stasis in the rectum may cause histological changes in the rectal muscularis mucosae (RMM). Therefore, we investigated the histological characteristics of the RMM in children with constipation symptoms. The aim of the study was to 1) evaluate thickness and organization of the RMM in functional constipation (FC), and compare these data with children with Hirschsprung's disease (HD) and controls and 2) to assess correlation between RMM thickness and duration of constipation symptoms. Between November 2000 and June 2008, rectal suction biopsies (RSB) from patients with intractable FC who presented to the department of paediatric gastroenterology or paediatric surgery, were retrospectively evaluated. RSBs were taken to diagnose HD and were considered positive for HD when the acetylcholinesterase activity was elevated in combination with absence of ganglion cells. Patients without evidence for HD were diagnosed as FC. Rectal colonic tissue of patients undergoing endoscopy was considered control tissue when no macro- and microscopic evidence was found for pathology. An experienced pathologist, blinded for diagnosis, reviewed all biopsies to assess RMM hypertrophy (thickness >80µm) or disorganization (extension of the RMM between the crypts). Two observers, blinded for diagnosis, measured RMM thickness (µm). A total of 75 biopsy specimens were reviewed; 15 were of poor quality and 60 were finally used for analysis. RMM thickness and disorganization were significantly different between FC compared to HD patients and controls (table 1). No difference was found in RMM thickness between HD and control patients (p=0.20). Correlation between RMM thickness and constipation symptom duration was found in FC (r=0.50;p=0.02), but not in HD patients (r=-0.21;p=0.34).
In conclusion, we demonstrated that children with FC have hypertrophied and disorganized RMM compared to HD and control patients. These data suggest that RMM hypertrophy is a secondary consequence of constipation. Interestingly, the RMM characteristics might be useful as additional diagnostic tools distinguishing FC from HD in inconclusive rectal suction biopsies.

Treatment of rectal fecal impactiona - a randomized controlled trial: enemas versus high doses of PEG 3350*

N.Bekkali[1], M.G.W. Dijkgraaf[2], M.M. van den Berg[1], M.P. van Wijk[1], M.E.J. Bongers[1], O. Liem[1], M.A. Benninga[1], [1]Dept of Pediatric gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre, Amsterdam, the Netherlands, [2]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, Amsterdam, the Netherlands

Rectal fecal impaction is common in childhood constipation. No comparable data exist evaluating the effect and tolerability of disimpaction with rectal enemas versus oral laxatives (PEG: polyethylene glycol). We hypothesized that 1) rectal enemas and oral laxatives are equally effective but 2) enemas are less tolerated and 3) colonic transit time (CCT) improves during disimpaction. Children (4-16 yrs) with functional constipation and rectal fecal impaction were eligible. A rectal fecaloma was defined as a large fecal mass, noted rectal examination, which is unlikely to be passed on demand. After rectal examination and CTT measurement, patients were randomly assigned to receive enemas once daily or oral PEG (1.5 g/kg/day) for 6 consecutive days. After 6 days disimpaction, second CTT and a child's behavior questionnaire (containing items affecting a child's behavior such as increased anxiety during disimpaction week) were assessed. Primary outcome: successful disimpaction (absence of a fecaloma upon rectal examination or on X-ray). Secondary outcomes were: frequency of fecal incontinence and defecation, presence of watery stools and abdominal pain, behavior questionnaire scores and CTT values. A total of 95 patients were eligible; 5 refused participation. Included patients (60 male) had mean age of 7.5±2.8 years and 46 were assigned to enemas and 44 to PEG. Five patients dropped out in both groups. Disimpaction was equally achieved with enemas (88%) and PEG (77%); p=0.32. Fecal incontinence ($p<0.001$) and watery stools ($p<0.001$) were more frequently reported with PEG ($p<0.01$) but defecation frequency (p=0.68) and abdominal pain (p=0.23) were not different between the groups. Anxiety (93% vs. 79%; p=0.13) was not different between respectively enema and PEG group. Although the enema group (n=39) and the PEG group (n=33) showed decreasing CTT (minus 63 and 66 hours respectively) and RSTT values (minus 31 and 38 hours respectively), between baseline and after six days disimpaction, no differences between both groups were noted, (after adjustment for baseline values) with regard to CTT and RSTT values after disimpaction (p=0.85 and p=0.06 respectively).
In conclusion rectal enemas and oral laxatives are equally effective in treating rectal fecal impaction. Compared to enemas, oral laxatives caused more fecal incontinence with comparable behavior scores. Both treatments should therefore be equally considered as first line therapy for rectal fecal impaction.

Effect of weight reduction on NAFLD in children: results of a Dutch second line weight reduction program*

B.G.P. Koot[1], O.H. van der Baan-Slootweg[2], T.H. Pels Rijcken[3], P.L.M. Jansen[4], M.A. Benninga[1], [1]Academic Medical Centre (AMC), Dept of Pediatric gastro-enterology, [2]Heideheuvel Obesity Clinic, Hilversum, [3]Ter Gooi Ziekenhuizen, Dept of Radiology, [4]AMC, Dept of Hepatology, the Netherlands

Limited data is available regarding the prevalence and the effects of weight reduction programs on non-alcoholic fatty liver disease (NAFLD) in children. Moreover, most studies have been performed in selected populations usually consisting of patients referred to tertiary liver centres. Aim of this study was to determine the prevalence of NAFLD and effect of treatment on NAFLD in children admitted to a second line weight reduction program for morbidly obese in the Netherlands. Between 2005 and 2007 all children participating in a weight reduction program were included. The program consisted of dietary and behavioural counselling and exercise during 6 months. Ultrasound of liver (US), blood sampling and physical examination were performed at the start and the end of treatment. The degree of liver steatosis on US was graded in 4 stages according to Saverymuttu (stage 0 equals no steatosis, stage 1-3 equals mild to severe steatosis). An elevated serum ALT was defined as serum ALT level> 35 Units/Liter. A total of 126 (63% females) children were included. Mean age was 14.2 (± 2.4) years, weight 108 (± 25) kg, BMI z-score 3.36 (± 0.40), HOMA-IR index 3.37 (± 1.7), diastolic blood pressure 80 (± 12) mmHg and waist circumference 105.3 (± 13.2) cm. None showed signs of diabetes mellitus during an oral glucose tolerance test.At the start of the program, the prevalence of hepatic steatosis on US (stage 1-3) was 28%, the prevalence of an elevated serum ALT was 26%. At the end of the program, mean weight (-14.7 kg) and BMI z-score (-0.55) were significantly decreased ($p<0.001$). The prevalence of hepatic steatosis decreased to 9% ($p<0.001$) and the prevalence of an elevated ALT decreased to 10% ($p<0.001$). In multifactorial analysis the decrease in serum ALT level was independently correlated with a decrease in US stage of steatosis ($p<0.001$) and a decrease in BMI z-score ($p<0.02$).
Conclusion: Weight reduction programs seem effective in resolving NAFLD in morbidly obese children. This effect occurs despite limited loss of weight. Studies using more accurate methods for measuring liver steatosis are needed to determine the exact effects of weight loss programs on NAFLD and the association between changes in NAFLD and other parameters.

Constipation and colonic transit time in morbidly obese children*

O. Liem[1], O.H. vd Baan-Slootweg[1,2], N. Bekkali[1], W.M.C. van Aalderen[3], T.H. Pels Rijcken[4], M.A. Benninga[1,1]. Dept of pediatric gastroenterology and nutrition, Emma's Children's Hospital/AMC, Amsterdam, the Netherlands[2], Childhood Obesity Centre Heideheuvel, Hilversum, the Netherlands[3], Dept of pediatric pulmonology, Emma's Children's Hospital / AMC, Amsterdam, the Netherlands[4], Dept of Radiology, Tergooi-ziekenhuizen, Hilversum, the Netherlands

Childhood obesity is associated with a number of comorbidities. Recent studies in children found an increased prevalence of constipation in obese children and vice versa; a higher prevalence of obesity in constipated children. These studies, however, did not use the Rome III definition for constipation making it difficult to compare the data with other studies. The mechanisms underlying these relationships are still unknown but are suggested to arise from motor and sensory abnormalities. Our aim was to determine the prevalence of functional constipation according to the Rome III criteria in children with morbid obesity and to evaluate whether delayed colonic motility is present in these children. Participants were children aged 8-18 years who entered a prospective, randomized controlled study evaluating the effect of an outpatient vs. inpatient treatment of obesity at a specialized obesity clinic between 2004 and 2007. Inclusion criteria included a body mass index (BMI), adjusted for age and sex, of 35 and greater, or a BMI-for-age of 30 in the presence of obesity related morbidity. At intake, all children filled out a standardized questionnaire regarding their bowel habits. Functional constipation was defined using Rome III criteria. Colonic transit times were determined using radio-opaque markers. A CTT of more than 62 hours was considered delayed. A total of 91 consecutive morbidly obese children (34% boys) filled out our standardized questionnaire and underwent a CTT study. The median age at intake was 15 years (8-18 yrs) and the median BMI was 38.7 (25.6 - 59.5) kg/m^2. Overall, 21% (n=19) of all children fulfilled the Rome III criteria for functional constipation. Only one child suffered from functional non-retentive fecal incontinence. Delayed colonic transit times were found in 8.8% of all obese children. In total 10.5% of the children with constipation had a total CTT exceeding 62 hours. In the non-constipated group 8.3% had a delayed CTT. No correlation was found between total or rectosigmoid CTT and BMI. (r=-0.15, p=0.224 and r=0.10, p=0.73, respectively).
Conclusion: Our study confirms a high prevalence of childhood constipation in obese children, using the Rome III criteria. This could not be explained with delayed colonic motility. No correlation was found between BMI and colonic transit times.

Intestinal flora directs infiltrate composition and disease severity in a novel zebrafish colitis model

S. Brugman[1], K-Y. Liu[1], D. Lindenbergh-Kortleve[1], J.N. Samsom[1], G.T. Furuta[2], S.A. Renshaw[3], R. Willemsen[4], E.E.S. Nieuwenhuis[1] ,[1]Laboratory of Pediatrics, Dept of Pediatric Gastroenterology, Erasmus Medical Center, Rotterdam, the Netherlands, [2]Section of Gastroenterology, Hepatology and Nutrition, The Children's Hospital, Aurora, Colorado, USA, [3]MRC Centre for Developmental and Biomedical Genetics, University of Sheffield, UK, [4]Dept of Clinical Genetics, Erasmus Medical Center, Rotterdam, the Netherlands

The pathogenesis of inflammatory bowel disease involves dysfunctional mucosal immune responses to commensal bacteria in genetically predisposed hosts. The complicated interactions between innate cells and bacteria however, have left researchers with exceeding difficulties to assess the relative contribution by each of these cells to the intestinal pathology. We altered the intestinal flora of zebrafish with antibiotics and assessed the effects on the mucosal infiltrate and severity of intestinal inflammation in a novel colitis model. Colitis was induced by intra-rectal administration of the hapten oxazolone in adult wildtype and myeloperoxidase-reporter transgenic zebrafish in the presence or absence of antibiotics. Intestinal inflammation was evaluated by histology, flow cytometry and cytokine profiling through quantitative Real Time PCR. Next, shifts in intestinal flora composition due to antibiotic treatment were assessed by 16SrRNA PCR, cloning and sequencing of intestinal content. Zebrafish oxazolone colitis is flora-dependent and characterized by an influx of granulocytes, epithelial damage, Goblet-cell depletion and increased expression of IL-1β, TNFα and IL-10. Vancomycin treatment diminished the intestinal microbial load and resulted in a bacterial composition dominated by Fusobacteria. Vancomycin conferred strong protection from colitis associated with reduced percentages of infiltrating neutrophils. In contrast to vancomycin, administration of colistin sulphate resulted in a predominance of γ-proteobacteria in the intestine that correlated with reduced infiltration of eosinophils and lymphocytes and no significant reduction in colitis.
Conclusion: Components of the intestinal microbiota drive zebrafish oxazolone colitis and directly affect the severity of disease and composition of the intestinal infiltrate.

A polymorphism in the coding region of il12b promotes IL-12p70 heterodimer formation in colitis sensitive SJL/J mice

A. Zwiers[1,2], D. Seegers[3], T. Konijn[2], B.J. Verwer[1], J.J.B. Garcia-Vallejo[2], J. Samsom[4], I. Fuss[3], W. Strober[3], G. Kraal[2] and G. Bouma[1], Dept. of Gastroenterology[1] and Molecular Cell Biology and Immunology[2], Vrije Universiteit Medical Center, Amsterdam, the Netherlands, [3]The Mucosal Immunity Section, National Institutes of Health, Bethesda, MD, USA, [4]Dept. of Pediatric Gastroenterology and Nutrition, Erasmus University Medical Centre–Sophia Children's Hospital, Rotterdam, The Netherlands

Interleukin-12 (IL-12) and interleukin-23 (IL-23) are key cytokines involved in the induction of Th1 and Th17 immune responses. Both cytokines are heterodimers, sharing a common subunit (IL-12p40) coded for by the IL12b gene. Genome wide association studies have recently implicated IL12b as a susceptibility gene for IBD. In a previous study in mice we identified the locus harboring this gene as a susceptibility region for trinitrobenzene sulfonic acid (TNBS) induced colitis. Here we investigated whether polymorphisms in the IL12b gene influence the synthesis of IL-12 in the highly susceptible SJL/J mouse strain.By generating two sets of constructs, in which p35 was linked to either the polymorphic SJL/J IL-12p40 or the wild type IL-12p40 from C57Bl/6, it was found in transfection studies that constructs with the SJL/J derived variant synthesized significantly more IL-12p70 relative to IL-12p40 compared to the wild type C57BL/6 variant. This could not be attributed to differences in synthesis rate or secretion implicating a higher affinity of SJL/J derived IL-12p40 for its IL-12p35 subunit. The in-vitro observations were subsequently confirmed in-vivo. IL-12p40 $^{-/-}$ mice which were made transgenic for either the SJL/J or C57Bl/6 variant of IL-12p40 synthesized significantly more IL-12p70 in the case of the SJL/J variant than did mice transgenic for the C57BL/6 variant, while there was no difference in IL-12p40 synthesis between both transgenic strains. This higher affinity is not confined to IL-12 synthesis but is also implicated in IL-23 synthesis. Conformational changes in the p40 molecule, possibly linked to differences in glycosylation, may underlie more efficient binding to p35, resulting in enhanced synthesis of the mature dimeric cytokine. It is concluded that the higher susceptibility found in the SJL/J strain for TNBS induced colitis is based on an aberrant high synthesis rate of the IL-12p70 cytokine, leading to a rapid pro-inflammatory skewing of the immune response and distortion of the homeostatic balance.

5-Aminosalicylic acid suppresses colitis-associated but not sporadic colorectal cancer

P.J. Koelink[1], E.C. Robanus-Maandag[2], J.A.D. Jankie[2], C.B.H.W. Lamers[1], D.W. Hommes[1] and H.W. Verspaget[1], Depts of [1]Gastroenterology-Hepatology and [2]Human Genetics, Leiden University Medical Center, Leiden, the Netherlands

Patients with inflammatory bowel disease (IBD) have an increased risk of developing colorectal cancer (CRC). The impact of 5-Aminosalicylic acid (5-ASA, mesalazine) treatment on the risk of colorectal cancer in these IBD patients remains controversial. In sporadic CRC, mutations are frequently found in adenomatous polyposis coli (APC), leading to deregulation of the Wnt pathway. We mimicked sporadic CRC by the generation of conditional Apc mutant mice with exon 15 of Apc flanked by loxP sites, and with Cre recombinase specifically expressed in the distal small intestine and large intestine under the influence of the fatty acid-binding protein (Fabpl) promoter. In these FabplCre;$Apc^{15lox/+}$ mice, Cre-mediated excision of exon 15 leads to mainly large intestinal tumorigenesis. Dextran sodium sulfate (DSS), an inducer of intestinal inflammation (colitis), accelerates the intestinal tumorigenesis in these mice. We aimed to evaluate the effect of 5-ASA treatment on DDS-colitis-accelerated and spontaneous intestinal tumorigenesis in FabplCre;$Apc^{15lox/+}$ mice. Therefore, 5-ASA or placebo medication was given to FabplCre;$Apc^{15lox/+}$ mice daily as an enema during 3 weeks starting at 5 weeks of age and colitis was induced by 2% (w/v) DSS in the drinking water for 5 days at 5 weeks of age. Mice were examined for intestinal tumorigenesis at 8 weeks of age. Tumors were evaluated for activation of the Wnt pathway, cellular proliferation and apoptosis by β-catenin, Ki67 and active caspase-3 immunohistochemistry, respectively. 5-ASA significantly reduced DSS-accelerated tumor numbers in FabplCre;$Apc^{15lox/+}$ mice, mimicking colitis-associated colorectal cancer (mean ± SEM: 18.0 ± 3.0 vs 28.8 ± 3.1, p=0.03). No effect of 5-ASA was seen on spontaneous intestinal tumorigenesis in FabplCre;$Apc^{15lox/+}$ mice, mimicking sporadic colorectal cancer (mean ± SEM: 5.2 ± 1.2 vs 4.8 ± 1.9). All tumors showed activation of the Wnt pathway, and similar levels of tumor cell apoptosis. The chemopreventive effect of 5-ASA was accompanied by a reduction in tumor cell proliferation in the colitis-associated tumors.
Conclusion: 5-ASA inhibits the development of colitis-associated CRC but has no effect on sporadic CRC in the FabplCre;$Apc^{15lox/+}$ mouse model. These observations provide prove for the concept of chemopreventive efficacy of chronic 5-ASA treatment in IBD-associated colorectal cancer.

Generation of a tightly regulated doxycycline-inducible model for studying mouse intestinal biology

S. Roth[1], P. Franken[1], W. van Veelen[2], L. Blonden[1], L. Raghoebir[3], B. Beverloo[4], E. van Drunen[4], E.J. Kuipers[2,5], R. Rottier[3], R. Fodde[1], and R. Smits[2],[1]Dept of Pathology, Josephine Nefkens Institute, Erasmus MC, Rotterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, [3]Dept of Cell Biology, [4]Dept of Clinical Genetics, [5]Dept of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Mouse models are frequently being used to address basic research questions about intestinal development, tumor formation, and inflammatory bowel disease. Inducible transgenic mouse models represent unique experimental tools to study the expression of specific genes in a tightly regulated fashion. Ideally, such an inducible mouse model should drive homogeneous transgene expression in the tissue of interest exclusively upon induction and in a dosage-dependent manner. Furthermore, induction of gene expression should be reversible. Such a model has not been available for the intestinal tract. Therefore, we set out to generate a mouse model allowing robust induction of intestine-specific gene expression by providing doxycycline in the drinking water. We generated a transgenic mouse model expressing the reverse tetracycline transactivator rtTA2 (Tet-On) under control of the 12.4 kb murine intestine-specific Villin promoter. To assess inducibility and tissue-specificity of the newly generated Villin-rtTA2 model, mice were bred with the tetO-H2B/GFP strain and administered with doxycycline. If the Villin-rtTA2 model functions correctly, the nuclear localized green fluorescent H2B/GFP protein will only be expressed in cells where the rtTA2 protein is expressed and activated by doxycycline. Expression of the H2B/GFP fusion protein was observed exclusively in double transgenic mice upon doxycycline induction and was uniformly distributed throughout the intestinal epithelium. The Villin-rtTA2 was also found to drive transgene expression in the mouse intestine during embryonic development. Furthermore, by administering different concentrations of doxycycline, we show that the Villin-rtTA2 system drives transgene expression in a dosage-dependent fashion.
In conclusion, we have successfully generated a novel intestinal-specific doxycycline-inducible mouse model, providing a valuable tool to study the effect of intestinal-specific expression of basically any gene of interest on intestinal physiology and pathology. Currently, this model is being used to identify H2B/GFP label-retaining cells that because of their slow-cycling capacities might represent intestinal stem cells.

Intravenous Immunoglobulins trigger direct functional activation of CD4+CD25+Foxp3+ regulatory T cells and promote skin allograft acceptance

T. Tha-In[1,2], A.R. Bushell[2], H.J. Metselaar[1], K.J. Wood[2], J. Kwekkeboom[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam and [2]Nuffield Dept of Surgery, University of Oxford, Oxford, UK

We have previously shown that Intravenous Immunoglobulins (IVIg) reduce the incidence of acute rejection after liver transplantation (LTx) two-fold, and suppress T-cell function in vitro as effectively as calcineurin inhibitors which form the basis of current immunosuppressive therapy after LTx. Since treatment with IVIgs is safe and not associated with the adverse effects of global immunosuppression, IVIgs may be an attractive candidate compound for preventing rejection after LTx. However, how IVIGs inhibit T-cell activation is not known. Here we show that IVIgs activate regulatory T-cells (Treg) both in vitro and in vivo, and prevent via this mechanism allogeneic skin graft rejection in a mouse model. *In vitro*, IVIgs bound to both human and mouse CD4+CD25+Foxp3+ Treg, and enhanced their activation as detected by increased expression of the surface activation markers HLA-DR, CD38 and CD69, and phosphorylation of the intracellular signal transducer ZAP70. IVIg binding to activated mouse T cells, but not to human T-cells, was partially mediated by Fcγ-receptors. IVIgs enhanced the capacity of human Treg to suppress proliferation of CD4+CD25- effector T-cells upon allogeneic stimulation (IVIg Treg: 63±8% versus control Treg: 37±10% inhibition, n=5, $p<0.05$). Moreover, when CD25+ T cells were depleted from responder CD4+ T-cells, IVIg-mediated inhibition of allogeneic CD4+ T-cell proliferation was twofold reduced. In an adoptive transfer model using $H2^k$ CBA/$Rag^{-/-}$ mice, IVIgs protected against T-cell mediated rejection of fully mismatched C57BL/10 ($H2^b$) skin grafts, but only when the mice were reconstituted with total CD4+ T cells (mean survival time: IVIg-treated mice >100 versus control mice 16 days, $p<0.01$). Importantly, this effect was completely lost upon selective depletion of CD4+CD25+ Treg from transferred T-cells, indicating that IVIgs induce dominant allograft protection mediated by Treg.
Conclusion: This study identifies direct binding and activation of naturally occurring Treg as an additional, novel immunomodulatory property of IVIgs. Our data indicate that IVIgs can induce a graft-protective activation of naturally occurring Treg, suggesting that the use of IVIgs as a component of tolerance induction strategies should be evaluated in the clinical setting.

Wilson disease is a novel target for pharmacological folding chaperones 4-phenyl-butyrate and curcumin

P.V.E. van den Berghe[1], E. Spijker[1], E. van Beurden[1], R.E.A. de Groot[1], J.M. Stapelbroek[1], S.F.J. van de Graaf[1], P. de Bie[1], R. Berger[1], L.W.J. Klomp[1], [1]Dept of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, the Netherlands

Wilson disease (WD) is an autosomal recessive disorder, which results in aberrant copper accumulation in several tissues. WD is caused by mutations in the gene encoding the hepatic P_{1B}-type ATPase *ATP7B*, a protein localized to the Golgi-apparatus that primarily facilitates hepatic copper excretion. Different mutations result in a variety of clinical phenotypes, ranging from primary hepatic failure due to liver cirrhosis, and neurological defects. Current therapy is focused on reduction of circulating copper by dietary zinc supplementation or copper chelation. Despite treatment, 5% of all patients develop fulminant liver failure, and 10-50% of the patients have neurological deterioration. The aim of this study was to investigate the possibility that some WD mutations lead to protein misfolding and are therefore potential candidates for drug treatment to improve protein folding and restore protein function. This necessitated detailed and systematic characterization of the molecular consequences of seven distinct *ATP7B* missense mutations (p.G85V, p.R778L, p.H1069Q, p.C1104F, p.V1262F, p.G1343V, and p.S1363F) associated with WD. With the exception of p.S1363F, all mutations resulted in reduced *ATP7B* protein expression, whereas mRNA abundance was unaffected. This coincided with (partial) retention of mutant *ATP7B* in the endoplasmic reticulum (ER) and increased expression of almost every mutation after culturing cells at 30°C, suggesting that these proteins were indeed misfolded. Furthermore, protein localization of ATP7B-R778L, ATP7B-H1069Q, and ATP7B-V1262F was normalized after this treatment. Residual copper export capacity was observed for ATP7B-G85V, ATP7B-H1069Q, ATP7B-R778L, and ATP7B-V1262F, whereas other mutations resulted in complete disruption of copper export by *ATP7B*. Treatment with pharmaceutical chaperones curcumin and 4-phenylbutyrate (4-PBA), a clinically approved compound, indeed partially restored expression of most WD mutations, among them the most abundant Asian and Caucasian mutations, p.R778L and p.H1069Q, respectively.

In conclusion, a surprisingly large proportion of *ATP7B* mutations resulted in aberrant folding and mislocalization to the ER, thus confirming that WD is a protein folding disease. Folding, expression and localization were partially restored by pharmaceutical chaperones. These findings enable novel treatment strategies that directly affect the protein function in addition to conventional therapy.

Microvillus inclusion disease is caused by mutations in apical recycling endosome -associated myosin Vb*

A.M. Szperl[1,8], M.R. Golachowska[2,8], M. Bruinenberg[1], R. Prekeris[3], A.M. Thunnissen[4], D. Hoekstra[2], C. Wijmenga[1,5], J. Ksiazyk[6], E.H. Rings[7,9], M.C. Wapenaar[1,9], S.C. van IJzendoorn[2,9], Depts of [1]Genetics, [2]CellBiology/Membrane Cell Biology and [7]Pediatrics, University Medical Center Groningen and University of Groningen, Groningen, the Netherlands, [3]Dept of Cellular and Developmental Biology, School of Medicine, University of Colorado Health Sciences Centre, Denver, Colorado, USA, [4]Dept of Biophysical Chemistry, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, The Netherlands, [5]Dept of Medical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands, [6]Dept of Pediatrics, Children's Memorial Health Institute, Warsaw, Poland. [8,9]Theseauthors contributed equally

Microvillus inclusion disease (MID) is a life threatening enteropathy characterized by intractable diarrhea andmalabsorption. Enterocytes in the intestinal mucosa typically display brushborder atrophy, microvillus-containing membrane inclusions, and an accumulation of (lysosomal) vesicles. This rare disease (incidence ~1:100,000) may present immediately or within weeks after birth (early- or late-onset) and occurs predominantly in the offspring of consanguineous parents. The likely mode of inheritance is autosomal recessive. The only treatment available is total parenteral nutrition or a bowel transplant. The aim of this study was to identify thegenetic cause of MID, and thus gain insight into the cell biological processes that underlie proper brush border development. We analyzed the genomic DNA from three MID patients with different ethnic backgrounds: a Dutch-Moroccan son ofconsanguineous parents (early-onset), a late-onset Dutch boy, and an early-onset Polish girl. The parents of the later two MID patients were not related. Genetic homozygosity mapping was performed with microarrays and mutations were identified by DNA sequence analysis. Intestinal tissue of the patients was examined with electron microscopy, immunohistochemistry, and expression microarrays. Four large blocks of homozygosity (20-30 cM) were presentin the Moroccan patient. In the block on chromosome 18q21 we identified MYO5B as a functional-positional candidate gene. MYO5B encodes for the two-headed motor protein myosin Vb, which is involved inapical recycling endosomes and actin filament binding. Sequence analysis in these three patients revealed five independent causative mutations in MYO5B. These mutations were associated with an aberrant expression and subcellular distribution of myosin Vb and several interacting proteins, alsoinvolved in apical recycling endosome-mediated protein trafficking. Here we demonstrate that mutations in MYO5B are primarily responsible for MID and cause an impairment of the apical endosomal system that ensures recycling of brush border proteins. It further shows that the proper biogenesis of the brush border requires a functionalapical recycling endosome system in which myosin Vb acts as a critical regulator. The identification of MYO5B as the causative gene for MID will aid the (prenatal) diagnosis of this rare but severe disorder and should pave the way to developing alternativetherapies, including that of stem cell-based gene therapy.

COMMD1 is a novel inhibitor of the CCS-dependent activation of Copper/Zinc Superoxide Dismutase

W.I.M. Vonk[1,2], B. van de Sluis[1,2,3], R. Berger[1], C. Wijmenga[2,4], L.W.J. Klomp[1], [1]Dept of Metabolic and Endocrine Diseases, University Medical Center Utrecht, and Netherlands Metabolomics Center, the Netherlands, [2]Complex Genetics Section, University Medical Center Utrecht, the Netherlands, [3]Dept of Pathology and Laboratory Medicine, University Medical Center Groningen, the Netherlands, [4]Dept of Genetics, University Medical Center Groningen, the Netherlands

Copper toxicosis (CT) in Bedlington terriers is an autosomal recessive disorder, characterized by hepatic copper overload and caused by a deletion of the COMMD1 gene. Recent protein-protein interaction studies implicated COMMD1 in multiple different cellular pathways, but the exact biochemical function of COMMD1 in hepatic copper homeostasis remains unknown. To unravel the role of COMMD1 in copper metabolism, we determined if COMMD1 interacted with proteins known to be involved in copper homeostasis. Using GST-pull down assays, we identified an interaction between COMMD1 and the cytosolic cuproenzyme Cu/Zn Superoxide Dismutase (SOD1), an important and ubiquitously expressed scavenger of superoxide radicals. The interaction between endogenous COMMD1 and SOD1 was verified by co-immunoprecipitation, appeared strictly copper-dependent and was enhanced by overexpression of CCS, the copper chaperone for SOD1. Consistent with this observation, COMMD1 also associated with CCS, and RNAi-mediated reduction of CCS expression resulted in amelioration of the COMMD1-SOD1 interaction. Next, we determined the effect of these interactions on SOD1 activity. The formation of active SOD1 requires the subsequent incorporation of zinc, the CCS-dependent incorporation of copper, isomerisation of an intramolecular disulphide bond and formation of SOD1 homodimers. Overexpression of COMMD1 markedly inhibited SOD1 activity, as assessed by an in-gel activity assay and precluded the formation of active SOD1 dimers, while RNAi of COMMD1 had opposite effects. Taken together, these data indicate that COMMD1 is involved in regulating SOD1 activity under normal conditions. Since oxidative stress plays an important role in the pathogenesis of toxic liver diseases accompanied by chronic inflammation, liver fibrosis and cirrhosis, these findings have implications for a variety of liver diseases. Nevertheless, the predicted effect of the COMMD1 deletion on SOD1 activity in CT-affected Bedlington terriers is unlikely to provide an explanation for the hepatic copper overload phenotype in these dogs.

Angiotensin II protects rat hepatocytes from bile acid- induced apoptosis

G. Karimian, M. Buist-Homan, R. Henning, K.N. Faber, H. Moshage, Dept. Gastroenterology and Hepatology and *Dept. Clinical Pharamcology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

Background: Angiotensin II (AT-II) is the key effector of the Renin Angiotensin System (RAS), which is the systemic blood pressure regulatory mechanism. Recently, a local RAS in the liver has been identified, with the hepatic stellate cell (HSC) playing a central role: the HSC produces AT-II and is responsive to AT-II via the AT-II-type-1 receptor (AT-1R) present on HSCs. The local RAS is activated in patients with chronic liver diseases and AT-II could promote fibrosis due to activation of HSCs. AT-II antagonists are anti-fibrotic in experimental models of liver fibrosis and AT-II antagonists are considered in the treatment of liver fibrosis. However, the effects of AT-II and AT-II antagonists on hepatocytes exposed to toxic factors present in chronic liver diseases, e.g. bile acids, has not been investigated. Aim: to investigate the effects of AT-II on glycochenodeoxycholic acid (GCDCA)-induced apoptosis in primary cultures of rat hepatocytes. Methods: Rat hepatocytes were isolated from male Wistar rats. To induce apoptosis, primary hepatocytes were exposed to GCDCA (50µmol/L). AT-II (100nmol/L) was added 10 minutes prior to GCDCA. Hepatocytes were also treated with AT-1R antagonists (losartan, candesartan, irbesartan and valsartan at 1µmol/L) or the PI-3-kinase inhibitor LY294002 (50µmol/L) 30 min prior to apoptotic stimuli. Apoptotisis was determined by measuring caspase-3 activity and acridine orange staining. Necrosis was measured by Sytox green staining. AT-1R mRNA expression was assessed using quantitative PCR. Results: AT-II reduces GCDCA-induced apoptosis by 60%, but does not increase necrosis in hepatocytes. All AT-1 receptor antagonists tested abolish the protective effect of AT-II against GCDCA-induced apoptosis. Furthermore, inhibition of PI3-kinase reversed the protective effect of AT-II. AT-II was protective when added prior to or simultaneously with GCDCA, but failed to protect when added after GCDCA.
Conclusion: AT-II protects primary rat hepatocytes from bile acid-induced apoptosis but does not increase necrosis. The protective mechanism is due to cell survival pathway activation, especially the PI3-kinase pathway. Our results suggest that AT-II antagonism treatment of liver fibrosis could lead to sensitization of hepatocytes to bile acid-induced cell death, which is especially relevant in chronic cholestatic liver diseases.

NK-cell chimerism is a unique feature of liver transplantation and may modulate the recipient's immune response against the graft

V. Moroso[1], H.J. Metselaar[1], B.M. Bosma[1], S. Mancham[1], L.J.W. van der Laan[2], N.M. van Besouw[3], H.W. Tilanus[2], E.J. Kuipers[1], D. Eissen[4], A.van der Meer[4], I. Joosten[4], J. Kwekkeboom[1], Depts of [1]Gastroenterology and Hepatology, [2]Surgery and [3]Internal Medicine, Erasmus MC, Rotterdam, and [4]Dept of Blood Transfusion and Transplantation Immunology, UMC St Radboud, Nijmegen., the Netherlands

Liver grafts have tolerogenic properties, as shown by the low incidence of chronic rejection compared to other solid organ grafts. In addition, immunosuppressive medication can be completely discontinued in about 20% of liver transplant (LTx) recipients. We hypothesized that this unique property of liver grafts may be related to their high content of organ-specific NK cells. In the present study, we determined whether hepatic NK-cells of donor origin migrate into recipients after clinical LTx, and characterized NK-cells that detach from human liver grafts during vascular perfusion before transplantation ex vivo. Using antibodies that recognize donor HLA-alleles, we found that a variable percentage, ranging from 1.1% to 7.9%, of circulating NK-cells in LTx-recipients (n=13) were of donor origin, for an average time of 15 days after LTx. In contrast, no NK cell chimerism was observed in renal transplant (RTX) recipients (n=6). Fourty-six ± 6% of NK-cells present in perfusion fluid belonged to the CD56bright/CD16- subset, reminiscent of the NK-cell subset present in human lymph nodes. Hepatic CD56bright NK-cells were highly activated (95±3% CD69+, versus 12±4% CD69+ in blood CD56bright NK cells; $p<0.001$), and had an increased perforin/granzyme content compared to its counterpart in blood. Purified perfusate NK-cells killed MHC class I devoid K562 cells and both CD56dim and CD56bright hepatic NK-cells showed CD107a degranulation upon incubation with K562 cells, demonstrating their cytotoxic capacity. Importantly, liver graft NK-cells were able to kill activated allogeneic T-cells.
Conclusions: After clinical LTX, but not after RTX, donor NK cells migrate into the recipient. NK-cells that detach from liver grafts are enriched for CD56bright NK-cells, which are highly activated and cytotoxic. Since liver graft NK-cells are able to kill activated allogeneic T-cells, they may combat T-cell mediated rejection of the liver graft.

Systematic evaluation of the Over-The-Scope-Clip (OTSC) for NOTES gastric closure

R.P. Voermans[1,2], M.I. van Berge Henegouwen[2], W.A. Bemelman[2], P. Fockens[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, [2]Dept. of Surgery, Academic Medical Center, University of Amsterdam, the Netherlands

Secure transluminal closure remains a fundamental barrier to safe translation of NOTES into humans. Aims were 1) To compare acute ex vivo strength of Over-The-Scope-Clip (OTSC; Ovesco) gastrotomy closure to surgical suture. 2) To evaluate feasibility, safety and reliability of gastrotomy closure using OTSC in acute and survival porcine experiments. The gastric opening was created by needle knife puncture followed by dilatation with 18 mm balloon. The closure procedure consisted of 3 steps: 1. Approximation of muscular layers using a flexible twin grasper; 2. Pulling the tissue into the OTSC cap fitted at the tip of the scope; 3. Releasing the clip. *1) Ex vivo comparison study* was conducted in an ex vivo porcine stomach model as a previously described by our group. Fifteen control gastrotomies (surgical suture) resulted in a mean leak pressure of 206 mmHg (SD 59). Using a non-inferiority design a sample size of 11 specimens needed to be included in the OTSC group. *2) In vivo experiments* were planned in 3 non-survival and 16 survival pigs. Sample size for survivals was based on the fact that the lower end of the 95% confidence interval (CI) of successful closure must be at least above the 80% and a success rate of 100%. In all pigs a standardized hybrid cholecystectomy was performed and gastrotomies were closed using the OTSC. In the survivals necropsy was performed after 10 days with inspection of peritoneal cavity and the gastrotomy site, which was excised and sent for histology. *1) Ex vivo*: Closure was successful in all specimens. Mean leak pressures was 224 mmHg (SD 61), which was non-inferior to the gold standard (p=0.003). *2) In vivo:* Closure was endoscopically successful in all acute experiments and the 6 survival experiments performed until 11/08. Median closure time was 7 minutes. All survival animals thrived during 10 days follow up. At necropsy there were no signs of infection or other complications and only 3 adhesions from the gastrotomy to the omentum. The gastrotomy was macroscopically full-thickness closed in all cases. In 2/6 the clip was still present at the closure site. Histology confirmed full-thickness healing with 100% success (95% CI: 61-100%).
Conclusions: Use of OTSC for gastrotomy closure is feasible and provides ex vivo burst pressures comparable with surgical closure. OTSC gastrotomy closure is easy to apply, safe and reliable and results in histological proven full-thickness closure in survival experiments with 6 out of 16 experiments completed.

Preliminary experience with the novel Spyglass peroral cholangioscopy system

R.K. Weersma, Dept of Gastroenterology and Hepatology University Medical Center Groningen, the Netherlands

Introduction: peroral cholangioscopy using the baby-mother technique has been possible since long. However, adoption of this technique in routine clinical practice have been hampered by technical limitations, poor visualization and frequent breakage of the endoscopes. The recently introduced Spyglass® cholangioscopy system (Boston Scientific) is a disposable endoscope with a multi-usable fiberoptic. The scope can be advanced through the working channel of a regular duodenoscope. Taking intraductal biopsies is possible using the Spybite forceps. Preliminary experience with this novel technique is presented. Methods: From the introduction in November 2007 till December 2008 all procedural data and clinical data were prospectively collected. Results: 20 procedures were performed in 19 patients. Indications for peroral cholangioscopy were analysis of biliary strictures of unknown origin (n=10), evaluation of strictures in PSC (n=3), intraductal laserlithotripsy of complex bile duct stones (n=3) and miscellaneous (n=3). Mean procedural time was 75 min (range 45-180) with the actual cholangioscopy lasting 27 min (range 10-60). 18 procedures were performed under conscious sedation with midazolam (mean 7.3 mg) and pethidine (mean 70 mg) and two under general anesthesia. Biliary introduction was possible in all procedures and easy in 16 of 20 procedures. Visibility was reasonable to good in 18 / 20 procedures. One patient developed post procedural fever which was treated with oral antibiotics. No other complications were observed. Intraductal biopsies were succesfully obtained in 9 cases. Intraductal laserlithotripsy of common bile duct stones using the Holmium:Yag Laser was succesfull in 2 of 3 patients. In the unsuccesfull case it was impossible in two procedures to position the laser fiber safely due to an impacted stone. The laser fiber was succesfully used in one patient to dissect an impacted and broken extraction basket. Cholangioscopy led to changes in patient management in 14 of 19 patients. Diagnosis or succesfull therapy led to avoiding an operation in 10 of 19 and led to operation in 4 of 19 patients.
Conclusion: Peroral cholangioscopy using the Spyglass system is feasable and safe and has good diagnostic and therapeutic qualities. Cholangioscopy led to changes in patient management in 14 of 19 patients, showing its clinical usefullness in a selected group of patients.

Performance of endoscopic ultrasound-guided fine-needle aspiration in patients with mediastinal lymphadenopathy during routine patient care

M.M. Hirdes[1], M.P. Schwartz[1,4], K.M. Tytgat[1], N.J. Schloesser[2], D.M. Sie Go[3], M. Brink[4], B. Oldenburg[1], P.D. Siersema[1], F.P. Vleggaar[1], Depts of Gastroenterology & Hepatology[1], Pulmonary Medicine[2] and Pathology[3], University Medical Center Utrecht, the Netherlands, Dept of Gastroenterology[4], Meander Medical Center, Amersfoort, The Netherlands

Background: Clinical trials have shown that mediastinal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a valuable diagnostic tool in high-volume expert centers. Little is known on its performance characteristics during routine care of patients with mediastinal lymphadenopathy of various etiology. Aim: To evaluate performance of EUS-FNA of mediastinal lymphadenopathy in daily practice.Materials and methods: All consecutive patients (Sept. 2002 - March 2008) referred for EUS-FNA of enlarged mediastinal lymph nodes in two Dutch centers were reviewed. Cytological diagnosis was verified by histology or clinical follow-up (>6 months). Impact on clinical management was divided in the following categories: positive impact, by providing a true cytological diagnosis and facilitating or avoiding surgery, or diagnosing a benign inflammatory disorder, or negative impact, by providing false negative cytology, inconclusive cytology, or not influencing patient management despite adequate cytology. Costs of a theoretical diagnostic work-up without EUS-FNA as established by an expert panel of a gastroenterologist and a pulmonologist were compared with costs of actual work-up. Results: In total, 232 patients (72% male, median age 62 years (23-88)) underwent 237 mediastinal EUS-FNA procedures. Sensitivity, specificity, negative predictive value, positive predictive value and accuracy were 87%, 100%, 76%, 100% and 91%, respectively. EUS-FNA had a positive impact on clinical management in 83% of cases, by facilitating surgery (8%), avoiding surgery (40%) or excluding malignant lymph-adenopathy (35%). In 8% of cases, EUS-FNA had a negative influence because of inadequate (5%) or false negative (3%) cytology. Nine percent of patients underwent EUS-FNA without an established indication. The complication rate was 0.8% (2 perforations). Total cost reduction was Euro 111.390, the mean cost reduction for diagnostic evaluation per patient was Euro 480 (SD: 607).
Conclusion: The performance characteristics of mediastinal EUS-FNA in daily practice are not different from those reported in high-volume centers. EUS-FNA plays a significant role in the optimal management of patients with mediastinal lymphadenopathy of various etiology and reduces diagnostic costs. A more precise pre-procedural evaluation of the indication by excluding patients in whom cytological results a priori will not influence decision making, may further improve the yield of EUS-FNA in this patient group.

How effective and safe is EUS-guided Fine Needle Aspiration (EUS-FNA) in the evaluation of cystic lesions of the pancreas?

K. de Jong[1], M.J. Bruno[2], M. Visser[3], C.Y. Nio[4], D.J. Gouma[5], J.J. Hermans[6], C.H.J van Eijck[7], J.W. Poley[2], P. Fockens[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [3]Dept of Pathology, Academic Medical Center, Amsterdam, [4]Dept of Radiology, Academic Medical Center, Amsterdam, [5]Dept of Surgery, Academic Medical Center, Amsterdam, [6]Dept of Radiology, Erasmus Medical Center, Rotterdam, [7]Dept of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands

EUS-guided FNA is considered to be an important, safe and effective technique for the investigation of pancreatic cysts (PC). We investigated the yield of EUS-FNA in a prospective cohort of patients with PC(s). Aims were to determine the effectiveness and safety for obtaining PC fluid using FNA to perform cytologic and tumormarker analysis. Consecutive patients with PCs of unknown etiology were enrolled in our PC protocol, which included abdominal MRI and EUS-FNA. EUS was performed by two experienced endosonographers with a linear array echoendoscope (GF-UC(T)140(P), Olympus). 22 or 19 G needles (Cook) were used for aspiration. PC fluid was analyzed primarily for cytopathology, secondly for tumormarkers (CEA, CA 19.9, amylase). Management was determined by the combination of clinical presentation, morphologic features on MRI and EUS, and PC fluid analysis. In this ongoing study 75 (M:F=43:32) patients, median age of 63 (19-81) were enrolled between 12/2006 and 11/2008. FNA was performed in 70 of 75 patients (93%) who underwent EUS. Two cysts were considered too small, one was not identified at EUS, one was considered a pseudocyst with debris and in one case FNA was technically unsuccessful. The median amount of fluid was 4 ml (0.5-145). Material was sent for cytology in 100% of patients undergoing FNA. A classifying cytopathologic diagnosis was obtained in 23 of 70 patients (33%). Sufficient fluid for chemical analysis was obtained in 33 patients (47%). Failure of determination of tumormarkers was mainly caused by a high viscosity of the fluid or small size of the cysts. Complications occurred in 1 patient (1.4%) who had an infected cyst and was treated with i.v. antibiotics. Eventually 24 patients (32%) were operated and 51 (68 %) entered a surveillance program. Surgery showed the following histological diagnoses (1 adenocarcinoma, 1 acinar cell carcinoma, 3 malignant IPMN`s, 9 benign IPMN`s, 3 mucinous cystadenomas, 1 serous cystadenoma, 5 pseudocysts, 1 lymphatic malformation). The PPV for cytopathology was 67% (16/24) for the operated patients.
Conclusions: FNA was feasible in 93% of all cases (70/75) and not possible in 7%. Complications occurred in 1.4%. A cytopathologic diagnosis was possible in 33% and tumormarkers could be determined in 47%. In the surgical group FNA-cytology showed a PPV of 67%. Long-term surveillance of all patients will show the true value of EUS-FNA in cystic lesions of the pancreas.

The value of endoscopic ultrasound in detecting periampullary tumors after a negative CT

N.A. van der Gaag[1], C.Y. Nio[2], J. Hoogmoed[1], O.R.C. Busch[1], M.J. Bruno[3], P. Fockens[4], T.M. van Gulik[1], P.M.M. Bossuyt[5], D.J. Gouma[1,1]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands. [2]Dept of Radiology, Academic Medical Center, Amsterdam, the Netherlands, [3]Dept of Gastroenterology, Erasmus Medical Center, Rotterdam, the Netherlands, [4]Dept of Gastroenterology, Academic Medical Center, Amsterdam, the Netherlands, [5]Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, the Netherlands

CT scan can detect suspected periampullary malignancy non-invasively and assess local tumor extension and potential distant metastases. Since sensitivity is not 100% a negative CT (no 'visible' lesion) does not rule out the presence of a (pre)malignancy. Endoscopic ultrasound (EUS) has been proposed to serve as an add-on test after a negative CT, but its added value has not been well established. Data from a consecutive series of 587 patients, referred to our tertiary center between April 2001 and June 2007, were analyzed. Of this series patients with a potentially resectable solid periampullary lesion who had CT were included. Cystic lesions were excluded. In our center no attempts are made to obtain cytology or histology preoperatively in patients with a pancreatic mass lesion. Availability of malignant brush/biopsy obtained by endoscopic retrograde cholangiography (ERC) in referral centers was an exclusion criterion for the present study. We used results from pathology and follow-up to determine or refute the presence of (pre)malignant lesions. Data from 335 patients could be analyzed. Their mean age at the time of investigation was 62 (SD 12) years; 38% were women. CT detected a solid lesion in 198 (59%) patients and was inconclusive or negative in 137 (41%) patients. Of the 198 patients with positive CT 189 (95%) had a confirmed (pre)malignant lesion. In 106 (77%) of the 137 patients with an inconclusive CT EUS was performed, which was positive in 63 (59%), of which 53 had a (pre)malignant lesion. Of the 43 patients in which EUS did not demonstrate a lesion 10 (23%) had a (pre)malignant lesion. The sensitivity of the CT+EUS strategy was 0.96, versus 0.75 for CT only, for a specificity of 0.64 versus 0.83. The gain in accuracy was highly significant (P <0.001). In the 43 patients with no lesion on EUS 29 had no prior biliary stent placement of which 4 (14%) had (pre)malignant lesion versus 6 (43%) of the 16 patients that had a stent in place (P 0.044).
Conclusions: Implementation of EUS as add-on test after negative CT in the diagnostic algorithm for detection of periampullary (pre)malignancies results in a significant gain of accuracy. In case EUS does not confirm the presence of a lesion, this does not completely rule out (pre)malignancy. Refinement of the technique and increased experience might further enhance the yield of EUS.

Endoscopic Tri-Modal Imaging improves the detection of early neoplasia in Barrett esophagus; an international multi-center randomized cross-over study

W.L. Curvers[1], L. Alvarez Herrero[1,2], H.C. Wolfsen[3], V. Subramanian[4], G.A. Prasad[5], M.B. Wallace[3], K. Ragunath[4], L-M. Wong Kee Song[5], P. Fockens[1], B.L.A.M. Weusten[2], J.J.G.H.M. Bergman[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, Netherlands, [2]Dept of Gastroenterology and Hepatology, St Antonius Hospital, Nieuwegein, Netherlands, [3]Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, Florida, USA, [4]Wolfson Digestive Disease Centre, Queen's Medical Centre, Nottingham, United Kingdom, [5]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA

Introduction: Endoscopic tri-modal imaging (ETMI) incorporates high-resolution endoscopy (HRE), autofluorescence imaging (AFI) and narrow band imaging (NBI) in one single endoscopy system. In a recent uncontrolled multi-centre feasibility study, we found that ETMI may improve the detection of high-grade dysplasia (HGD) and early carcinoma (EC) in Barrett esophagus (BE). The aim of the current study was to compare ETMI with standard endoscopy (SE) for the detection of HGD/EC using a randomized cross-over design.

Methods: This study was performed in 5 tertiary referral centers for early BE neoplasia. All BE pts referred for the work-up of inconspicuous HGD/EC were eligible. Pts underwent 2 consecutive endoscopies (SE and ETMI) within an interval of 6-12 weeks. Prior to the first procedure randomization to SE or ETMI was performed. Both procedures were performed by 2 different endoscopists experienced in early BE neoplasia. The endoscopist assigned to the second procedure was blinded for the results of the first procedure. During SE, targeted Bx were performed from any visible lesion followed by 4q/2cm random Bx. During ETMI, inspection with HRE was followed by AFI. All detected lesions were inspected in detail with NBI and biopsied followed by 4q/2cm random Bx. The combined histological outcome of both endoscopic procedures was regarded as gold standard. The sample size was calculated on 84 patients.

Results: Up to today 54 pts (38 male; 68 years SD 10) have undergone both procedures (10 pts await 2nd procedure). HGD/EC was detected in 37 pts (69%). The overall sensitivity of SE for HGD/EC was 70% compared to 86% for ETMI. The sensitivity for *targeted* detection of HGD/EC was 49% for SE and 70% for ETMI. In total 48 suspicious lesions were detected with SE of which 23 (48%) contained HGD/EC. ETMI detected 152 suspicious lesions of which 45 (30%) contained HGD/EC: 25 lesions were detected with HRE and 20 with AFI only. NBI reduced the FP-rate of ETMI from 70% to 45%, at the expense of misclassifying 8 lesions containing HGD/EC as NBI unsuspicious.

Conclusion: ETMI has a higher sensitivity for the detection of HGD/EC in BE compared to SE. The *targeted* detection-rate of ETMI is comparable to the overall detection-rate of SE. The improved detection of ETMI is due to the additional value of AFI that detected 18 lesions (45%) containing HGD/EC not apparent with HRE. Although NBI reduced the FP-rate of ETMI, detailed inspection with NBI was associated with a 20% FN-rate.

Endoscopic radiofrequency ablation for very long segments of Barrett esophagus containing neoplasia

L. Alvarez Herrero[1,2], R. Pouw[1], F.G. van Vilsteren[1], C.M. Sondemeijer[1], F.J. ten Kate[3], P. Fockens[1], B. Weusten[2], J.J. Bergman[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Netherlands, [2]Dept of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, Netherlands, [3]Dept of Pathology, Academic Medical Center, Amsterdam, the Netherlands

Radiofrequency ablation (RFA) is safe and effective for eradicating Barrett esophagus (BE) and neoplasia. Most studies limited the baseline length of BE (<10cm) and little is therefore known about RFA for very long BE segments. The aim was to assess the safety and efficacy of RFA for BE ≥10cm containing neoplasia. Eligible patients (pts) had BE ≥10cm with LGD, HGD or early cancer (EC). Pts underwent focal endoscopic resection (ER) for visible lesions, followed by circumferential (C-RFA) and focal RFA (F-RFA) every 2-3 mo until complete remission (CR, defined as endoscopic resolution of BE and no intestinal metaplasia (IM) or neoplasia on biopsy). Follow-up (FU) endoscopy with 4Q/2cm biopsies was performed at 2, 6, and 12 mo. 26 consecutive pts were included (21 M, age 66yrs, median BE length 11cm, range 10-20). Baseline ER was performed in 18/26 pts: EC (11), HGD (6), LGD (1). Worst grade of residual BE prior to RFA (and after ER as applicable): HGD (16), LGD (10). At entry, 13 pts (50%) had a proximal reflux stenosis (3 required dilation). After C-RFA, 7/26 (27%) had a non-transmural laceration (4 at the reflux stenosis, 3 at the prior ER). All were able to complete RFA. One pt with a relative stenosis after ER, developed dysfagia after RFA and required dilatation. By Nov'08, 9 pts are still under treatment (median regression: 95%), in 3 pts (12%) treatment was discontinued due to poor neosquamous regeneration. 14 pts have completed treatment with CR achieved after a median of 1(IQR 1-1) C-RFA and 2(IQR 1-3) F-RFA sessions. Two pts had a focal ER for small persisting islands after RFA. After a median FU of 9 mo, no recurrence of neoplasia was found. In 1 pt a 0.5mm island was found during FU. One pt had focal IM detected at the neo-z-line at a single FU endoscopy. No buried BE was found in 752 neosquamous biopsies.
In conclusion, pts having very long segments of BE (10-20cm in this evaluation) present challenges that are not observed in more typical BE pts: 12% showed poor healing after RFA, probably reflecting the severity of the underlying reflux disease. Reflux stenoses and scarring after ER resulted in superficial laceration after C-RFA in 27% of pts, but these events were manageable. Overall we were able to achieve a CR in 14/17 who completed therapy in a similar number of RFA sessions as required in shorter segment BE cohorts. Aside from the challenges noted, very long segments of BE can be treated safely and effectively with RFA.

Radiofrequency ablation for eradication of Barrett esophagus containing high-grade dysplasia or early cancer: a prospective series of 73 patients

R.E. Pouw[1], F.G. van Vilsteren[1], L. Alvarez Herrero[2, 1], J.J. Gondrie[1], C.M. Sondermeijer[1], F.J. ten Kate[3], P. Fockens[1], B.L. Weusten[2], J.J. Bergman[1], [1]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, The Netherlands, [3]Pathology, Academic Medical Center, Amsterdam, The Netherlands

Radiofrequency ablation (RFA) is a novel endoscopic ablation technique for eradication of Barrett esophagus (BE). Aim was to report the combined results of published and ongoing studies on RFA of BE with high-grade dysplasia (HGD)/early cancer (EC) and baseline endoscopic resection (ER) in case of visible lesions. We included all patients treated with RFA at our centre starting July 2005 under EC approved protocols. Enrolled patients had BE ≤12cm with HGD/EC. Non-flat lesions were removed with ER prior to RFA. Excl. criteria: cancer >T1sm1 or N+ disease on EUS. Primary circumferential RFA was performed using a balloon-based catheter, secondary focal RFA was performed with an endoscope-based catheter (BARRX Medical). Primary RFA was performed 6 wks after ER, followed by secondary RFA every 2 months until clearance of BE was confirmed endoscopically by inspection with narrow-band imaging, and histologically by biopsies. Thereafter, follow-up endoscopy and biopsy was performed at 2, 6, and 12 months and then annually. 73 pts were included (59M, mean age 65yrs, median BE 5cm). 57/73 pts (78%) underwent ER prior to RFA revealing EC (n=32), HGD (n=20), LGD (n=4) or non-dysplastic BE (n=1). The worst histological grade of residual BE prior to RFA was HGD (n=42), LGD (n=24), or non-dysplastic (n=7). By November 2008, 11 pts are still under treatment, 62 pts have completed treatment (results of 44 pts have been published). Complete histological eradication of dysplasia and intestinal metaplasia (IM) was achieved in 59/62 pts (95%) after a median of 1 (IQR 1-1) circumferential RFA and 2 (IQR 1-2) focal RFA sessions, and additional ER in 5 pts. There were 3 failures: 2 pts had persisting dysplasia (5%), in 1 pt (2%) treatment was ceased due to poor mucosal healing after RFA. Complications after RFA: asymptomatic non-transmural laceration at an ER-scar after circumferential RFA (n=7), dysphagia (n=5), melena (n=1). No lacerations or dysphagia occurred in patients without prior ER. 17 months (IQR 14-33) after the last treatment, no dysplasia had recurred. In one patient a 1mm BE isle was identified at 12 months follow-up. 8 pts had focal IM detected distal to the neo-Z-line at a single FU. Of 2515 biopsies obtained from neosquamous epithelium during any follow-up, 2 showed buried IM (0.08%).
Conclusion: RFA of BE-HGD/EC ± prior ER of visible lesions is effective in achieving complete eradication of dysplasia and IM (95%) without serious adverse events.

Patient-based assessment of prolonged colonoscopy simulator training

A.D. Koch[1], J. Haringsma[1], E.J. Schoon[2], R.A. de Man[1], E.J. Kuipers[1], [1]Erasmus MC, Rotterdam, [2]Catharina Hospital, Eindhoven, the Netherlands

Introduction: Virtual reality endoscopy simulators are increasingly used in the training of novice endoscopists. This is the result of several developments, including the continued further development of simulators to high levels of virtual reality, the introduction of competency models in GI training, and demands from health authorities and the public regarding physician training in general. There are insufficient data regarding the contribution of simulator training to the early learning curve of novice endoscopists. The aim of this study therefore was to assess the performance of novice endoscopists during patient-based colonoscopy after intensive and prolonged training on a virtual reality endoscopy simulator. Methods: Trainees without any endoscopic experience were included in the study. The simulator-training program consisted of 100 virtual-reality colonoscopies on the GI Mentor II simulator (Simbionix, Israel). After 20, 60 and 100 virtual colonoscopies, trainees were assessed both simulator-based (SBA) and patient-based (PBA). At each PBA 2 single-handed colonoscopies were performed with a 20-minute time limit. Objective assessment consisted of the time to reach the cecum, or the maximum distance from the anal verge after fully straightening the colonoscope. Subjective assessment was done by two independent expert endoscopists using tri-split video assessment including camera view, endoscope view, and ScopeGuide magnetic imaging view. Results: Ten novices participated in the study. All participants completed virtual training and assessments. The mean cecal intubation time on the SBA improved from baseline 7.08 min. to 2.08 min. at completion of the training (P=0.007). Colonic insertion depth during PBA improved from 37 to 58 and 60 cm (P=0.002). The cecum was intubated 4 times by 3 novices, during 2nd PBA (n=1), and during the final PBA (n=3) (P=0.11). Subjective PBA demonstrated a general increase in the efficiency of movements, instrument handling and planned endoscopy. Measured on a 5 point scale, performance significantly improved form 1.67 to 2.20 (P=0.02).
Conclusion: Virtual reality training on the GI Mentor II simulator leads to a significant improvement of performance on the simulator itself and –more importantly- to significantly improved performances during patient-based colonoscopy. This study is the first to demonstrate the rationale for intensive simulator training in the early learning curve of novices performing colonoscopy.

Autofluorescence endoscopy allows better differentiation than white light video colonoscopy in classifying adenomatous and non-adenomatous colorectal polyps

P.G. van Putten[1], D. Ramsoekh[1], J. Haringsma[1], J.W. Poley[1], H. van Dekken[2], E.W. Steyerberg[3], M.E. van Leerdam[1] and E.J. Kuipers[1,4], [1]Dept of Gastroenterology and Hepatology, [3]Dept of Public Health and [4]Dept of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, [2]Dept of Pathology, St. Lucas Andreas Hospital, Amsterdam, The Netherlands

Background: Colorectal cancer (CRC) is the second leading cause of cancer mortality in the United States and Europe. Removal of adenomatous polyps has been proven to reduce CRC incidence and mortality. Idealy, polypectomies should be limited to adenomatous lesions. It has been suggested that autofluorescence endoscopy has the potential to differentiate between adenomatous and non-adenomatous polyps. Aim: To compare autofluorescence endoscopy (AFE) and white light endoscopy (WLE) for the differentiation between adenomatous and non-adenomatous colorectal polyps.Methods: 70 polyps were evaluated with both WLE and AFE. The polyps were detected in a back to back comparative study of WLE with a video colonoscope (CF180, Olympus Optical) and AFE using Xillix OncoLife (CF40, Olympus Optical) in patients from Lynch syndrome or familial CRC families (CAESAR study). Back to back colonoscopy was performed by two blinded endoscopists. The lesions were graded as adenomatous or non-adenomatous based on the macroscopic appearance. During AFE, the autofluorescence ratio (AFR) was calculated for each polyp. All lesions were removed during second or third pass and histologically characterized according to current guidelines. Diagnostic test statistics of accuracy, sensitivity, specificity and predicted values were calculated by using histopathology as the reference value. Results: Histopathology identified 43 adenomatous and 27 non-adenomatous polyps. No significant difference was found between the size of adenomas and non-adenomas (mean of 5.2 and 5.0mm, p=0.65). 44 polyps were <5mm and 26 polyps ≥5mm. Adenomas had significantly higher AFR as compared to non-adenomas; mean 0.72 and 0.45, respectively (p<0.001). When using a ROC determined AFR cut-off value of 0.5, AFR predicted histology in 78% correctly. The sensitivity of AFR for identifying adenomas was 81% (100% for polyps ≥5mm), specificity was 73%, PPV was 83% and NPV was 70%. Considering fluorescence intensity and macroscopic appearance, AFE predicted histology in 73% correctly. The sensitivity of AFE for identifying adenomas was 88%, specificity was 48%, PPV was 88% and NPV was 72%. Subdividing polyps in <5mm and ≥5mm, AFE sensitivity for identifying adenomas was 85% and 94%, respectively. During WLE 45/70 polyps (64%) were correctly classified as adenoma or non-adenoma. The sensitivity of WLE for identifying adenomas was 81%, specificity was 37%, PPV was 67% and NPV was 44%. Subdividing polyps in <5mm and ≥5mm, WLE sensitivity for identifying adenomas was 74% and 94%, respectively.
Conclusion: AFE has a higher accuracy than WLE for differentiating between adenomatous and non-adenomatous colorectal polyps.

Outcome of a progressive stenting protocol inthe treatment of anastomic strictures after orthotopic liver transplantation

J.W. Poley[1], G. Kazemier[2], H.J. Metselaar[1], E.J. Kuipers[1], M.J. Bruno[1], Depts of Gastro-enterology & Hepatology[1] and Surgery[2], Erasmus MC, University Medical Center Rotterdam, the Netherlands

Background: Biliary complications after orthotopic livertransplantation (OLT) occur in up to 25% of cases and are associated withconsiderable morbidity and mortality. Anastomic strictures (AS) can occur early due to edema or late as a consequence of ischaemia induced fibrosis. Most centers treat patients with late AS according to an endoscopic treatmentprotocol derived from protocols used to treat benign post-cholecystectomy-strictures, which involves inserting an increasing number of endoprostheses. However, about the efficacy of such treatment in OLT patients with AS little is known. Methods: Patients were identified from an endoscopicdatabase prospectively maintained since 2003. Follow-up had to be at least 2 months after the end of endoscopic treatment. Charts and X-rays were reviewedof all patients. Success of treatment was defined as having either minimal cholestasis or normalization of liver enzymes making further surgical or radiological interventions unnecessary. Results: Between January 2003 and June 2008 223 OLT's were performed. In 184 patients (82%) aduct-to-duct biliary anastomosis was created. A total of 33 patients (male:female 23:10, mean age 51 years (range 25 – 67)) were treated endoscopically for AS after duct-to-duct anastomosis. Six patients were treated with temporary placement of a single biliary stent. In 27 patients progressive stenting was undertaken. Median number of procedures was 5 (range 1 – 14). Complications were seen in 10 patients (37%): pancreatitis in 2 (7%), cholangitis in 6 (22%) and non-specific pain in 2 (7%). Median number of days between OLT and first ERCP was 62 (mean 155; range 6 – 1963). The median number of endoprostheses placed was 3 (range 2 – 8). Follow-up was 30 months (mean, range 2 – 81). Successful treatment was achieved in 17 patients (63%); the remaining 10 patients underwent Roux-en-Y hepaticojejunostomy, re-OLT, or are stent dependent. Logistic regression analysis revealed successful outcome to be dependent onmaximum number of stents ($p=0.04$) and length of stenosis ($p=0.02$). Duration oftreatment, age and sex was not predictive of outcome.
Conclusions: The efficacy of progressive stenting of AS in OLT patients is less compared to whatis reported in benign post-cholecystectomy strictures. Nevertheless, endoscopic treatment using progressive stenting prevents the majority of patients from having to undergo more complex invasiveprocedures such as Roux-en-Y hepaticojejunostomy or re-OLT.

Risk of esophageal adenocarcinoma and mortality in patients with Barrett esophagus: a systematic review and meta-analysis

M. Sikkema[1], P.J.F. de Jonge[1], E.W. Steyerberg[2], E.J.Kuipers[1,3] ,Depts of Gastroenterology and Hepatology[1], Public Health[2] and Internal Medicine[3], Erasmus MC – University Medical Center, Rotterdam, The Netherlands

Patients with Barrett esophagus (BE) are at increased risk to develop esophageal adenocarcinoma (EAC). Therefore, surveillance in BE patients is recommended. The magnitude of the annual cancer risk in BE remains uncertain, as published estimates are highly heterogeneous ranging from 0.2% to almost 2.0% per year. Moreover, mortality due to EAC in BE patients under surveillance is supposed to be low. As EAC risk and mortality in BE are important determinants of cost-effectiveness of BE surveillance strategies, clarification of these factors is essential. We performed a systematic review and meta-analysis to determine the incidence of EAC and mortality due to EAC in BE. Pubmed, EMBASE and Web of Science databases were searched for relevant cohort studies in English language published between 1980 and September 2008 that reported EAC risk and mortality due to EAC in BE. Studies had to include patients with histologically proven BE, documented follow-up, and histologically proven EAC on surveillance. We used a random effects model for the meta-analysis, with assessment of heterogeneity by the I^2 statistic and publication bias Begg's and Egger's tests. Fifty-one studies were included in the main analysis, 19 from the UK, 13 from other European countries, 17 from the USA and 2 from Australia. The overall mean age of BE patients was 62 years (31 studies); the mean overall male percentage was 64% (40 studies). In total, these studies included 13.869 patients followed up for 60,781 person-years, during which 341 patients developed EAC. The pooled estimate for EAC incidence was 6,7/1.000 person-years (95%CI: 5,0-8,8) with considerable heterogeneity ($p<0,001$; $I^2=77\%$). Eighteen studies reported data on mortality due to EAC. These studies included 6.274 patients followed up for 30.407 person-years, with 75 deaths due to EAC and 1.173 deaths due to other causes. The pooled incidence of fatal EAC was 2,9/1,000 person-years (95%CI: 2,2-3,7) with no evidence for heterogeneity ($p=0,5$; $I^2=0\%$). No evidence of publication bias was found.

Conclusion: Patients with BE are at low risk of malignant progression and predominantly die from other causes than EAC. This undermines the cost-effectiveness of generalized BE surveillance, and supports the search for valid risk stratification tools to identify the minority of patients that is likely to benefit from surveillance.

P53 protein overexpression by immunocytochemistry (ICC) and p53 gene locus loss by DNA Fluorescent in situ hybridization (FISH) are complimentary tools for detecting abnormal P53 status in Barrett's esophagus patients

A.L. Davelaar[1], A.M. Rygiel[1], F. Milano[1], J.J.G.H.M. Bergman[2], B. Elzer[2], P. Fockens[2], K.K. Krishnadath[2], [1]Labolatory of Experimental Gastroenterology, [2]Dept of Gastro enterology, Academic Medical Centre, Amsterdam, the Netherlands

Background: Several studies showed that p53 gene abnormalities may serve as an alternative important biomarker to identify Barrett's esophagus (BE) patients at risk for esophageal adenocarcinoma (EAC). In a recent study we used fluorescent in-situ hybridization (FISH) to evaluate p53 gene abnormalities in a large cohort of BE patients. FISH, however, only detects gene loci losses and cannot detect gene mutations, thus potentially may miss certain p53 abnormalities. Immunocytochemistry (ICC) is a simple methodology that can be used to investigate p53 protein accumulation that frequently is the result of p53 gene mutations. Aim: To compare p53 protein accumulation assessed by ICC to TP53 locus loss as earlier determined by DNA FISH on a BE surveillance cohort. Methods: ICC for p53 was performed on BE brush cytology specimens of 125 BE patients to detect p53 protein accumulation. ICC results were compared to DNA FISH results. The p53 abnormalities were further evaluated with respect to histological outcomes as assessed on simultaneously taken biopsy specimens.Results: The BE population included 71 intestinal-type metaplasia (IM), 23 indefinite for dysplasia/low grade dysplasia (IND/LGD), 17 high grade dysplasia (HGD) and 14 esophageal adenocarcinoma (EAC). FISH and ICC detected p53 abnormalities in 14 % (17/125) and 26% (32/125) of the cases, respectively. However, only 6 out of the 43 cases with abnormal p53 status showed both p53 locus loss and p53 accumulation, resulting in a concordance between FISH and ICC in detecting abnormal p53 status of only 14%. When combining DNA FISH with ICC, the frequencies of abnormalities correlated significantly with the increasing histological stages of dysplasia ($p<0.001$). Combining positive FISH and ICC for detecting cases with dysplasia (IND/LGD/HGD/EAC) versus no dysplasia (IM) also showed a higher sensitivity of 49% than the two techniques alone. However, the specificity decreased from 94% (FISH) and 80% (ICC) to 75%.
Conclusion: P53 aberrations as detected by FISH and ICC do not correlate and seem to detect different p53 abnormalities. A combination of the two methods significantly increased the sensitivity to detect cases with abnormal p53 status and dysplasia. Therefore, these technologies may be used as complimentary tools for determining abnormal p53 status. Yet, future follow up studies will further proof whether combining these techniques will have higher prognostic power for identifying BE patients at risk as compared to the individual techniques.

Quality of life as a predictor for survival in patients with oesophageal cancer

M. van Heijl[1], A.G.E.M. de Boer[2], J.B. Reitsma[3], O.R.C. Busch[1], H.W. Tilanus[4], M.A.G. Sprangers[2], J.J.B. van Lanschot[4], M.I. van Berge Henegouwen[1], [1]Dept of Surgery, [2]Dept of Medical Psychology, [3]Dept of Clinical Epidemiology, Academic Medical Centre, Amsterdam, [4]Dept of Surgery, Erasmus Medical Centre, Rotterdam, the Netherlands

Quality of life (QOL) is known to be associated with survival in oncological patients. In patients with oesophageal cancer evidence for prognostic significance of QOL is limited. Aim of the present study is to determine whether pre- and postoperative QOL measurements can predict survival independently from clinical and pathological factors, in patients with potentially curable oesophageal cancer. Included patients participated in a randomised controlled trial performed in two academic medical centers. From 1994 to 2000 a total of 220 patients were randomised for transthoracic or transhiatal oesophagectomy. QOL questionnaires were sent before and 3 months after surgery. Generic QOL was measured with the Medical Outcomes Study Short Form-20 (MOS-SF20). Physical and Psychological Symptoms, Level of Activity and Global QOL were measured with the disease-specific Rotterdam Symptom Checklist (RSCL). First, uni- and multivariate Cox regression analysis were used to determine the influence of preoperative QOL and clinical factors like age, weight loss and preoperative staging on survival. Secondly, uni- and multivariate Cox regression analysis were used to assess prognostic significance of postoperative QOL, clinical factors and pathological staging. Out of 220 randomised patients, 199 participated in the QOL-study. The 5-year survival rate after transthoracic or transhiatal resection was 35.5%. The preoperative RSCL Physical Symptom scale was a significant predictor of survival in univariate Cox regression analysis ($p=0.006$). In a multivariate model preoperative endosonographical T-stage ($p=0.003$) was significantly predictive for survival while endosonographical N-stage was not. In this model, RSCL Physical Symptom scale was also a predictor for survival ($p=0.025$). Univariate analysis of the postoperative QOL measurements showed that many QOL scales were significantly associated with survival. In multivariate analysis, MOS-SF20 Social Functioning ($p=0.003$) and RSCL Physical Symptom scales ($p=0.006$) predicted survival significantly, as well as pathological T-stage ($p<0.001$) and N-stage ($p<0.001$).

Conclusion: Preoperative QOL is a significant predictor of long term survival in patients with oesophageal cancer, independent from other preoperative factors like age, weight loss and endosonographical T- and N-stage. QOL measured 3 months after surgery is also a significant predictor of survival, independent even from prognostic factors like pathological T- and N-stage.

Overexpression of p53 and Ki67 and aneuploidy as markers for neoplastic progression in Barrett esophagus: a nested case-control study

M.Sikkema[1], M. Kerkhof, H. van Dekken[3], J.G. Kusters[1], E.W. Steyerberg[2], C.W.N. Looman[2], P.D. Siersema[1], E.J. Kuipers[1,4] on behalf of the CYBAR-study group, Depts of Gastroenterology and Hepatology[1], Public Health[2], Pathology[3] and Internal Medicine[4], Erasmus MC – University Medical Center, Rotterdam, The Netherlands

Surveillance in patients with Barrett esophagus (BE) aims at early detection and treatment of neoplastic changes to prevent further progression to esophageal adenocarcinoma (EAC). However, histological evaluation of biopsies has its limitations. Biomarkers have been suggested to improve early identification of patients at risk for progression to high-grade dysplasia (HGD) or EAC. The aim of this study was to determine the predictive value of p53, Ki67 and flow cytometry (FC) as markers for neoplastic progression in BE. A case-control study was conducted nested within a large ongoing prospective cohort study of 703 patients with BE (≥2 cm). Incident cases of HGD and EAC were identified during follow-up. For each case up to four controls were matched for age, sex, and baseline histology. Baseline DNA ploidy status was determined by FC, whereas Ki67 and p53 expression were determined by immuno-histochemistry. The presence of these markers was scored (Ki67 and p53 expression: 0=normal, 1=moderate or 2=strong; FC: normal=diploid or abnormal=aneuploid) in duplicate and blinded for long-term outcome data with discrepancies solved by consensus. Hazard ratios (HR) were calculated by Cox regression analysis.After two years of follow-up, 22 cases (82% male; mean age 61.8 ± 11.2 yr) and 84 controls (82% male; 60.9 ± 9.9 yr) were included. Univariate analysis, adjusted for age and gender, showed that neither FC abnormalities (HR 1.0; 95%CI: 0.3-3.6; p=097) nor Ki67 overexpression (moderate overexpression: HR 0.6 (95%CI: 0.2-2.3); strong overexpression: HR 5.8(95%CI: 0.7-46); p=0.17) were associated with an increased risk of neoplastic progression, whereas p53 overexpression was (p<0.001). This risk was increased in the category moderate p53 overexpression (HR 4.9; 95%CI: 1.3-19) and even more pronounced in the category strong p53 overexpression (HR 17; 95%CI 5.3-56). After multivariable analysis, with adjustment for age, gender and baseline histology, p53 overexpression remained associated with an increased risk of neoplastic progression (moderate overexpression: HR 5.7 (95%CI: 1.5-22.3) and strong overexpression: HR 24 (95%CI: 6.1-98); p<0.001).
Conclusion: Independent of the histology result, overexpression of p53 predicts neoplastic progression in BE. Therefore, p53 is a useful marker that could be used in a panel of biomarkers with adequate sensitivity and specificity to identify patients at an increased risk of developing EAC.

Improving the quality of the pre-operative work-up of patients with esophageal carcinoma; implementation of a fast-track staging protocol

P. Didden[1], M.C.W. Spaander[1], B.P.L. Wijnhoven[2], E.J. Kuipers[1], M.J. Bruno[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Dept of Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands

According to the guidelines for preoperative work-up of patients with esophageal cancer, a set of investigations is indicated including upper endoscopy (UE), endoscopic ultrasonography (EUS), computed tomography of the chest and abdomen (CT) and ultrasonography of the neck (US). A fast-track (FT) staging method could lead to prompt staging, however it may result in the overuse of diagnostic investigations. In this study we evaluated the impact of the implementation of a FT staging protocol in these patients.A FT staging protocol, supported by the departments of gastroenterology, surgery and radiology, was implemented with the aim to complete the program, from primary consultation to final treatment proposal, within five days. All standard investigations were performed in day-care. After results were discussed by a multidisciplinary team, patients were informed about their final staging and treatment strategy in the out-patient clinic. We compared our results with a historic cohort of patients who underwent the preoperative work-up in 2006. Between January-November 2008, 54 patients with esophageal carcinoma were included. UE, CT, EUS and US were performed in 54(100%), 54(100%), 50(93%) and 49(91%) of patients. EUS was not performed due to a stricture of the esophagus (n=3) and because a metastasis was discovered on CT (n=1). US was not performed because a CT of the neck was available (n=4) and US results were available from a referring hospital (n=1). In 35 patients (65%) staging was completed within 5 days. In 18 patients (33%) the work-up period of 5 days was exceeded because additional investigations for proper staging were indicated (mean 17 d(range 5- 38 d)).The additional investigations resulted in a different staging in 5 patients(28%). One patient died before staging was completed. The overall duration of staging in the historic cohort (n=50) was 22 d(range 1- 49 d) compared to 9 d(range 5-38 d) in the patients participating the FT program($p<0.05$). Overuse of diagnostic imaging (EUS and US) was found in 8 patients (15%) in the FT program. Finally, the proposed treatment strategy (curative vs palliative) did not correlate with completing the preoperative work-up in five days ($p=0.7$).
Conclusion: Implementation of a fast-track staging protocol for patients with esophageal carcinoma leads to prompt staging in almost two-third of patients within 5 days and reduces the time for work-up by 13 days at the expense of overuse of diagnostic investigations in 15% of patients.

Risk of Malignant Progression in Patients with Barrett's Esophagus; a Dutch Nationwide Cohort Study

P.J.F. de Jonge[1], M. van Blankenstein[1], C.W.N. Looman[2], M.K. Casparie[3], G.A. Meijer[4], E.J. Kuipers[1,5], [1]Depts. of Gastroenterology and Hepatology, [2]Public Health and [5]Internal Medicine, Erasmus MC - University Medical Center Rotterdam, [3]Stichting PALGA, Utrecht, [4]Dept. of Pathology, VU University Medical Center, Amsterdam, The Netherlands

Reported incidence rates of esophageal adenocarcinoma (EAC) in Barrett's esophagus (BE) vary widely. As the effectiveness of BE surveillance is crucially dependent on this rate, its clarification is essential. To estimate the rate of malignant progression in BE patients, all patients with a first diagnosis of BE with no dysplasia (ND) or low-grade dysplasia (LGD) between 1991 and 2006 were identified in the Dutch nationwide registry of histopathology (PALGA). Follow-up data were evaluated until November 2007. In total, 42,207 BE patients were included, 4,132 (8%) of them had LGD. BE patients with LGD were significantly older than patients without (mean age ± SD: 64±14 vs. 61±15 yrs, p<0.001), and more often male (64% vs. 61%, p<0.01). Re-evaluation endoscopies at least 6 months after initial diagnosis were performed in 16,434 patients (39%), who were significantly younger than those not re-examined (58±13 vs.63±16 yrs, p<0.001). Mean interval between initial and re-evaluation endoscopy was 2.0±2 yrs in BE patients without dysplasia, and 1.4±2 yrs in those with LGD. These 16,434 BE patients were followed-up for a total of 78,480 person years (pyrs), in whom 666 (4%) HGD/EACs occurred (mean age: 69±12 yrs, 76% male). Mean interval between BE diagnosis and developing HGD/EAC was 5.8±4 yrs for patients without dysplasia, and 5.1±4 yrs for patients with LGD (p=0.09). After excluding HGD/EAC cases detected within 1 year after BE diagnosis (n=212, 32%), incidence rates per 1,000 pyrs at risk were 4.3 (95%CI: 3.4-5.5) for EAC and 5.8 (95%CI: 4.6-7.0) for HGD/EAC combined. Risk factors for HGD/EAC were increased age (e.g. >75 years HR: 12: 95%CI: 8.0-18), male sex (2.01: 1.68-2.60), and presence of LGD at baseline (1.91: 1.53-2.40). For patients who did not undergo re-evaluation and were unlikely to have developed symptomatic EAC throughout the study period, life expectancy based on general survival data of the Dutch population was imputed. This rendered a total follow-up of 234,821 pyrs for the whole cohort of 42,207 BE patients, with an overall EAC incidence of 1.4 cases per 1,000 pyrs at risk (95%CI: 1.1-1.8).

Conclusion: In this largest reported cohort of unselected BE patients, the annual risk of EAC in BE patients was at most 0.4%. Male sex, older age, and LGD at diagnosis are independent predictors of malignant progression, and should enable an improved risk assessment in BE.

A Multi-Center Randomized Trial Comparing Stepwise Radical Endoscopic Resection versus Radiofrequency Ablation for Barrett Esophagus containing High-Grade Dysplasia and/or Early Cancer

F.G.I. van Vilsteren[1], R.E. Pouw[1], S. Seewald[2], L.A.H. Alvarez Herrero[3], C.M.T. Sondermeijer[1], F.J. ten Kate[4], P. Fockens[1], K. Yu Kim Teng[2], T. Rösch[2], N. Soehendra[2], B.L. Weusten[3], J.J. Bergman[1], [1]Gastroenterology, Academic Medical Center, Amsterdam, the Netherlands, [2]Interdisciplinary Endoscopy, University Medical Center Hamburg-Eppendorf, Germany, [3]Gastroenterology, Sint Antonius Hospital, Nieuwegein, Netherlands, [4]Pathology, Academic Medical Center, Amsterdam, the Netherlands

Background: After endoscopic resection (ER) of high-grade dysplasia (HGD) and early cancer (EC) in Barrett esophagus (BE), the residual BE remains at risk for neoplasia. Complete eradication of all BE is therefore a preferred approach. One method is stepwise radical ER (SRER), which is highly effective and provides a pathology specimen, yet is technically challenging and has a moderate complication risk. By comparison, radiofrequency ablation (RFA) is highly effective with a low complication risk, yet yields no pathology specimen. Aims: Compare the safety and efficacy of SRER vs. RFA for treatment of BE-HGD/EC. Methods: Under an IRB approved protocol, 3 centers enrolled pts BE ≤ 5 cm containing HGD and/or EC (max T1sm1). SRER pts underwent piecemeal ER of 50% of BE (including visible lesions if present) followed by ER sessions every 2 mos. RFA pts (after focal ER of visible lesions if present) underwent RFA every 2 mos. Treatment was continued until a complete response for intestinal metaplasia (CR-IM, no IM on biopsy) was achieved. After CR-IM, biopsy (4Q/2cm) was performed at 2, 6, and 12 mo. Results: 47 pts were randomized (25 SRER, 22 RFA). By Dec ’08, data is available for 43 (22 SRER, 21 RFA). Age, gender, BE length (median C2M4 in both), entry histology (SRER: 10 HGD/12 EC vs. RFA: 7 HGD/14 EC), and the proportion visible lesions at entry were similar between SRER and RFA. A CR-HGD/EC was achieved in 22 (100%) SRER and 20 (95%) RFA, and CR-IM in 21 (96%) SRER and 20 (95%) RFA. The total number of therapeutic sessions to achieve CR was similar (median SRER 2, RFA 3). SRER, however, required more sessions when dilations were included (6 vs. 3; p<0.001).Acute SRER-related complications: 1 perforation (5%), 5 bleeds (23%). There was one RFA-related delayed bleeding (5%). Prior RFA, 3 of 18 bled (17%) after entry ER. The incidence of stenosis was higher in SRER (86%) vs. RFA (14%)(p<0.001). All RFA stenoses had an entry ER. All stenoses resolved with dilation. Median follow-up is 13 mo in both groups. Once CR-IM was achieved, no pt in either group had recurrence of dysplasia or visible BE.
Conclusions: In pts with BE≤ 5 cm containing HGD/EC, SRER and RFA achieved comparably high rates of CR for both IM and neoplasia. However, SRER carried a higher risk of complications and had more procedures per pt. Based on these results, we recommend a combined approach of focal ER for visible lesions followed by RFA for complete eradication of remaining BE.

The effect of operator experience on outcome of laparoscopic Nissen fundoplication

J.A.J.L. Broeders[1], W.A. Draaisma[1], H.G. Rijnhart–de Jong[1], A.J.P.M. Smout[2], J.J.B. van Lanschot[3], I.A.M.J. Broeders[4], H.G. Gooszen[1], Gastrointestinal Research Unit of the University Medical Center Utrecht, Depts of Surgery[1] and Gastroenterology[2], Dept of Surgery[3], Erasmus Medical Center, Rotterdam; Dept of Surgery[4], Meander Medical Center, Amersfoort, the Netherlands

In 2000 a Randomised Controlled Trial (RCT) was prematurely terminated at interim analysis, since laparoscopic Nissen fundoplication (LNF) for gastro-oesophageal reflux disease (GORD) was associated with a higher risk to develop dysphagia than the open procedure (CNF). A second, long-term cohort study was initiated to eliminate alleged bias caused by relative lack of experience with LNF. This study aimed to investigate the effect of operator experience on outcome of LNF and compare it to the results of CNF. In the RCT, 74 patients underwent CNF and 93 patients underwent LNF (LNFI). The complete set-up of the cohort study (LNFII, n=121) mirrored the RCT, except for the experience that increased from a minimum of 5 to over 30 laparoscopic fundoplications/surgeon. Perioperative and in-hospital characteristics were registered, upper endoscopy and 24-hr oesophageal pH monitoring were performed before surgery and at 3 months and quality of life (QoL), general health, reflux symptoms, PPI use and surgical reinterventions were recorded at 5 years after surgery. In LNFII, mean operating time (110 vs 165 min; P<0.001) and percentage of patients with dysphagia (2.5 vs 12.3%; P=0.008) were reduced and conversions (3.5 vs 7.7%; P=0.192) were halved, compared to LNFI. Moreover, in LNFII splenectomies (0.8 vs 1.8 vs 4.3%; P=0.584 and P=0.126), percentage of in-hospital complications (5.1 vs 13.5 and 19.3 %; P=0.046 and P=0.005) and length of hospital stay were reduced (4.2 vs 5.6 and 7.6 days; P=0.073 and P<0.001) compared to LNFI and CNF respectively. Compared to LNFI, the prevalence of dysphagia in LNFII was reduced as well (12.3 vs 2.5%; P=0.008). The high early reintervention rate that was present 6 months after LNFI, was not found after CNF and LNFII (10.1 vs 1.4 and 0.8%; P=0.028 and P=0.002) and reoperation rates were similar at five years (15.2 vs 11.6 and 11.6%). The improvement of oesophagitis and oesophageal acid exposure at 3 months and the improvement of QoL, general health, reflux symptoms and PPI use at 5 years was similar.
Conclusions: Operating time, complications, hospital stay, prevalence of dysphagia and early reintervention rate after LNF, improve significantly when operator experience increases from a minimum of 5 to over 30 fundoplications. However, short-term objective reflux control and five-year clinical outcome do not improve with experience. In experienced hands, LNF reduces splenectomies, in-hospital complications and hospitalisation compared to CNF, with similar five-year effectiveness.

Surveillance in a prospectively followed cohort of patients with Barrett esophagus in the Netherlands: a cost-effectiveness analysis

M. Sikkema[1], E.W. de Bekker-Grob[2], M. Kerkhof[1], M.J.C. Eijkemans[2], C.W.N. Looman[2], J.B.Wong[4], D.T. Provenzale[5], E.J. Kuipers[1,3], P.D. Siersema[1,6], E.W. Steyerberg[2] on behalf of the CYBAR study group, Depts. of Gastroenterology and Hepatology[1], Public Health[2] and Internal Medicine[3], Erasmus MC - University Medical Center, Rotterdam, The Netherlands, Dept. of Medicine: Division of Clinical Decision Making[4], Tufts-New England Medical Center, Boston, USA, Dept. of Clinical Health Policy Research[5], Duke University Medical Center, Durham, USA, Dept. of Gastroenterology and Hepatology[6], University Medical Center Utrecht, The Netherlands

The annual risk to develop esophageal adenocarcinoma (EAC) in patients with Barrett esophagus (BE) is approximately 0.5%. Therefore, endoscopic follow-up is recommended in BE patients. In order to prevent one case of EAC many burdensome endoscopies need to be performed. The aim of this study was to evaluate cost-effectiveness of different intervals of surveillance in BE and to identify critical variables, based on a prospectively followed Dutch BE cohort.In this prospective, multicenter cohort study, 710 BE patients were included with no dysplasia (ND; n=601) or low-grade dysplasia (LGD; n=109) at baseline. Endoscopic surveillance was performed according to ACG guidelines. Using pre-specified misclassification rates, the true transition rates from ND to LGD, high-grade dysplasia (HGD) and EAC were estimated by a Multi-State-Markov model, based on the observed transition rates in this cohort. The estimated true transition rates and misclassification rates were incorporated into a decision analytic model. In this model we also included quality of life data and real costs. Evaluated strategies were surveillance intervals every 1, 2, 3, 4 or 5 years and no surveillance in BE with baseline ND or LGD, with esophagectomy being performed if HGD or EAC was diagnosed. The incremental cost-effectiveness ratios (ICER) were calculated for each strategy.Based on 2 years of follow-up, the incidence of EAC was 0.7% and the annual true transition rate from ND to LGD was 3%, from LGD to HGD 21% and from HGD to EAC 43%. In BE patients with ND or LGD, all evaluated surveillance strategies were cost-effective vs. less frequent alternatives. The most frequent strategy, i.e. yearly, was a cost-effective alternative compared to 2-yearly surveillance, with an ICER of € 21.500/quality-adjusted life year (QALY) gained in patients with ND and an ICER of € 5.200/QALY gained in patients with LGD. Sensitivity analyses showed that the true transition rates were the most critical factors for cost-effectiveness of this model. If these rates were halved, yearly surveillance was no longer cost-effective; however, 2-yearly surveillance still was.
Conclusion: Based on these transition rates, yearly surveillance seems a cost-effective strategy, which would become even more cost-effective when patients with HGD or mucosal EAC are treated endoscopically. This analysis also shows that progression risks are the most critical components for decision making regarding surveillance in BE.

Predictors for neoplastic progression in patients with Barrett Esophagus: a prospective cohort study

M. Sikkema[1], M. Kerkhof[1], C.W.N. Looman[2], E.J. Kuipers[1,3], P.D. Siersema[1] on behalf of the CYBAR-study group, Depts. of Gastroenterology and Hepatology[1], Public Health[2], Internal Medicine[3], Erasmus- University Medical Center, Rotterdam, The Netherlands

Patients with Barrett esophagus (BE) are at an increased risk of developing esophageal adenocarcinoma (EAC). However, the absolute risk remains low. The reasons why only a small subgroup of patients with BE develop EAC are still unclear, but such knowledge is valuable to tailor surveillance programs. The aim of this study was to identify predictors for the development of progression from baseline no dysplasia (ND) or low-grade dysplasia (LGD) to high-grade dysplasia (HGD) or EAC in patients with BE after 4 years of surveillance.

In this multicenter, prospective cohort study, 703 patients with BE (≥2 cm) were included. Data on age, gender, BMI, reflux symptoms, tobacco and alcohol use, medication use, upper gastrointestinal endoscopy findings and histology were prospectively collected. Surveillance was performed as recommended by current guidelines. Cases with progression to HGD or EAC during surveillance were identified. Log linear regression analysis was performed to identify risk factors associated with the development of HGD or EAC.

After 4 years of follow-up, 24/703 (3.4%) patients developed either HGD or EAC, whereas the remaining 679 patients remained stable with ND or LGD. Univariate analysis revealed that length of BE (OR 1.13; 95%CI: 1.12-1.14; p=0.008) and baseline LGD (OR 11.5; 95%CI: 5.2-25.7; p<0.001) were significant predictors of development of HGD or EAC. Multivariate combination of these predictors showed that LGD remained a significant predictor (OR 10.7; 95%CI: 4.8-23.9; p<0.001) whereas length of BE was only borderline predictive (OR 1.11; 95%CI: 1.10-1.12; p=0.052). The annual risk to develop HGD or EAC in patients with BE and LGD ranged from 5% for patients with a BE length of 2 cm and up to 18% for a BE length of 16 cm. In patients with ND, this risk ranged from 0.4% up to 2.0% per year.

Conclusion: In patients with BE, the risk of developing HGD or EAC seems associated with the presence of LGD in biopsies and the length of BE. Patients with LGD on histology and a long BE segment are at an increased risk of neoplastic progression compared to those with ND and a short BE segment. Both these risk factors should be taken into account in determining the frequency of surveillance in BE patients.

Long-term results of endoscopic ablation therapy for early Barrett's cancer

N.C.M. van Heel, J. Haringsma, E.J. Kuipers, Erasmus MC University Medical Center, Rotterdam, the Netherlands

There is no consensus regarding the appropriate treatment modality for patients with intraepithelial neoplasia (IEN) in Barrett esophagus (BE). Endoscopic mucosal resection (EMR) and photodynamic therapy (PDT) are treatment strategies to remove IEN within BE. Unfortunately, published data with long-term follow-up are limited. Therefore, in the current cohort study we present our results of EMR followed by PDT.
All BE patients with focal or multifocal high grade IEN and well-differentiated mucosal cancer with a minimum follow-up of 24 months were included. Patients with diffuse IEN were excluded. Lesions were assessed endoscopically according to the Paris classification, histologically to the revised Vienna classification. Patients underwent EMR of suspected BE lesions and subsequently within 3 months PDT of the remaining Barrett epithelium using oral 5-aminolevulinic acid. Targeted biopsy specimen of suspect lesions and 4 quadrant random biopsy samples were taken at 2 cm intervals. Endoscopy was performed 3 and 6 months after PDT, subsequently every 6 months.
Seventy-three patients (median age 66 yrs, range 40-80, median Barrett length 4, range 1-12 cm) referred for IEN in BE completed multimodality ablation. Four patients were classified as Paris 0-Is, 31 0-IIa, 34 0-IIb, 4 0-IIc; histologically 30 as Vienna 4.1, 8 V4.2, 2 V4.3, 33 V4.4. Twelve patients had multifocal IEN. Ten patients (8%) were lost to follow-up and 2 died within 24 mo after therapy of unrelated cause. Fifty-six patients were in remission after primary treatment (92%). Nine out 56 patients (16%) developed recurrence of IEN after a median of 17 mo (range 3-30): 2 patients were operated upon, 2 were considered unfit for surgery - 1 of which died of Barrett's cancer - and 5 were retreated by EMR. Five patients were not in remission after primary treatment; 1 underwent surgery, 3 re-EMR, 1 refused further therapy. Complete conversion to neo-squamous epithelium occurred in 24/61 patients (39%). After a median follow-up of 44 months (24-89 mo), a total of 52/61 patients (85%) are in sustained remission for IEN.
Conclusions: In patients with early Barrett's cancer, endoscopic ablation by means of EMR and PDT is effective. Selection and endoscopic treatment should be performed in expert centers. Metachronic IEN occurs in a considerable number of subjects. Recurrent and remaining neoplasia can often be managed by repeat EMR. Surgery can be avoided in 97% of the patients.

Low frequency of Inflammatory Bowel Disease-related Colorectal Carcinoma (CRC) in non-tertiary centers: final results of a nation wide long-term survey

J.E. Baars[1], E.J. Kuipers[1], R. Beukers[2], A. Tan[3], B. Weusten[4], M.K. Casparie[5], C.J. van der Woude[1], Depts of Gastroenterology & Hepatology, Erasmus MC, Rotterdam[1], Albert Schweitzer Hospital, Dordrecht[2], Canisius Wilhelmina Hospital, Nijmegen[3], St Antonius Hospital, Nieuwegein[4], Nation-wide network and registry of histo-and cytopathology, Utrecht[5], the Netherlands

Guidelines for IBD recommend initiating surveillance after 8-10 yrs of extensive disease and 15-20 yrs of left-sided colitis. We investigated whether these guidelines reflect the natural history of IBD-related CRC in non-tertiary centers.IBD-related CRC patients (pts) in all non-tertiary centers in the Netherlands were identified using PALGA. Pts with IBD+CRC diagnosed synchronously or metachronously in pathology-reports from 1990-2005 were included. In a 2nd search we included pts <65 yrs old to minimize interference with sporadic CRC. Further clinical data were obtained from pts-charts to assess the IBD population and verify diagnosis of IBD-associated CRC. Statistical analysis was performed using descriptive statistics, Kaplan-Meier & log-rank tests and cox-regression analysis.Of all 93 non-academic centers, 78 participated, where we assessed 430 pts-charts. In 197 pts <65 yrs old, diagnosis of IBD-related CRC was confirmed: 125 had ulcerative colitis (UC), 69 Crohn's disease (CD) and 3 Indeterminate Colitis. Sixty-four percent were males (126/197), 20 pts had PSC (10%), mean age of diagnosis of IBD was 35 yrs (+15) and of CRC 50 yrs (+11). Eighty-four pts (44%) had T3 tumors and 31(16%) already had metastases at diagnosis. Mean time from IBD-diagnosis to CRC-diagnosis was 15.3 yrs (+12). Type of IBD, gender, concomitant PSC and/or pseudopolyps, and gravity- and extension of inflammation were not significantly associated with time to CRC-diagnosis. Although the latter was not significant (p=0.063), contrary to surveillance guidelines, there was a trend for pts with extensive UC to develop CRC at later stage (mean 16.7 yrs) than pts with left-sided colitis (mean 11 years). IBD-diagnosis at older age was associated with earlier development of CRC (HR 1.09; 95%CI 1.07-1.10). Forty-eight percent of tumors were located in rectum or sigmoid and 73% occurred in previous inflamed areas. Location of inflammation was not predictive for tumor-location, but UC pts developed more left-sided tumors than CD pts (p=0.022). In 58 hospitals the size of the IBD population could be assessed: 26,855 pts in total, of whom only 163 developed CRC during 15 yrs follow-up.
Conclusion: The risk of IBD-associated CRC is limited in a regular, secondary IBD population. Current surveillance strategies need to be adjusted, including equalisation of strategies for left-sided and pancolitis. A nested case-control is being performed, of which the results are expected early 2009.

Sex-related Differences in the Medication Use and Surgery for Inflammatory Bowel Diseases

Z. Zelinkova, L. Vogelaar, C. Bouziane, E.J. Kuipers, C.J. van der Woude, Dept of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, The Netherlands

Background: Previous studies have shown sex-related differences in inflammatory bowel diseases (IBD) phenotypes. However, it is unclear whether there is a sex-specific disease course that results in differential medication use and surgery rate. Aim: To analyze sex-related differences in the medication use and surgery for IBD.
Patients and methods: IBD patients (pts) attending the IBD outpatient clinic by December 2007 were included. The electronic medical records were reviewed and medication used since the diagnosis of IBD, side-effects of the medication and surgery was noted.
The sex-related differences were analyzed statistically using Fisher`s exact test.
Results: In total 856 IBD pts were included (females/males: 466/390, 54% females; average age 42 years, range 16-87; mean duration of the disease 14 years, range 0-54), 588 pts with Crohn`s disease (69%), 247 ulcerative colitis (UC) pts (29%) and 21 pts with unclassified colitis (2%). There were no differences with respect to average age and duration of the disease between females vs. males. Significantly more females (392 pts, 87%) than males (302 pts, 80%, p=0.014) were using systemic corticosteroids. No sex-related differences in the use of 5-aminosalicylates (365 pts, 78% of females vs. 313 pts, 80% of males, n.s.), immunosuppressive (326 pts, 70% of females vs. 266 pts, 68% of males, n.s.) and anti-tumor necrosis factor (anti-TNF) agents (138 pts, 30% of females vs. 107, 27% of males, n.s.) were found. During the disease course, significantly more females (242 pts, 52%) than males (167 pts, 43%, p=0.009) underwent surgical resection for IBD. No differences in the surgery rates for perianal disease were observed. Interestingly, a significantly higher percentage of females (46 female vs. 19 male patients; 34% vs. 18% of female vs. male patients treated with anti-TNF; p=0.006) had anti-TNF treatment related side-effects. In addition, the occurrence of side-effects to anti-TNF was associated with surgery (OR 1.9, 95%CI 1.04-3.38; p=0.042) in female patients. No differences in the occurrence of side-effects to other medications were noted.
Conclusion: Female IBD patients have a higher rate of steroids use and undergo surgery more frequently than male patients. The higher surgery rate is partly related to female-specific increased incidence of side-effect to anti-tumor necrosis factor agents, which limits the conservative therapeutic options in female patients.

Low yield of neoplasia and lack of clinical consequences of random biopsies do not warrant their use in colonoscopic surveillance of patients with ulcerative colitis

F.J.C. van den Broek, R.P.B. Boltjes, S.C.S. Wolfkamp, P. Fockens, C.Y. Ponsioen, P.C.F. Stokkers, E. Dekker, Dept.of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands

Patients with longstanding ulcerative colitis (UC) are at increased risk of developing colorectal cancer. As premalignant neoplasia is difficult to visualize in these patients, guidelines recommend random tissue sampling during surveillance colonoscopies. Taking random biopsies is expensive and labor-intensive, and distracts endoscopists from scrutinizing the colon. The aim of this retrospective study was to evaluate the yield of neoplasia by random biopsies and to asses their clinical impact. This is a retrospective review of UC patients undergoing colonoscopy at a tertiary referral centre.
Colonoscopies performed over the last 10 years were reviewed to extract the number of random biopsies taken, as well as the number of patients with neoplasia detected by random biopsies. In case neoplasia was detected, the clinical management was evaluated. 475 patients (53% male; mean 42 yrs) underwent 1,010 colonoscopies, of which 452 (in 188 patients) were performed for the purpose of surveillance. A total of 11,734 random biopsies were taken during surveillance (median 29; range 0-59) and 1,556 additional random biopsies were taken during colonoscopies for other indications.Overall, in 5 (1.1%) surveillance colonoscopies neoplasia was detected only by random biopsies; in 44 (9.7%) by targeted biopsies; and in 6 (1.3%) by both random and targeted biopsies. In addition, in 32 (5.7%) colonoscopies on indication neoplasia was detected by targeted biopsies and in 1 (0.2%) by both random and targeted biopsies. Random biopsies taken during surveillance colonoscopies led to the detection of 4 patients (2.1%) with neoplasia that was not visible (2 unifocal low grade intraepithelial neoplasia (LGIN) and 2 multifocal LGIN). Two patients with unifocal LGIN underwent intensified surveillance, however no further neoplasia was detected after that one occasion. One patient with multifocal LGIN and a recent history of visible neoplasia refused colectomy several times. The last patient with multifocal LGIN had a shortened and tubular colon with active ulcerative inflammation, and subsequently underwent colectomy. The resection specimen demonstrated several foci of high grade IN.
Conclusion: UC-associated neoplasia is macroscopically visible in 94% of cases. Besides, the few neoplasias detected by random biopsies only (2.1%) had little clinical consequences. The low yield of neoplasia and lack of clinical impact by random biopsies do not warrant their costs and effort. These results support the suggestion that advanced detection techniques (chromoendoscopy, autofluorescence imaging) may replace random biopsies during surveillance of patients with longstanding UC.

Mortality in Inflammatory Bowel Disease in the Netherlands 1991-2002; Results of a population based study; the IBD South-Limburg cohort

M.J.L. Romberg-Camps[1,5], E.M.M. Kuiper[2], L.J. Schouten[3], A.D.M. Kester[4], M.A.M. Hesselink-van de Kruijs[1], L.P. Bos[5], J. Goedhard[6], W.H.A. Hameeteman[1], F. Wolters[7], M.G.V.M. Russel[8], R.W. Stockbrügger[1], P.C. Dagnelie[3], [1]Dept of Gastroenterology and Hepatology, Maastricht University Medical Center, [2]Dept of Gastroenterology, Erasmus University Medical Centre, [3]Dept of Epidemiology, Maastricht University, [4]Dept of Methodology and Statistics, Maastricht University, [5]Dept of Internal Medicine and Gastroenterology, Maasland Hospital Sittard, [6]Dept of Internal Medicine and Gastroenterology, Atrium Medical Centre Heerlen, [7]Dept of Gastroenterology, Vie-Curi Medical Centre Venlo, [8]Dept of Gastroenterology, Medisch Spectrum Twente Enschede, the Netherlands

Although one would expect a decreasing mortality rate in IBD over time, due to better diagnostic tools and treatment facilities, this does not seem to be true. Even the debate whether this condition carries an increased mortality risk is still ongoing. The aim of the present study was to evaluate the mortality rate of IBD in a well defined regional Dutch population (South Limburg), which has been followed continuously over a prolonged period of time. IBD patients diagnosed between 1 January 1991 and 1 January 2003 were included. All medical records were reviewed. Standardized Mortality Ratios (SMRs) were calculated overall and with regard to cause of death, gender, age, phenotype. At the censuring date of January 1st 2006, 20 out of 476 Crohn's Disease (CD) patients, 44 out of 630 Ulcerative (UC) patients and 4 out of 81 Indeterminate Colitis (IC) patients had died. For CD, the SMR (95% CI) of the total group was 1.0 (0.6-1.6). In UC and IC this was 0.9 (0.6-1.1) and 0.7 (0.2-1.7) respectively. Mortality risk was significantly increased for gastrointestinal causes in CD (SMR 7.5, 95% CI; 2.8-16.4) and UC (SMR 3.4, 95% CI; 1.4-7.0). Within the group of CD patients that died due to a gastrointestinal cause, male patients, female patients, age at diagnosis < 40 years, colonic and ileo-colonic disease location at diagnosis and inflammatory disease behaviour at diagnosis showed to have an increased mortality risk. For UC patients who died due to a gastrointestinal cause, this was found in female patients, patients younger than 19 years at diagnosis, patients older than 80 years at diagnosis and "unknown" disease location at diagnosis. Overall in UC patients, a decreased mortality risk from cancer was found (SMR 0.5, 95% CI; 0.2-0.9). Within the category of cancer related deaths, UC male patients and UC patients having proctitis at diagnosis had a significantly lower mortality risk. For IC, sub analysis were not significantly influencing mortality risk, probably due to small numbers.

Conclusions, this population-based IBD study showed that the overall mortality for CD, UC and IC is comparable to the background population. However with regard to gastro-intestinal causes the SMR was significantly increased in CD and UC, probably reflecting a complicating disease course.

Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine in a Dutch nationwide study

A.C.W. Vos[1], N. Bakkal[1], R.C. Minnee[2], D.J. de Jong[3], G. Dijkstra[4], P. Stokkers[2], A.A. van Bodegraven[5], M. Pierik[6], C.J. van der Woude[7], B. Oldenburg[8], D.W. Hommes[1], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, [3]Dept of Gastroenterology, Radboud University Medical Center, [4]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, [5]Dept of Gastroenterology and Hepatology, VU University Medical Center, [6]Dept of Gastroenterology, University Hospital Maastricht, [7]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, [8]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht

A meta-analysis by Kandiel et al. (GUT 2005) suggest a fourfold increased risk of lymphoma in IBD patients treated with azathioprine/6-MP. In addition, the GETAID group recently confirmed this association when they reported the results of the CESAME study showing a standardized incidence ratio for lymphoma of 1.8 (DDW 2008). Hence, we undertook a nationwide database search to investigate similar associations in the Netherlands.

To identify the patients with both IBD and lymphoma, the Dutch National Database of Pathology (PALGA) was used. From this registry eligible patients were selected between 1997 and 2004. The data base search criteria used, included “ulcerative colitis”, “Crohn’s disease”, “inflammatory bowel disease”, “inflammation”, “malignant lymphoma”, “oesophagus”, “stomach”, “small intestine” or “colon”. The final selection of cases was made upon verifying individual medical records from all cooperative hospitals. In addition, data on IBD characteristics, -outcome, medication and lymphoma were collected in CRFs. If possible, pathology specimens were tested for EBV. The Dutch, age-adjusted incidence of malignant lymphoma was retrieved from the Central Bureau of Statistics of the Netherlands (2004). The total number of IBD cases was determined per participating hospital.

The database search identified 259 cases with both IBD and malignant lymphoma in a total estimated cohort of 16945 IBD cases. Only 186 case histories were available for full analysis, a total of 35 lymphomas were identified, 151 cases were excluded because of lacking the objective diagnosis of IBD or lymphoma. The expected and age-adjusted lymphoma incidence was 6.28, with an observed incidence of 35, the relative risk for lymphoma was 5.57.

Of the 35 cases, 17 patients were exposed to AZA/6MP (min 3 months – max 12 yrs) and 18 cases never used AZA/6MP.

Remarkably, 10/13 (77%) lymphoma tissue specimens of IBD patients using AZA/6MP tested positive for EBV versus only 1/17 (6%) EBV+ in patients with no AZA/6MP use. Also, all EBV positive lymphoma’s were diffuse large B cell lymphoma’s whereas EBV negative tumors were lymphoma’s of different origin. Infliximab was not used in any of the studied cases.

Conclusion: This retrospective nationwide cohort study suggests an increased risk for malignant lymphoma in IBD patients. In IBD patients using AZA/6MP there seems to be a strong correlation with the development of EBV-positive diffuse large B cell lymphoma’s.

Laparoscopic-assisted versus open ileocolic resection for Crohn's Disease: Long term results of a prospective randomized trial

E.J. Eshuis[1,2], J.F.M. Slors[1], M.A. Cuesta[3], E.G. Pierik[4], P.C.F. Stokkers[2], M.A. Sprangers[5], W.A. Bemelman[1], [1]Dept of Surgery, Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept of Surgery, VU University Medical Center, Amsterdam, [4]Dept of Surgery, Isala Clinics, Zwolle, [5]Dept of Medical Psychology, Academic Medical Center, Amsterdam, the Netherlands

Four meta-analyses exist evaluating the short term results of laparoscopic versus open ileocolic resection for Crohn's disease. Little is known about the long term results of both procedures with respect to surgical recurrence rate, overall reoperation rate, incidence of incisional hernia and adhesive small bowel obstruction, quality of life (QOL) and Body Image (BI) and cosmesis. The objective of this study was to determine the long term results of a randomized multicenter study comparing laparoscopic to open ileocolic resection for Crohn's disease.
Sixty patients who participated in this trial were prospectively followed in the outpatient clinic. Patients had an ileocolic resection between 1999 and 2003. Primary outcome parameters were reoperation and readmission rate and re-resection rate for recurrent Crohn's disease. Secondary outcomes were QOL, BI and cosmesis. Five patients, 1 from the laparoscopic group and 4 from the open group were lost to follow up. The groups were comparable for characteristics as sex, age, and maintenance therapy. Mean follow-up was 6.8 years. Overall, 16/29 (55%) and 16/26 (62%) patients remained relapse-free after the ileocolic resection in the laparoscopic and open group respectively (p=NS). Resection of recurrent Crohn's disease occurred in 2/29 (7%) and 3/26 (12%) patients (p=NS). Two reoperations for incisional hernia were done in the open group (2/26= 8%) vs. nil in the laparoscopic group (p=NS). Reoperation for adhesive small bowel obstruction was done twice in the open group (2/26=8%) vs. nil in the laparoscopic group (p=NS). QOL was similar in both groups. BI and cosmesis scores were significantly higher in the laparoscopic group (p=0.029 and p=0.000 respectively). Conclusions: Surgical recurrence and QOL after laparoscopic and open ileocolic resection for Crohn's disease are comparable. Laparoscopic-assisted ileocolic resection was associated with a significantly better BI and cosmesis.

Adequately dosed 6-thioguanine is a well tolerated and safe rescue drug in azathioprine or 6-mercaptopurine intolerant IBD patients

D.P. van Asseldonk[1], B. Jharap[1], N.K.H. de Boer[1], A.A. van Bodegraven[1] and C.J. Mulder[1], [1]Dept of Gastroenterology and Hepatology, VU university medical center, Amsterdam, the Netherlands

Introduction: For over 40 years thiopurines have successfully been used in the treatment of IBD. The use of 6-thioguanine (6-TG) has largely been discarded partly due to its association with nodular regenerative hyperplasia (NRH). This relation is less critical when 6-TG is being more adequately dosed. It may be an attractive alternative, or rescue therapy, for patients failing azathioprine (AZA) and 6-mercaptopurine (6-MP) therapy. Aim: The aim of this study was to assess the tolerability and safety of more adequately dosed 6-TG in a cohort of Dutch AZA and 6-MP intolerant IBD patients. Methods: Retrospective database analysis of 113 IBD-patients (62 (55%) with Crohn's disease (CD and 51 (45%) with ulcerative colitis (UC)) from hospitals across The Netherlands. Results: The median age of patients was 38 (16-62) yrs. Forty-two (37%) were males. Of all patients 93% was intolerant and 7% unresponsive to AZA or 6-MP. Mean dose of 6-TG was 0.3mg/kg/day. The median 6-TG treatment duration was 26 months (1-72) cumulating to 245 treatment years. Eighty-two of 113 (73%) patients tolerated and continued 6-TG therapy to the last evaluation with a median duration of 40 months. The 31 patients who withdrew therapy had taken 6-TG for a median of 8 months (p=0,001). Eleven (36%) of these 31 patients were refractory to 6-TG therapy, whereas the other 20 patients were intolerant. Of the latter, 2 (10%) had leukopenia, 2 (10%) thrombocytopenia, 1 (5%) hepatotoxicity, 3 arthralgia (15%), 5 (25%) gastro-intestinal complaints and 7 (35%) other intolerances. In 42 (51%) of the 82 patients who tolerated 6-TG, a liver biopsy was performed after a median treatment period of 29 months (4-44) that showed aspecific regeneration but no NRH in 9 (21%), sinus dilation in 3 (7%) and no abnormalities in 30 (72%) patients.
Conclusion: 6-TG is well tolerated over a median period of 40 months in 73% of those patients who had previously been intolerant or refractory to AZA or 6-MP. In 245 treatment years no NRH was observed, corroborated by liver biopsy findings in more than halve of this cohort. However, mild architectural changes were observed in 28% of the biopsies. In conclusion, 6-TG is a relatively safe and well tolerated alternative for AZA and 6-MP in the treatment of IBD.

Determinants of hyperoxaluria and urolithiasis in Crohn's disease: results of a pilot study

T.E.H. Römkens[1], F.M. Nagengast[1], D.J. de Jong[1], Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, the Netherlands[1]

The incidence of urolithiasis in patients with Crohn's disease (CD) is elevated compared to the general population. A possible explanation is hyperoxaluria as consequence of impaired faecal oxalate excretion.The aim of this pilot study was to determine the prevalence of hyperoxaluria and urolithiasis in consecutive patients with CD visiting our outpatient IBD clinic, and to determine predictors for hyperoxaluria and urolithiasis. In a three month period we included 34 consecutive patients with CD, after informed consent was obtained. Demographic variables were obtained from the medical records. Twenty-four hours urine samples and laboratory tests were obtained at the outpatient clinic. Patients were asked to complete a dietary questionnaire. A total of 28 (11M/17F) patients, who completed the questionnaire and returned the 24 hours urine samples, were included for statistical analyses. Mean age was 46.9 ± 12.6 years, with a mean disease duration of 20.12 ± 14.8 years. Location of CD was ileocolonic (N=14, 50%), confined to colon (N=6, 21.4%), ileum (N=4, 14.3%), more proximal (N=2, 7.1%), or proximal combined with colon (N=2, 7.1%). A history of bowel resection was present in 16/28 (57.1%) of the patients, with 9/28 (32.1%) ileocecal resections. Of all patients 17.9% (5/28) had a history of urolithiasis. The serum levels of CRP, hemoglobin and creatinine were normal. The overall mean 24 hour excretion of oxalate was 0.45± 0.13 mmol/l, hyperoxaluria (>0.60 mmol/24 hr) was present in 5/28 patients (17.9%). Using the Mann-Whitney U test, patients with and without urolithiasis were compared. Possible determinants for urolithiasis were higher levels of urinary oxalate excretion (P= 0.04), urinary creatinine excretion (P<0.01) and higher serum hemoglobin (P<0.01). Using Spearman rank correlations, urine oxalate excretion (mmol/l) was correlated with total calcium intake (r=0.43, P=0.03), serum ureum level (r=0.43, P=0.02) and levels of serum bicarbonate (r=-0.56, P=0.02). In conclusion this pilot study showed a high prevalence of both hyperoxaluria and urolithiasis in consecutive out-patients with CD, irrespective of CD localization. A high level of urinary oxalate excretion was a determinant for developing urolithiasis. Calcium intake seems to be correlated with higher urinary oxalate excretion. These findings may lead to preventive (dietary) measures, in order to decrease the prevalence of urolithiasis in IBD patients.

High prevalence of fatigue in patients with Inflammatory Bowel Disease: results of a case-control study

M.W.J. van Vugt- van Pinxteren[1], T.E.H. Römkens[1], F.M. Nagengast[1], M.G.H. van Oijen[1], D.J. de Jong[1], University Medical Center St. Radboud Nijmegen, Dept. Gastroenterology and Hepatology[1], the Netherlands

Many patients with Inflammatory Bowel Disease (IBD) complain about severe fatigue even if their disease is in remission. Therefore we performed a study to examine the prevalence and severity of fatigue and to define possible determinants of fatigue. In a three month period we conducted a case-control study in consecutive patients at our outpatient clinic. Patients with confirmed Crohn's Disease (CD) and Ulcerative Colitis (UC) were studied. Lynch syndrome gene carriers (Lynch) served as a control group. Demographic variables, clinical history and laboratory results were obtained from the medical records. In IBD patients severity of disease was assessed by the Harvey Bradshaw Index. (Severity of) Fatigue was scored using the revised Piper Fatigue Scale (PFS), a validated questionnaire consisting of 22 numerically (0-10) scaled items, that measures four dimensions of subjective fatigue: (1) behavioral/severity; (2) affective meaning; (3) sensory and (4) cognitive/mood. Mean PFS (overall and dimensions) scores were compared between the three groups. Within the IBD patient group we looked for possible determinants of fatigue, by comparing demographic and clinical variables between patients with a high (≥4) and low (<4) PFS score.A total of 300 patients were included of whom 222 (117 CD; 55 UC; 50 Lynch) returned the questionnaires. Of these 6 (3 CD, 2 UC, 1 Lynch) were excluded because of missing data in the PFS. The remaining 216 patients (82M/134F) were included in the statistical analysis. Demographic variables were not different between groups. Mean age was 44.4±13.1 years. IBD patients scored significantly higher on the PFS than the control group, with a mean (SD) PFS score of 4.8 (2.1) for CD and 4.2 (2.3) for UC versus 2.0 (2.0) for the control group, respectively ($P<0.01$). This statistically significantly difference was found throughout all four dimensions.Within IBD patients, gender distribution and age did not alter PFS scores. Moreover, patients with laboratory-defined anemia or high CRP did not score differently. Only the Harvey Bradshaw index was positively correlated with the overall PFS score ($r=0.37$, $p<0.01$), and throughout all four dimensions.In conclusion we found a high prevalence (in all dimensions) of fatigue in patients with IBD. This prevalence was significantly higher compared to the control group, for both CD and UC patients. Within the IBD group, only the Harvey Bradshaw Index correlated with the Piper Fatigue Scale.

Visceroperception in Patients with Ulcerative Colitis; role of colorectal mast cells

E.A. van Hoboken[1], A.Y. Thijssen[2], P.P.J. van der Veek[1], D.M.A.E. Jonkers[2], H.W. Verspaget[1], A.A.M. Masclee[2], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Centre, The Netherlands, [2]Division of Gastroenterology and Hepatology, Maastricht University Medical Centre, The Netherlands

A considerable subset of patients with inactive colitis (UC) experience symptoms that resemble Irritable Bowel Syndrome (IBS). Increased visceroperception is a hallmark of IBS and is related to inflammation. This correlates with the number of mast cells and inversely correlates with the distance of mast cells to nerve endings in IBS. In patients with UC, little is known about these features. Aim of our study was to investigate visceroperception, mast cell counts and proximity of mast cells to nerve endings in the colorectal mucosa of (in)active UC patients and healthy volunteers (HV). Nineteen patients with inactive UC (UC-I;9F;50±3 yrs), 12 patients with active UC (UC-A;5 F;49±3yrs) and 17 HV (8F;43±3 yrs) were enrolled. Rectal perception was studied using a barostat with a random staircase protocol (0-40 mmHg). Urge and pain perception were scored on a Visual Analogue Scale (0-100 mm). During a colonoscopy biopsies were taken from rectal and sigmoid mucosa. Mucosal mast cells were identified immunohistochemically and quantified per 100 crypts. The distance from mast cells to nerve endings was scored using electron microscopy. Rectal compliance was not significantly different between UC-A, UC-I and HV: 25±3, 28±4 and 21±3 ml/mmHg, respectively. Perception of urge at the highest rectal pressures (32-40 mmHg) was significantly increased in UC-I versus both UC-A and HV (70±4 mm vs 52±7 and 54±7 mm resp.; $p<0.05$). This was also found for pain in UC-I vs UC-A ($p<0.05$). The number of mucosal mast cells in the rectum was significantly higher in both UC-A and UC-I than in HV (320± 57 and 228±20 vs 163±18 cells/100 crypts; $p<0.05$). The percentage of degranulating mast cells only was significantly higher in UC-I (40±7%) ($p<0.05$) and not in UC-A (24±5%) vs HV (16±4%). Pain perception at the highest rectal pressures correlated with the number of mast cells in the rectal mucosa in UC-I ($r=0.39;p<0.05$). In sigmoid mucosa no differences in mast cell profiles were found. The percentage of mast cells in close proximity to nerve endings was significantly higher in UC-I (58±4%) ($p<0.05$), but not in UC-A (48±5%) vs HV (38±3 %).
Mast cell counts in the rectal mucosa are increased in all UC patients. Rectal visceroperception is increased in inactive but not in active UC. Increased pain perception in the UC-I patients is associated with an increased number as well as a higher percentage of degranulating mast cells in closer proximity to nerve endings in the rectal mucosa.

Treatment of refractory Crohn's Disease patients with autologous bone marrow derived Mesenchymal Stem Cells – first results

M. Duijvestein[1], M.H. Verwey[1], H.H. Fidder[1], G.R. van den Brink[1], H. Roelofs[2], J. Zwaginga[2], W.E. Fibbe[2], D.W. Hommes[1], [1]Dept of Gastroenterology and Hepatology and [2]Dept of Immunohematology and Blood Transfusion, Leiden University Medical Center (LUMC), Leiden, the Netherlands

Despite the improvements in Crohn's Disease (CD) management with introduction of anti-TNF compounds, a proportion of patients suffer from a poor quality of life due to disease relapse, repeat surgery, extraintestinal manifestations and drug side-effects.
Mesenchymal Stem Cells (MSCs) are pluripotent cells that have potent immunosuppressive effects on T and B cells in vitro and in animal models of chronic inflammation. Promising results have been obtained in patients with acute and severe graft versus host disease (GvHD), including GvHD of the gut.The objective of this study is to determine the safety and feasibility of autologous bone marrow derived MSCs in patients with refractory CD. Methods: 8 adult patients (6 females/2 males, median age 33,5 years) with refractory, moderate to severe CD with a Crohn's Disease Activity Index (CDAI) score of at least 220 underwent bone marrow aspiration (100 ml) under local anesthesia. Mononuclear cells were isolated and MSCs were expanded in culture until passage 1-3. To date, 5 patients received 2 doses of 1-2x10^6 cells/kg bodyweight, intravenously, 7 days apart. Primary outcomes were feasibility and safety of autologous MSC expansion and infusion. Secondary outcomes were changes in the CDAI score and Crohn's Disease Endoscopic Index of Severity Score (CDEIS). Results: MSC from CD patients showed the typical spindle-shaped morphology and similar growth potential and yield comparable to MSCs from healthy donors (n=8). The initial median CDAI score in the first five patients treated was 334 (range 254-350). MSC infusion was successful and without side effects, with exception of a mild allergic reaction to the cryopreservant DMSO in one patient. The first patient was a chronic severe steroid refractory patient on the waiting list for surgery. Although an initial drop of her CDAI score was seen, she was operated upon due to poor general condition and persistent rectal blood loss. The other 4 treated patients showed an average decrease in median CDAI score of 107 points 6 weeks post transplant. Endoscopic improvement was seen in 2 patients with extensive CD localized in the colon whereas no significant improvement was seen in 2 patients with ileal CD.
Conclusion: Administration of autologous bone marrow derived MSCs seems to be safe and feasible in the treatment of refractory CD, no serious adverse events were detected during harvesting and study follow up. In addition, both clinical- and endoscopic efficacy was observed.

Genetic Variants in the Region Harbouring IL2/IL21 Associated to Ulcerative Colitis

E.A.M. Festen[1,2], P. Goyette[3], R. Scott[4], V. Annese[5], A. Zhernakova[6], S.R. Brant[7,8], J.H. Cho[9], M.S. Silverberg[10], K.D. Taylor[11], D.J. de Jong[12], P.C. Stokkers[13], D. McGovern[11], O. Palmieri[5], J.P. Achkar[14], R.J. Xavier[15], R.H. Duerr[4,16], M.J. Daly[17,18], C. Wijmenga[2], R.K. Weersma[1] and J.D. Rioux[3], [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands, [2]Dept of Genetics, University Medical Center Groningen and University of Groningen, Groningen, the Netherlands, [3]Laboratory in Genetics and Genomic Medicine of Inflammation, Montreal Heart Institute Université de Montréal, Montreal, Canada, [4]Division of Gastroenterology, Hepatology and Nutrition, Dept of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, USA, [5]UU.OO. Gastroenterologia ed Endoscopia Digestiva, Ospedale "Casa Sollievo della Sofferenza", IRCCS, San Giovanni Rotondo, Italy, [6]Complex Genetics Section, Dept of Medical Genetics, University Medical Center Utrecht, Utrecht, the Netherlands, [7]Harvey M. and Lyn P. Meyerhoff Inflammatory Bowel Disease Center, Dept of Medicine, Johns Hopkins University, Baltimore, USA, [8]Dept of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA, [9]Depts of Medicine and Genetics, Division of Gastroenterology, Inflammatory Bowel Disease (IBD) Center, Yale University, New Haven, USA, [10]Mount Sinai Hospital IBD Centre, University of Toronto, Canada, [11]Medical Genetics Institute and Inflammatory Bowel Disease (IBD) Center, Cedars-Sinai Medical Center, Los Angeles, USA, [12]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, the Netherlands; [13]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands, [14]Center for Inflammatory Bowel Disease, Dept of Gastroenterology & Hepatology, Cleveland Clinic, Cleveland, Ohio, USA, [15]Center for Computational and Integrative Biology and Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston, USA, [16]Dept of Human Genetics, Graduate School of Public Health, University of Pittsburgh, USA, [17]Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, USA, [18]Molecular Biology Dept, Massachusetts General Hospital, Harvard Medical School, Boston, USA.

Genetic susceptibility is known to play a large part in the predisposition to inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC). The IL2/IL21 locus on 4q27 is known to be a common risk locus for inflammatory disease (shown in celiac disease, type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus and psoriasis), while the roles that IL2 and IL21 play in the immune response also make them attractive candidates for inflammatory bowel disease. Our objective was to prove an association between inflammatory bowel disease and the IL2/IL21 locus.

The four single nucleotide polymorphisms (SNPs) in the IL2/IL21 locus most associated to celiac disease were genotyped in 1590 IBD cases and 929 controls from the Netherlands, and then replicated in a North American cohort (2286 cases and 1239 controls) and an Italian cohort (805 cases and 421 controls), yielding a total of 4681 cases (3194 UC, 1487 CD) and 2589 controls. Allelic association testing and a pooled analysis using a Cochran-Mantel-Haenszel test were performed.

All four SNPs were strongly associated with UC in all three cohorts and reached genome-wide significance in the pooled analysis (Rs13151961 $p= 1.35x10^{-10}$, rs13119723 $p= 8.60x10^{-8}$, rs6840978 $p= 3.07x10^{-8}$, rs6822844 $p= 2.77x10^{-9}$). We also found a moderate association with CD in the pooled analysis (p value range 0.0066-0.0003).

Conclusions: We found a strong association for the IL2/IL21 locus with UC, which confirms this locus as a general susceptibility locus for inflammatory disease.

Flat colonic neoplasia are left undetected by Fecal Immunochemical Tests (FIT) and will be missed in colorectal cancer screening

F.A. Oort[1], J.S. Terhaar sive Droste[1], R.W.M. van der Hulst[2], H.A. van Heukelem[3], R.J.L.F. Loffeld[4], I.C.E. Wesdorp[5], Q.J.M. Voorham[6], G.A. Meijer[6], C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Slotervaart Hospital, Amsterdam, [4]Internal Medicine, Zaans Medical Center, Zaandam, [5]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [6]Pathology, VU University Medical Center, Amsterdam, the Netherlands

Introduction: In Japan, flat colorectal adenomas and carcinomas (flat lesions) have been reported to represent 10-40% of all colorectal neoplasia. The occurrence of flat lesions was considered to be rare in Western countries, however recent studies have reported the opposite. Population screening by faecal occult blood testing (FOBT) can decrease mortality and incidence of colorectal cancer (CRC). Occult blood loss by a proportion of adenomas and carcinomas will result in a positive test and subsequently referral for colonoscopy. However, FOBT accuracy may be limited in case of flat lesions, e.g. due to a smaller surface area and the fact that they are less protruding than
polypoid adenomas. Aim: Here we describe whether flat lesions are detected by a quantitative Immunochemical FOBT (FIT) in a head to head comparison to colonoscopy.
Methods: All patients aged ≥ 18 years and scheduled for a colonoscopy in 5 participating hospitals were asked to sample a FIT (OC sensor®, Eiken chemical Co, Japan) with stool from a bowel movement one day prior to colonoscopy. Excluded were those patients with incomplete colonoscopy or insufficient bowel lavage. All FIT's were analysed with the desktop analyser "OC-SENSOR μ". Test results were compared with colonoscopy findings in every individual patient. A haemoglobin concentration >50 ng/ml in the test sample was considered a positive test result, which is considered to be a low cut off.
Results: In 78 out of 1897 individuals a flat lesion was the exclusive finding at colonoscopy. Histology of 45/78 flat adenomas was classified as adenomatous. Of the remaining 33 lesions histology revealed hyperplastic or normal colon mucosa. One of the 45 flat adenomatous lesions appeared to be an adenocarcinoma and 11 were advanced adenomas (diameter ≥ 1cm, villous features or high grade dysplasia). The FIT was negative in 38/45 flat adenomatous lesions. Nine out of 11 flat advanced adenomas were not detected nor was the carcinoma.
Conclusions: In our colonoscopy controlled population, we found the FIT tested negative in most patients with flat colorectal lesions even at a low cut off. Consequently, these flat (pre)cancerous lesions will remain undetected in screening programs using FIT.

Randomized trial comparing the test characteristics of immunochemical fecal occult blood test at different cut-off levels to Guaiac-based fecal occult blood test

L. Hol[1], J.A. Wilschut[2], M. van Ballegooijen[2], A.J. van Vuuren[1], H. van der Valk[3], J.C.I.Y. Reijerink[4], A.C.M. van der Togt[5], E.J. Kuipers[1,6], J.D.F. Habbema[2], M.E. van Leerdam[1], [1]Depts of Gastroenterology and Hepatology, [2]Public Health, and [6]Internal Medicine, Erasmus MC, University Medical Centre, Rotterdam, [3]Association of Laboratory Pathology and Cytology (Pathan), Rotterdam, [4]Association of Nation-wide Screening South-west Netherlands, Vlaardingen, [5]Comprehensive Cancer Centre, Rotterdam, the Netherlands

Introduction: Immunochemical fecal occult blood testing (FIT) provides quantitative test results, which allows optimization of the cut-off value for follow-up colonoscopy. The optimal cut-off value is however unknown. We conducted a randomized population-based trial to determine test characteristics of FIT (OC-Micro Latex, Eiken, Japan) screening at different cut-off levels and compare it to guaiac-based fecal occult blood test (gFOBT) screening in an average risk population. Methods: A representative sample of the Dutch population (n=10,011), aged 50-74 years, was 1:1 randomized prior to invitation to gFOBT and FIT screening. Colonoscopy was indicated for screenees with a positive gFOBT or FIT (cut-off 50ng hemoglobin/ml).Results: When varying the cut-off-level between 50 and 200ng/ml, the positivity rate of FIT ranged between 8.1% (95% CI:7.2-9.1%) and 3.5% (95%CI:2.9-4.2%), the detection rate of advanced neoplasia ranged between 3.5% (95%CI:2.9-4.2%) and 2.2% (95%CI:1.7-2.7%), and the specificity ranged between 95.7% (95%CI:94.8-96.4%) and 98.9% (95%CI:98.5-99.1%). The detection rate was two-times higher at a cutoff value of 75ng/ml than with gFOBT screening (gFOBT:1.3%; FIT:2.9%; p<0.001), while the number needed to scope to find one screenee with advanced neoplasia was similar (2.0 vs. 2.2; p=0.69). Conclusion: FIT is considerably more effective than gFOBT screening within the range of tested cut-off values. From our experience, a cut-off value of 75ng/ml provided an acceptable trade-off between detection rate and number needed to scope.

Table: Test characteristics of gFOBT and FIT at different cut-off levels

	Cut-off	Positivity rate	NNscope		Specificity**		Detection rate	
			Adv neoplasia	CRC	Adv neoplasia	CRC	Adv neoplasia	CRC
	ng/ml	n(%)	n	n	%	%	n(%)	n(%)
gFOBT		64 (2.8)	2.0	10.3	98.7	97.6	31 (1.3)	6 (0.3)
FIT	50	241 (8.1)*	2.2	14.1	95.7*	92.9*	103 (3.5)*	16 (0.5)
	75	170 (5.7)*	1.9	11.6	97.4*	95.0*	86 (2.9)*	14 (0.5)
	100	143 (4.8)*	1.8	9.8	98.0	95.8	78 (2.6)*	14 (0.5)
	125	128 (4.1)*	1.7	9.5	98.3	96.3	74 (2.5)*	13 (0.4)
	150	120 (4.0)*	1.6	8.8	98.6	96.6	73 (2.5)*	13 (0.4)
	175	107 (3.6)*	1.5	8.3	98.8	97.0	67 (2.3)*	12 (0.4)
	200	103 (3.5)*	1.5	8.2	98.9	97.1	64 (2.2)	12 (0.4)

*p<0.05 compared to gFOBT; Advanced neoplasia: adenoma ≥10 mm, villous component (≥25% villous) or high-grade dysplasia; serrated adenoma; three or more adenomas; CRC. CRC: colorectal cancer; NNscope: number needed to scope to detect one screenee with an advanced neoplasia; **The specificity for advanced neoplasia and CRC was calculated under the rare disease assumption as the ratio of number of all negative screenees and total number of screenees subtracted by the number of true positives

Advanced neoplasia of the left hemicolon are better detected by FIT than right sided lesions

F.A. Oort[1], R.W.M. van der Hulst[2], J.S. Terhaar sive Droste[1], H.A. van Heukelem[3], R.J.L.F. Loffeld[4], I.C.E. Wesdorp[5], R. Duijkers[1], R.A.M. Ooteman[1], Z.D. Valdehueza[1], M.Q. Wentink[1], V.M.H. Coupe[6], G.A. Meijer[7], C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Slotervaart Hospital, Amsterdam, [4]Internal Medicine, Zaans Medical Center, Zaandam, [5]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [6]Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [7]Pathology, VU University Medical Center, Amsterdam, the Netherlands

Introduction: Fecal Immunochemical Tests (FITs) have been proposed as a screening tool for Colorectal Cancer (CRC). FITs detect the globin part of human haemoglobin using specific antibodies. Globin is degraded by digestive enzymes present in the intestinal lumen. Theoretically, this makes FIT selective for occult blood loss in the colon since globin from blood lost proximal to the colon will be degraded. On the other hand, this could have a negative effect on the detection rate of right sided colonic lesions as well. Since the incidence of right sided adenomas and cancers is rising, this could be a pitfall of the use of FIT in CRC screening.Aim: To assess whether there is a difference in sensitivity of FIT for right and left sided advanced neoplasia. Methods: All adult patients scheduled for a colonoscopy in 5 participating hospitals were asked to perform a FIT (OC sensor®, Eiken chemical Co, Japan) on one bowel movement the day prior to colonoscopy. The desktop analyser “OC-SENSOR μ” was used for analysis. The cut off value was set at 100ng/ml according to the manufacturers instructions. Test results were compared with colonoscopy outcome as gold standard. Advanced neoplasia are all cancers and advanced adenomas (i.e. ≥1 cm in diameter and/or villous architecture and/or high-grade dysplasia). The right colon was defined as the caecum, ascending and transverse colon including the splenic flexure. The left colon includes the descending colon, sigmoid and rectum. The location of all lesions was assessed by the endoscopist. The chi-square test was used to determine statistical significance.Results: In 1808 individuals who underwent total colonoscopy, 193 advanced adenomas and 62 cancers were found. Individuals with multiple lesions on both sides of the colon were excluded from this analysis (N=48). In the right colon 41 advanced adenomas were found as well as 23 cancers. In the left hemicolon 104 advanced adenomas and 23 cancers were found. The OC-sensor at cut off 100 ng/ml was positive in 11.7% of 1808 individuals. Detection rate for right sided advanced neoplasia was 39.1% versus 56.6% for left sided advanced neoplasia, (P=0.01).
Conclusions: Left sided colonic advanced neoplasia are better detected by FIT than right sided lesions. This is an important limitation of FIT when applied in CRC screening, while the incidence of right sided lesions is increasing.

Routine MSI-analysis in Colorectal Cancer patients ≤70 years leads to the identification of more patients at high risk for Lynch Syndrome

M.G.F. van Lier[1], A. Wagner[2], W.N.M. Dinjens[3], E.J. Kuipers[1,4], M.E. van Leerdam[1], E.W. Steyerberg[5], Dept of Gastroenterology and Hepatology[1], Dept of Clinical Genetics[2], Dept of Pathology[3], Dept of Internal Medicine[4], Dept of Pubilic Health[5], Erasmus MC, University Medical Center, Rotterdam, the Netherlands

Lynch Syndrome (LS), an inherited disorder caused by a germline mutation in a mismatch repair (MMR) gene, is responsible for ± 3% of all colorectal carcinomas (CRC). The molecular hallmark of these CRCs is microsatellite instability (MSI). Early detection of LS is of great importance, since surveillance colonoscopies reduce CRC morbidity and mortality. However, a considerable proportion of patients at high risk for LS are not recognized. In the search for a new diagnostic strategy, we prospectively studied the yield of routine molecular analysis in CRC patients ≤ 70 years. In six hospitals all patients ≤ 70 years diagnosed with invasive CRC were included from May 2007-September 2008. Tumorspecimens were analyzed for MSI, immunohistochemistry (IHC) of the MMR proteins, MLH1 promoter hypermethylation and BRAF mutation. Tumors were classified as; 1) suspect for LS if MSI-H and simultaneously showing absent MMR protein expression with exclusion of epigenetic silencing, 2) sporadic MSI-H tumors displaying absent MLH1 expression with MLH1 promoter hypermethylation and/or BRAF-mutation, 3) sporadic, microsatellite stable (MSS) tumors. Clinical data including age at diagnosis, sex, tumor localization and presence of MSI-related histology features were recorded. Tumors of 365 patients (60% males) with a mean age of 60 years (SD ±8) were analyzed. CRCs were left-sided in 75%, right-sided in 22% and in 3% the location was unknown. MSI-related pathology features were seen in 43 tumors (12%). The molecular analyses revealed 9 sporadic MSI-H tumors (2,5%) and 13 CRCs suspect for LS (3,6%; 95% CI 1,7-5,5). Among the 13 patients suspect for LS, 8 (62%) were > 50 years. Based on IHC, 3 patients were suspect for a MLH1 gene defect, 3 for MSH2, 4 for MSH6 and 3 for a PMS2 defect. In logistic regression analyses patients suspect for LS were significantly younger (OR 1,1; 95% CI 1,03-1,17) and CRCs were located more often right-sided (OR 27; 95% CI 6-117) than in patients with MSS tumors. Sporadic MSI-H tumors were significantly more often located right-sided than in the MSS group (OR 27; 95% CI 3-228).

Conclusion: Molecular screening for LS in patients with CRC ≤ 70 years leads to identification of a profile pathognomic for LS in 3,6% of patients. More than half of those do not meet the age-criterion routinely used for LS assessment. The routine use of molecular screening thus helps to identify more LS patients. The cost-effectiveness of such an approach has to be determined.

Screening for colorectal cancer in the Netherlands; acceptance of FOBT and flexible sigmoidoscopy screening

V. de Jonge[1], L. Hol[1], M. van Ballegooijen[2], J.D.F. Habbema[2], M.L. Essink-Bot[2], J. van Vuuren[1], E.J. Kuipers[1], M .E. van Leerdam[1], Dept of Gastroenterology and Hepatology[1] and Public Health[2], Erasmus University Medical Center, Rotterdam, The Netherlands

Introduction: Colorectal cancer (CRC) is the second cause of cancer death in the Western world. Randomized controlled trials provided evidence for the effectiveness of CRC screening. Available screening strategies are fecal occult blood test (FOBT) or endoscopy. Population acceptance of CRC screening test is of paramount importance for the efficacy of a screening program. The aim of this study was to determine the acceptance and perceived burden of CRC screening using FOBT or flexible sigmoidoscopy (FS).Methods: A representative sample of the Dutch population aged 50-74 years old was randomized to guaiac based fecal occult blood test (gFOBT), immunochemical FOBT (FIT) or flexible sigmoidoscopy (FS) screening. A questionnaire was sent to gFOBT/FIT screenees one week after performing the test. Participants of sigmoidoscopy were asked to complete a questionnaire prior to FS screening and seven days afterwards. The survey contained questions assessing discomfort, burden and acceptance of the screening method. Furthermore, gastrointestinal symptoms before (baseline) and after FS were determined.Results: In total 1298 of 1602 (81%) of FOBT screenees (men 49%; mean age 61 ± 6yrs) and 850/1148 (74%) of the FS screenees (men 52%; mean age 61 ± 6yrs) completed the questionnaires. Dicomfort and embarrassment were by respectively 12% and 5% of FOBT screenees during performing the test. Discomfort during FS was reported by 56% and 17% perceived FS as very painful. Embarrassment during sigmoidoscopy was reported by 22% of patients. FS was described as more burdensome than FOBT screening (12% vs. 2% respectively, $p < 0.001$). Significantly more FOBT screenees were willing to attend a successive screening round (78% vs. 68% respectively, $p < 0.001$). Eighty-six percent of FOBT and 69% of FS screenees would recommend others to attend screening. FOBT screenees judged the overall screening test slightly better than FS screenees (8.6 vs 8.2; $p < 0.001$; scale 1-10).
Conclusions: Fecal occult blood testing and flexible sigmoidoscopy screening were generally well tolerated. Significantly more discomfort was reported during FS screening. However, acceptance for repeat examination is considerable high for both strategies. FOBT and FS are therefore acceptable screening tests.

Epidemiological time trends of gastric cancer in Lynch syndrome families in the Netherlands

L.G. Capelle[1], N.C.T. Van Grieken[2], W.J. Klokman[3], M.J. Bruno[1], H.F.A. Vasen[4,5], E.J. Kuipers[1,6], Depts of [1]Gastroenterology and Hepatology and [6]Internal Medicine, Erasmus MC University Medical Center, Rotterdam, [2]Dept of Pathology, VU University Medical Center, Amsterdam, [3]Dept of Epidemiology, The Netherlands Cancer Institute, Amsterdam, [4]The Netherlands Foundation for the Detection of Hereditary Tumors, [5]Dept of Gastroenterology, Leiden University Medical Centre, Leiden, the Netherlands

Over the past decades, the incidence of gastric cancer has shown a steady decrease in most of Western countries. This decrease is thought to be due to changes in socioeconomic circumstances influencing H. pylori prevalence and diet. Gastric cancer also forms part of the Lynch syndrome tumour spectrum. Whether the incidence of gastric cancer in Lynch syndrome subjects is declining similarly is unknown. This knowledge however, is relevant for planning optimal surveillance strategies in these subjects. Therefore, the aim of this study was to evaluate the epidemiological time trends of gastric cancer in Lynch syndrome families in the Netherlands.Known mutation carriers and putative mutation carriers of Lynch syndrome with a diagnosis of gastric cancer between 1970 and 2003 were identified in the Dutch HNPCC Registry. Putative carriers were subjects with colorectal or endometrial cancer diagnosed before 60 years who were not tested. Standardized incidence rates (SIR) were evaluated for the designated period. In addition, time trends within the birth cohorts from 1900 to 2000 were evaluated.Within 276 families, 1765 subjects (M/F 805/960) were included. Overall, 78% were known mutation carriers and 22% were putative mutation carriers. Gastric cancer was diagnosed in 20 (1.1%) patients (M/F 14/6, median age 57.5 years, range 36-86 years).The SIR of gastric cancer in known and putative mutation carriers declined from 5.4 (95% CI 2.0-11.7) in 1970-1979, to 4.1 (95% CI 1.5-8.9) in 1980-1989, to 2.8 (95% CI 0.8-7.1) in 1990-1999. Within subsequent birth cohorts, the relative risk of developing gastric cancer increased from a RR of 3.4 (95% CI 1.5-6.4) in the birth cohort of 1900-1925 to a RR of 5.7 (95% CI 2.6-10.8) in the birth cohort of 1925-1949 to a RR of 9.5 (95% CI 1.2-34.5) in the birth cohort of 1950-1974.
Conclusions: From 1970 to 2003, the SIR of gastric cancer in Lynch syndrome mutation carriers has declined by approximately 50%. This decline likely reflects an interaction between persistent genetic predisposition, decreased environmental risk factors, in particular H. pylori colonization, and presumably surveillance and early intervention. Most markedly, the declining incidence was more pronounced in LS families than in the general Dutch population, which led to the decreasing SIR of gastric cancer over the past decades.

Gastric cancer risk in Lynch syndrome families in the Netherlands

L.G. Capelle[1], N.C.T. Van Grieken[2], W.J. Klokman[3], M.J. Bruno[1], H.F.A. Vasen[4,5], E.J. Kuipers[1,6], Depts of [1]Gastroenterology and Hepatology and [6]Internal Medicine, Erasmus MC University Medical Center, Rotterdam, [2]Dept of Pathology, VU University Medical Center, Amsterdam, [3]Dept of Epidemiology, The Netherlands Cancer Institute, Amsterdam, [4]The Netherlands Foundation for the Detection of Hereditary Tumors, [5]Dept of Gastroenterology, Leiden University Medical Centre, Leiden, the Netherlands

Colorectal cancer and endometrial cancer are the most frequent cancers in Lynch syndrome (LS) carriers with a cumulative risk of 60-80% and 30-50% respectively. Consequently, screening of LS families for these types of cancer has been widely accepted. Gastric cancer also forms part of the LS tumour spectrum. However, the risk of developing gastric cancer in LS families is largely unknown, resulting in a lack of clear guidelines for surveillance. Therefore, the aim of this study was to evaluate the risk of developing gastric cancer for mutation carriers and their relatives in comparison to the risk of gastric cancer development in the general Dutch population. Known mutation carriers, putative mutation carriers and their relatives were selected from the Dutch HNPCC Registry. Putative carriers were subjects with colorectal or endometrial cancer diagnosed before 60 years who were not tested. The incidence of gastric cancer in LS family members was compared to the incidence of gastric cancer in the general Dutch population between 1970 and 2003. Relative risk and absolute excess risk (AER) of developing gastric cancer were calculated by a Poisson Model. Within 276 families, 6682 subjects were identified. Overall, 24% were known mutation carriers, 10% were putative mutation carriers and 66% were relatives of known and putative carriers. Gastric cancer was diagnosed in 69 (1%) subjects (M/F 44/25 median age 51.7 years, range 24 to 86 years) of which 29 (42%) were known mutation carriers, 9 (13%) were putative mutation carriers, and 31 (45%) were relatives of known- and putative mutation carriers. Of the patients with gastric cancer, 45% had a first diagnosis of gastric cancer between 1970 and 2003. During this period, LS family members had a 2.6-fold (95% CI 1.7-3.7) increased risk to develop gastric cancer compared to the general Dutch population. This risk was 5.2 fold increased for both males and females with a known mutation (both $p<0.001$). In addition, the AER of developing gastric cancer was significantly increased for known mutation carriers (AER 3.6 (95% CI 1.7-6.3)).
Conclusions: The overall risk of developing gastric cancer risk in LS families is rather low (1%). However, known mutation carriers have a five times higher risk of developing gastric cancer compared to the general population. Therefore, it seems prudent to limit surveillance for gastric cancer to known mutation carriers, most particular to those of families with gastric cancer.

Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicenter cohort study

K.S. Boparai[1], E.M.H. Mathus-Vliegen[1], J.J. Koornstra[2], F. Nagengast[3], M. van Leerdam[4], C.J.M. van Noesel[5], M. Houben[6], A. Cats[7], L. van Hest[8], P. Fockens[1], E. Dekker[1], [1]Depts of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, the Netherlands, [2]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, the Netherlands, [3]Dept of Gastroenterology and Hepatology, Radboud Medical Center, Nijmegen, The Netherlands, [4]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands, [5]Dept of Pathology, Academic Medical Center, University of Amsterdam, the Netherlands, [6]Dept of Gastroenterology and Hepatology, Haga Teaching Hospital, The Hague, The Netherlands, [7]Dept of Gastroenterology and Hepatology, Antonie van Leeuwenhoek Hospital, The Netherlands, [8]Dept of Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands

Hyperplastic polyposis syndrome (HPS) is believed to be associated with an increased colorectal cancer (CRC) risk. However, the risk of developing CRC in a large HPS cohort during a clearly described follow-up period of multiple years has not been reported. Hence, a causal relationship between HPS and CRC cannot be made by default. The aims of this study were to assess the cumulative risk of developing CRC during follow-up in the largest HPS cohort described thus far and to examine a possible association with frequency and interval of surveillance endoscopies. Databases of 7 medical centers were searched for patients satisfying the criteria for HPS (WHO) who were retrospectively analysed in this study. Endoscopy reports and corresponding histopathology reports were collected to evaluate the length, interval and frequency of endoscopic surveillance and to derive information regarding polyp characteristics. Information regarding CRC was examined by evaluating endoscopy and histopathology reports made at the time of CRC diagnosis and histopathology reports of colon resection specimens. In this study, 77 patients with HPS with a median follow-up period of 2.8 years (range: 0.2-20.8) were included. During surveillance, 1984 polyps were identified: 1407(71%) hyperplastic polyps (HPs), 302(15%) serrated adenomas (SAs), 273(14%) adenomas and 2 admixed polyps. SAs and adenomas were identified in 52% and 69% of patients, respectively. In 27(35%) patients, CRC was detected of which 22 at initial endoscopy. Five (6.5%) patients developed CRC after the diagnosis HPS was made during a median follow-up time of 1.3 years (0.4-6.7) and a median of 3 previous surveillance endoscopies (range: 2-4). In these patients with an interval CRC, the median interval between the last surveillance endoscopy and CRC detection was 11 months (range: 4-43). The cumulative risk of developing an interval CRC under surveillance was 7% at five years and 16% at ten years. In 4/5 patients with interval carcinomas CRC was detected within a HP (3/4) or SA (1/4). In patients with interval carcinomas, 4/5(80%) had SAs and multiple polyps (≥30) compared to only 15/72(21%) patients without an interval carcinoma (p=0.01).

Conclusions: HPS is causally related with CRC development. Moreover, despite regular surveillance endoscopies, 6.5% of HPS patients in this study developed CRC. The presence of SAs and multiple (≥30) polyps seem to be associated with CRC development in HPS. Future prospective studies are required to assess the risk of polyp progression in HPS and to determine the optimal surveillance and treatment protocol for these patients.

Stated willingness-to-be-screened for colorectal cancer or not: the participation paradox

L.G.M. van Rossum[1], M.G.H. van Oijen[1], A.L.M. Verbeek[2], R.J.F. Laheij[1], J.B.M.J. Jansen[1] [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [2]Dept of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

In a previous study we observed, that over 70% of a Dutch population reported to be willing-to-be-screened in a questionnaire. However what proportion of subjects who reported to be willing to be screened will actually participate in screening and what proportion of subjects who reported to be unwilling will participate?
In October 2005, from a Dutch population of 5,219 individuals between 50 and 75 years of age, a random selection of 500 subjects was approached with a questionnaire containing 46 items, including one item regarding willingness-to-be-screened ('yes', 'possibly', 'no', 'don't know') with an unspecified 'easy faecal test'. In October 2006 all subjects of the 500 still between 50 and 75 years of age and at average risk for colorectal cancer were invited for colorectal cancer screening with an immunochemical faecal occult blood test (iFOBT, OC-Sensor®). Participation proportions of prior willing and unwilling subjects were compared with risk ratios (with 95% confidence intervals). Of the initially 500 invited subjects, 42 had to be excluded; 29 were older than 75 years of age in October 2006, 2 were diagnosed with colorectal cancer, 3 had a recent bowel investigation and 8 for other reasons. Overall 74% responded to the questionnaire: 86% of the responders participated in the iFOBT screening compared to 41% of the non-responders (RR 2.2 95% CI 1.7-2.7). Participation of responders who reported willing ('yes' or 'possibly') to be screened was 89%, compared to 73% of responders who reported unwilling to be screened (RR 1.2 95%CI 1.0-1.4). Other factors associated with participation were 'awareness' of colorectal cancer and screening related issues (RR 1.2 95%CI 1.1-1.4), age below 60 years (RR 1.1 95%CI 1.0-1.3) and perceived relatively good health (RR 1.1 95% CI 1.0-1.3). Only relative perceived health seemed to be a factor predicting participation independent of willingness-to-be-screened.
In conclusion, previously reported willingness-to-be-screened predicts actual participation in colorectal cancer screening with iFOBT. However participation was also high in subjects who previously reported unwilling to be screened. Reasons for the apparent paradox remain unclear; moreover participation in non-responders to the questionnaire proved to be much lower than participation in unwilling responders.

Two samples for immunochemical fecal occult blood tests in screening for colorectal cancer: implementation and participation

L.G.M. van Rossum[1], M.G.H. van Oijen[1], J. Schuurmans[2], A.L.M. Verbeek[3], R.J.F. Laheij[1], J.B.M.J. Jansen[1], [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [2]Dept of Palliative care, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [3]Dept of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

A previous colorectal cancer (CRC) screening study was performed with a single immunochemical faecal occult blood test (iFOBT). In a few other studies an increased sensitivity for CRC of iFOBT screening with two samples on separate days was observed. However more testing days might decrease participation, as has been observed in screening with guaiac FOBTs, for which participants sample on 3 separate days. We aimed to compare the difference in participation between one day and two days of iFOBT testing and between screening with an without input of the general practitioner (GP).
As in the original study, we designed a pilot study with average risk persons aged 50-75 years, invited for iFOBT (OC-Sensor®) screening. A written invitation was sent by the GP, who also applied exclusions (e.g. prior colonoscopy or CRC). Persons were randomly allocated to perform two iFOBTs on the same day (one-day group) or on separate days (two-day group). Data from the original study were compared with data from the pilot. We calculated rate differences with 95% confidence intervals (95%CI). In the original study 5283 persons were invited to perform an I-FOBT, compared to 884 in the pilot (442 one day and 442 two days). The GP excluded 3.6% of the subjects. In the original study 3286(62%) participated compared to 302(68%) in the one-day group. The 6.1% difference (95%CI 1.4-10.8) can probably be accounted to the input of the GP, but not only to the exclusions. Analysis according to intention-to-screen (i.e. including exclusions) a difference of 3.7% (95%CI -0.9% to 8.4%) remained. The effect of the GP was also observed in colonoscopy adherence: In the original study only 83% of iFOBT positives were adherent, compared to 98% in the pilot ($p<0.05$). Participation in the pilot's two day group was 1.6% (95% CI -3.1 to 6.3) higher than participation in the original study. However participation in the pilot's two-day group was 4.5% (95%CI -1.7% to 10.8%) lower, than in the pilot's one-day group.
In conclusion involving general practitioners in the invitation for CRC screening will increase participation, both according to per-protocol and intention-to-screen analysis. Two days of iFOBT testing reduces participation in colorectal cancer screening substantially compared to one day testing. Further study of two days of iFOBT testing should be analyzed according to intention-to-screen, as an increase in sensitivity might be cancelled out by a decrease in participation.

High Definition Chromoendoscopy for the detection of rectal Aberrant Crypt Foci

G. Delconte[1,3], M.E.I. Schipper[2], F.P. Vleggaar[1], T.Q. Nguyen[2], L. Laghi[3], A. Repici[3], A. Malesci[3], G.J.A. Offerhaus[2], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology and [2]Pathology, University Medical Center Utrecht, The Netherlands, [3]Dept. of Gastroenterology, IRCCS Istituto Clinico Humanitas, University of Milan, Italy

Background & aim: Aberrant crypt foci (ACF) have emerged as lesions associated with colorectal adenoma and cancer development. High magnification chromoendosocpy (HMC) allows in vivo ACF identification in colorectal mucosa. Using HMC, several inconsistencies such as different rates of agreement between endoscopic and histological findings have been reported. We speculate that this can be attributed to the non-standardized use of this technique. We therefore investigated a more standardized technique, high-definition chromoendscopy (HDC), for the identification of rectal ACF. Methods: Total colonoscopy involving rectal chromoendoscopy was performed using an Olympus CF-H180L and 0.2% methylene blue. An ACF was endoscopically defined as a cluster of crypts, that stained darker, was rounded, had larger diameters, and was slightly elevated compared to the normal mucosa. Biopsies obtained from each ACF were histologically evaluated. Results: Fifteen patients referred for screening underwent total colonoscopy (mean age 61.7 SD ±10.2). In total, 34 rectal ACF were identified, with at least one ACF being detected in all patients. Sixteen colorectal lesions including 12 tubulovillous adenomas, 3 advanced tubulovillous adenomas and one invasive cancer were also detected. The mean number of ACF in the 4 patients with advanced adenoma or cancer and in the 5 patients with non-advanced adenoma was 2.5 ±1.0 and 1.2 ±0.4 (p=0.034), respectively. Moreover, a correlation was found between age and increasing number of rectal ACF (r=0.45; p 0.009). Five (14.7%) ACF could not histologically be evaluated because of lymphoid follicles near the lesion (n=3) or damaged tissue (n=2). In the remaining 29 ACF, 5 (17%) had a normal epithelial structure, whereas 11 (38%) and 13 (45%) ACF were classified as non-dysplastic, non-hyperplastic and as non-dysplastic, hyperplastic, respectively. In none of the ACF, dysplastic foci were identified.
Conclusion: This is the first study reporting the use of HDC for the detection of rectal ACF. Consistently with data from the literature, we found a higher incidence of rectal ACF in older patients and in patients with advanced adenoma/carcinoma.

The role of bone morphogenetic protein signaling and transforming growth factor β signaling and their components in colorectal cancer

R.J. Jacobs[1], L.L. Kodach[1], N.F. De Miranda[2], D.W. Hommes[1], G.R. van den Brink[1], H. Morreau[2], J.C. Hardwick[1], [1]Dept of Gastroenterology & Hepatology and [2]Dept of Pathology, Leiden University Medical Center, Leiden, The Netherlands

Signaling pathways play a central role in tumorigenesis and may be used in the future as independent survival prognosticators. Bone Morphogenetic Proteins (BMPs) are members of the TGFβ superfamily of multifunctional cytokines. We have shown that intact BMP signaling is important for normal homeostasis of the intestinal epithelium and that loss of BMP signaling correlates tightly with progression of adenoma to cancer and occurs relatively early during cancer progression. Although in the early stages of cancer TGFβ exerts a tumor suppressor function, there is considerable evidence that in later stages activity of this pathway correlates with worse clinical outcome. Whether specific elements of the BMP pathway can be used as predictive markers for survival of patients is not known.
In this study we aimed to investigate whether activity of BMP and TGFβ pathways could be assessed by nuclear receptor phosphorylated SMADs and could predict survival outcome in patients with CRC. We used a large array of 250 colon cancers and performed immunohistochemical (IHC) analysis of BMP pathway components by BMP receptor 2 and pSMAD1/5/8, and a specific TGFβ signaling component: pSMAD2/3. We also assessed the expression of the key signal transduction element SMAD4, central to both TGFb and BMP pathways. The IHC staining was scored blinded, quantifying activity of BMP signaling by nuclear localization of SMAD4 and nuclear localization of pSMAD1/5/8 and activity of TGFβ signaling by nuclear localization of SMAD4 and pSMAD2/3 . The correlation between receptor phosphorylated SMAD staining, Dukes classification and clinical outcomes, including disease-free survival and overall survival, was analyzed with SPSS version 16 for Windows. The BMP pathway is inactivated, as judged by nuclear pSMAD1,5,8 expression, in 65% of CRCs and this correlates with BMPR2 and SMAD4 loss ($p<0.010$, Fisher's Exact Test). Analysis of Kaplan-Meier survival curves for all BMP pathway components revealed a significant difference in nuclear SMAD4 expression ($p<0.04$) between patient groups. At an early stage (Dukes A+B) loss of BMP signaling is associated with worse 5 year outcome, while, on the contrary, at a later stage (Dukes C+D) patients with active BMP signaling have worse survival.
In conclusion: our data suggest that BMPs play a dual role in colon cancer progression similar to TGF-β.

Higher cut off values for FIT in CRC-screening: less colonoscopies, same detection rates for curable cancers

F.A. Oort[1], J.S. Terhaar sive Droste[1], R.W.M. van der Hulst[2], H.A. van Heukelem[3], R.J.L.F. Loffeld[4], I.C.E. Wesdorp[5], I. Ben Larbi[1], S.L. Kanis[1], M. Neerincx[1], M.Räkers[1], V.M.H. Coupe[6], G.A. Meijer[7], C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Slotervaart Hospital, Amsterdam, [4]Internal Medicine, Zaans Medical Center, Zaandam, [5]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [6]Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [7]Pathology, VU University Medical Center, Amsterdam

The Fecal Immunochemical Test (FIT) is a next generation Faecal Occult Blood Test (FOBT)and has been proposed as screening tool for Colorectal Cancer(CRC). The goal of screening is to detect CRC in an early, curable stage (i.e. Dukes A+B). Some variants of FITs produce a quantitative outcome which allows for adjusting the threshold for calling a test positive. A higher cut off value will result in less positive tests and subsequently less screenees referred for colonoscopy and thus less strain on the endoscopic capacity. However it is unknown whether a higher cut off value will impair the detection rate of (curable) colorectal cancers. The aim of this project was to assess the effect of a higher cut off value of a quantitative FIT on the positivity rate and on the detection rate of curable early stage CRC's. For this all patients aged ≥18 years and scheduled for a colonoscopy in 5 participating hospitals were asked to perform a FIT (OC sensor®, Eiken chemical Co, Japan) on one bowel movement the day prior to colonoscopy. Tests of all patients were assessed using cut-off values of 50, 100, 150 and 200 ng haemoglobin per ml. For analysis of all tests, the desktop analyser "OC-SENSOR μ" was used. Test results were compared with the gold standard colonoscopy. Results: In 1,897 individuals, who underwent total colonoscopy, 62 cases of colorectal cancer(3.3%) were identified. 28/62 patients were diagnosed with early stage (Dukes A+B) colorectal cancer and 31 patients with late stage(Dukes C+D). Three rectal cancers could not be accurately staged due to the effects of neo-adjuvant radiotherapy. In our total population of 1,897 individuals, the OC sensor® was positive in 8.8%, 9.8%, 11.4% and 14.0% at cut offs of 200, 150, 100, and 50 ng/ml, respectively. The detection rates for early stage CRC's ranged from 75.0% to 78.5% depending on the threshold of FIT.
Conclusions: A higher cut off value for FIT can reduce strain on colonoscopy capacity with only a slight decrease in detection rates of curable, early stage, colorectal cancers.

Nicotine enhances phagocytosis in macrophages via recruitment of Dynamin-2 to the phagocytic cup

E.P. van der Zanden[1], G.E. Boeckxstaens[1,2], W.J. de Jonge[1], [1]Dept of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, Catholic University Leuven, Leuven, Belgium

The cholinergic nervous system attenuates the production of proinflammatory cytokines by macrophages and inhibits inflammatory processes. We previously showed that vagus nerve signaling not only blunts inflammation in macrophages, but also enhances their phagocytic capacity. Here, we study the molecular pathways involved in this process. The spleen macrophage cell line MF4/4 and primary peritoneal macrophages were pre-treated with nicotine (0-1μM) and challenged with Zymosan (5P/Cell). After 5 or 10min stimulation, membrane proteins were isolated using the proteome cell compartment kit (Qiagen) and prepared for Western Blot. Whole cell lysates for immunoblotting were isolated after 30min. For Rac1 GTPase activity assays, plates were coated with Rho-family effector proteins, to which the active GTP-bound form of Rac can bind. Cells were grown on glass slides (Nuncbrand), pretreated with nicotine, challenged with FITC-labeled Zymosan and phagocytosis was allowed for 5min. Cells were stained with antibodies against Dynamin-2 and F-actin and slides were analyzed using confocal laser scanning microscope. Recruitment to the phagocytic cup was scored by analysis of 80-100 cells in a blinded fashion.In peritoneal and MF4/4 cells, nicotine enhanced phagocytic uptake of Zymosan particles (up to 2.5 fold). Exposure to Zymosan stimulated pathways that are known to be involved in the phagocytic process; phosphorylation of PI-3K (10% vs 90% of total PI3K control vs Zymosan), Akt (10% vs 40% of total P38 in control vs Zymosan) and p38 MAP kinase (1% vs 35% of total P38 in control vs Zymosan). However, the phosphorylation of PI3K, Akt, or p38 MAPK was not affected by nicotine. In addition, nicotine did not enhance Rac1 GTPase activity. On the other hand, pretreatment with nicotine augmented the recruitment of the large GTPase Dynamin-2 towards the phagocytic cup and strongly stimulated cup formation ($p>0.03$, as quantified by confocal microscopy). This observation was corroborated by Western analysis of membrane protein: nicotine treatment led to a significant ($p>0.05$) increase in membrane-associated Dynamin-2 after 5min (increase to 190% of control) and 10min (increase to 160% of control) of Zymosan treatment.
Conclusion: Our data show that cholinergic agonists induce phagocytosis in splenic and peritoneal macrophages. This mechanism involves nAChR-mediated enhancement of Dynamin-2 recruitment to the phagocytic cup, rather than PI3K, Akt or p38 signaling pathways.

Differential TLR ligation of intestinal epithelial cells drives an inflammatory or regulatory T_h1 response in vitro

L.E.M. Willemsen[1], S. de Kivit[1], E. van Hoffen[2], N. Korthagen[1], J. Garssen[1], [1]Pharmacology and Pathophysiology, UIPS, Utrecht University, [2]Dermatology/Allergology, University Medical Center, Utrecht, the Netherlands

Emerging evidence points out the importance of intestinal epithelial cells in regulation of mucosal immune responses. In diseases like inflammatory bowel disease (IBD) and food allergy, tolerance towards the intestinal flora or dietary antigens is broken, resulting in local pathological inflammation. Under inflammatory conditions Toll-like receptor (TLR) expression by intestinal epithelial cells (IEC) is increased. Therefore we assessed potential modulation of the effector immune response by epithelial cells upon TLR ligation. In a transwell model human intestinal IEC (HT-29) were apically exposed to TLR2, TLR4 or TLR9 ligands and co-cultured with CD3/CD28-activated healthy donor peripheral blood mononuclear cells (PBMC). Mediator release in the basolateral compartment by PBMC or HT-29 cells was measured by means of ELISA. Flow cytometry was used to analyze the immune cell phenotype of T cells and monocytes and to assess intracellular cytokine expression. Neutralizing antibodies were used to determine epithelial mediator function. Upon co-culture with activated PBMC, HT-29 cells enhanced the surface expression of TLR2, TLR9 ($P<0.05$) and TLR4 ($P<0.01$). TLR4 ligation of HT-29 cells resulted in enhanced production of IL-6, TNF-α and epithelial derived MDC ($P<0.05$) and decreased numbers of $Foxp3^+$ regulatory T cells ($P<0.05$). Neutralization of epithelial derived TSLP abrogated TLR4-induced TNF-α secretion ($P<0.05$). In contrast, TLR9 ligation of HT-29 cells enhanced the IFN-γ and IL-10 secretion ($P<0.05$) and increased the numbers of activated T_h1 cells ($P<0.01$), while reducing IEC-derived mediators. In addition, CD14 expression on monocytes was reduced ($P<0.01$) which coincided with enhanced intracellular IL-10 ($P<0.05$) and decreased TNF-α ($P<0.01$) expression. In general, the TLR2 ligand had no effect. Conclusions: TLR4-induced epithelial derived TSLP supports an inflammatory type effector immune response by increasing TNF-α production. In contrast, TLR9-ligation on IEC supports a regulatory type immune response by enhancing IFN-γ and IL-10 production by T_h1 cells and monocytes respectively, whilst reducing chemoattractant secretion by IEC. Hence, Toll-Like Receptor ligation of IEC may potentially be involved in driving inflammatory or regulatory effector responses in the intestinal mucosa.

Hepatitis B virus inhibits TLR9-induced plasmacytoid dendritic cell function

A.M. Woltman, M.L. Op den Brouw, P.J. Biesta, H.L.A. Janssen, Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, the Netherlands

Chronic Hepatitis B virus (HBV) infection is due to an inadequate anti-viral immune response. Toll like receptor (TLR) triggering of plasmacytoid dendritic cells (pDC) is a key step in defense against viruses, leading to the mass production of interferon-α (IFNα). However, HBV seems to induce a weak IFN response in animal models, and pDC of chronic HBV patients are impaired in their IFNα production. This resulted in our hypothesis that HBV is a weak stimulator and even actively interferes with IFNα production by pDC and thereby hampers the induction of an effective anti-viral immune response. Therefore, we examined the effect of HBV on the function of pDC in vitro. Total PBMC or purified pDC from healthy donors were stimulated with TLR9-stimuli CpG-A (10 µg/ml) or HSV (moi 10), or TLR7-stimuli Loxoribine (Lox 0.4 mM) or Influenza (moi 0.2) with or without HepG2.215-derived HBV particles (0.08-2500 particles/cell), or single HBV proteins HBsAg, HBeAg or HBcAg (0-10 µg/ml). IFNα, TNFα and IL-8 production were assessed by intracellular flow cytometry (5h) and specific ELISA (24h). Cell viability (Annexin-V, 7AAD) and expression of maturation markers were also determined by flow cytometry.
In contrast to Influenza or HSV, HBV did neither induce pDC activation, as assessed by the expression of CD80, CD86, CD40 or HLA-DR, nor cytokine production by pDC. CpG stimulated PBMC showed IFNα and TNFα producing pDC, which were dose-dependently reduced by HBV (to 80% inhibition). CpG-induced IL-8 was hardly affected by HBV. Although less pronounced, HBV also significantly reduced CpG-induced IFNα/TNFα production and upregulation of CD40, CD80 and CD86 of purified pDC. Addition of CD14+ cells to purified pDC enhanced the number of IFNα producing pDC towards levels found in total PBMC cultures and increased the sensitivity to HBV. Analyzing the effects of HBV proteins revealed that HBeAg and especially HBsAg are involved in HBV-mediated suppression of pDC function, without affecting cell viability. Surprisingly, Lox-induced cytokine production by pDC was not affected by HBV.
Thus, in contrast to other viruses, HBV does not activate pDC. Moreover, HBV inhibits TLR9-induced activation and cytokine production by pDC via a direct effect on pDC that can be further enhanced by monocytes. These data demonstrate that HBV is not only a weak inducer of innate immunity, but also directly interferes with pDC function. This immune escape mechanism may contribute to HBV persistence.

The genetically modified *Lactococcus lactis* OVA modulates T-cells through an antigen-specific effect on dendritic cells

L. Huibregtse[1], H. Braat[2], T.M. van Capel[3], V. Snoeck[4], L. Boon[5], T. van der Poll[1], P. Rottiers[4], S.J.H. van Deventer[6], M.L. Kapsenberg[3] and E.C. de Jong[3], [1]Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept of Cell Biology & Histology, and Dermatology, Academic Medical Center, The Netherlands, [4]Dept for Molecular Biomedical Research, VIB, Ghent, Belgium, [5]Biosceros BV, Utrecht, The Netherlands, [6]Dept of Gastroenterology and Hepatology, Leids Universitair Medisch Centrum, Leiden, The Netherlands

Introduction: Obtaining antigen-specific immune suppression is an important goal in developing treatments of autoimmune, inflammatory and allergic gastro-intestinal diseases. Previously we have shown that mucosal delivery of ovalbumin (OVA) by genetically modified Lactococcus lactis (LL-OVA) induces suppression of local and systemic inflammatory OVA specific T-cell responses in OVA-TCR transgenic mice (DO11.10). The suppression is mediated by the induction of 'adaptive' $CD4^+CD25^-$ regulatory T-cells which are critically dependent on TGF-β. Here, we further wanted to unravel the regulatory mechanism involved. Methods: To determine the role of IL-10 and/or TGF-β experiments were performed in the absence or presence of neutralising antibodies in vivo and in vitro. Furthermore we compared the Lactococcus lactis (LL) antigen expression versus LL plus soluble antigen and evaluated the ability to induce OVA-specific tolerance in OVA TCR transgenic mice (DO11.10). Tolerance induction was assessed by analysis of DTH responses and OVA-specific proliferation of splenocytes. In addition phenotypical and functional analysis of the splenic CD11c+ dendritic cell population and its antigen presenting capacity was accessed by FACS analysis on expression markers and proliferation assay. Results: Bacterial expression of antigen is more efficient in the induction of antigen specific suppression than LL plus soluble antigen seen by a significant decreased DTH ($2x10^{-2}$ vs $10x10^{-2}$ mm, respectively $p=0.0047$). Moreover our data strongly suggest a combined regulatory mechanism comprising both IL-10 and TGF-β, as in vivo neutralisation of both cytokines breaks down oral tolerance as well as cancelled out the decreased proliferative capacity of bulk splenocytes in vitro. Finally, oral supplementation of LL-OVA decreases the antigen presenting capacity of CD11c+ splenic DC and significantly alters their phenotype by an increase of CD103 and decrease of CD86 and MHCII expression.
Conclusion: Mucosal antigen delivery by oral administration of genetically engineered L. lactis leads to antigen-specific tolerance, mediated by dendritic cells and critically dependent on both IL-10 and TGF-β. This approach can be used to develop effective therapeutics for systemic and intestinal immune-mediated allergic and inflammatory diseases.

The mannose receptor as a putative hepatitis B virus receptor regulating intrahepatic dendritic cell function

M.L. Op den Brouw[1], R.S. Binda[1], T.B.H. Geijtenbeek[2], H.L.A. Janssen[1] and A.M. Woltman[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam,, [2]Dept. of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

Chronic infection with hepatitis B virus (HBV) is the result of an inadequate anti-viral immune response. Dendritic cells (DC) play a key role in immune regulation. DC of chronic HBV patients are dysfunctional and can therefore contribute to HBV persistence. Recently, we showed that myeloid DC (mDC) display an impaired function after exposure to HBV surface antigen (HBsAg) in vitro. Whether HBsAg also interferes with DC function in vivo is not known. Here, we investigated the HBsAg internalization route and the presence of HBsAg-positive DC in chronic HBV patients in vivo. HBsAg (1 µg/ml) uptake and lectin expression were studied with isolated $CD1c^+$ peripheral blood-derived mDC from healthy controls. The presence of HBsAg and the expression of mannose receptor (MR) on peripheral blood and percutaneous needle liver biopsy-derived mDC from 14 chronic HBV patients and 10 patients with non-HBV related liver disease were investigated by (intracellular) flow cytometry.In vitro uptake of HBsAg was hardly detectable in freshly isolated peripheral blood-derived mDC, but resulted in 27±2% uptake at 18h of culture. The glycosylation pattern of HBsAg pointed towards the involvement of C-type lectins in its uptake. RT-PCR and FACS analysis on several C-type lectins revealed a significant upregulation of MR on mDC upon culture. Both the mannose-specific lectin inhibitor mannan and a neutralizing anti-MR antibody significantly reduced HBsAg-uptake by mDC. To test the possible involvement of MR in HBsAg uptake by mDC in vivo, mDC of chronic HBV patients were examined. FACS analysis showed that mDC in blood express hardly any HBsAg and only low levels of MR, while liver-derived mDC showed 4-fold more MR expressing mDC ($p<0.0001$). Also more HBsAg-positive mDC were detected in liver biopsies than in blood (range: 0.1-14.4 vs 0.2-3.8 $\%HBsAg^+$ mDC; $p<0.05$), which significantly correlated with HBsAg expression in hepatocytes. HBsAg-positive cells were not observed in non-HBV patients. Interestingly, a positive correlation was found between HBsAg positivity and MR expression level in both liver- and blood-derived mDC.

In conclusion, these data show a role for the mannose receptor in HBsAg uptake by mDC both in vitro and in vivo. The presence of HBsAg in intrahepatic mDC, together with the immune regulatory role of HBsAg on mDC as shown before, suggests that HBV actively interferes with DC function. This immune regulatory role of HBV may well contribute to HBV persistence.

Differences in disease progression of DSS induced colitis in C57BL/6 and BALB/c mice

B.J. Olivier[1], M.J. Greuter[1], M. Knippenberg[1], G. Bouma[2], G. Kraal[1] and R.E. Mebius[1], [1]Dept of Molecular Cell Biology & Immunology and [2]Dept of Gastroenterology, VU University Medical Center, Amsterdam, the Netherlands

The dextran sodium sulphate (DSS) mouse model is a commonly used model for colitis. The severity of disease differs in C57BL/6 and BALB/c mice, since BALB/c mice loose less weight and tend to recover more rapidly when compared to C57BL/6 mice. Here we addressed the differences in pathology by combined analysis of gene expression and immunohistology. To our surprise, the formation of tertiary lymphoid structures occurred more rapidly in BALB/c vs C57BL/6 mice. Colitis was induced in C57BL/6 and BALB/c mice by administration of DSS in drinking water (for 5-7 days). Small intestine and colon where removed at two time points i.e. acute colitis (7 days) and chronic colitis (35 days). Samples were frozen in tissue-tek for immunofluorescence analysis. Whole tissue was placed in trizol, homogenised and used for subsequent real time RTPCR analysis. BALB/c mice loose weight from day 4–7, while C57BL/6 mice loose weight from day 6-11, after the start of DSS administration. Immunoflourescence analysis of the colon at day 7 reveals that BALB/c mice have already formed tertiary lymphoid structures at this time point whereas the C57BL/6 mice have not. Further analysis reveals that these tertiary lymphoid structures contain a large number of FoxP3$^+$ cells within the T cell area, as well as IgA producing cells within the B cell area of these structures. Interestingly, FoxP3 and IgA production are influenced by retinoic acid (RA). Retinaldehyde dehydrogenases are enzymes involved in the conversion of Vitamin A to RA. Further real time analysis revealed an increased expression of retinaldehyde dehydrogenases in BALB/c intestine when compared to C57BL/6. BALB/c mice form tertiary lymph node structures earlier during colitis than C57BL/6 which coincides with recovery of the BALB/c. These tertiary lymph node structures contain FoxP3$^+$ cells and IgA producing cells which could serve to suppress inflammation and help clear antigen respectively. The mechanisms by which these tertiary structures are formed are under study, since our data suggest that formation of tertiary lymphoid structures in colitis may be beneficial for the animal.

Ribavirin is anti-fibrotic in a non-viral rat model for liver fibrosis

R.A Hannivoort, S. Dunning, J. Wallinga, K. van Pelt, M. Buist-Homan, K.N. Faber, H. Moshage, Dept. Gastroenterology and Hepatology, University Medical Center Groningen, the Netherlands

Background: Ribavirin, a nucleoside analogue, is used for treatment of hepatitis C virus (HCV) infection in combination with PEG-interferon-α (PEG-IFNα). The antiviral properties of both ribavirin and PEG-IFNα have been extensively documented. PEG-IFNα also has antifibrotic effects independent of viral clearance by inhibiting hepatic stellate cell (HSC) activation. In contrast, the effect of ribavirin on activated HSCs and liver fibrogenesis has never been studied. Ribavirin is a potent inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH). IMPDH inhibitors reduce proliferation in several cell types, including fibroblasts and leukaemia cells, and decrease renal fibrosis in nephrotoxic and immune-mediated kidney disease. Moreover, ribavirin monotherapy has been described to improve liver histology without reducing viral load. Aim: To investigate whether ribavirin inhibits HSC proliferation in vitro and whether ribavirin ribavirin reduces fibrosis in a non-viral in vivo model for liver fibrosis. Methods: In vitro: Culture-activated rat HSCs were treated with ribavirin in the presence of 20% serum. Proliferation was measured using a BrdU incorporation assay. Apoptosis and necrosis were visualized by Acridine orange and Sytox green staining. Bile duct ligation (BDL) was used as a model for liver fibrosis. Rats were administered ribavirin (75 mg/kg/day) or vehicle for 10 days. Serum markers for liver injury (ASAT, ALAT) and cholestasis (bilirubin) were measured. mRNA was isolated from total liver for real-time RT-PCR. Results: Ribavirin dose-dependently inhibited serum-induced HSC proliferation (up to 80% reduction at 600 μM), without inducing cell death. BDL-rats showed strongly induced mRNA expression of α-smooth muscle actin (α-SMA), TGF-β and collagen type 1 and increased serum markers for liver injury and cholestasis. Ribavirin-treated BDLrats had significantly lower α-SMA (59% decrease), TGF-β (51% decrease) and collagen type 1 (63% decrease) mRNA levels than BDL-rats receiving vehicle, without change in animal weight or serum markers.
Conclusion: Ribavirin inhibits proliferation of activated HSCs in vitro and decreases mRNA markers for fibrosis in a non-viral in vivo model for liver fibrosis. We suggest that ribavirin may improve liver histology in HCV patients independent of viral clearance, by direct inhibition ofHSC proliferation. Moreover, ribavirin may have therapeutic potential in non-viral fibrotic liver diseases.

Altered expression of fibroblast growth factor 15 (FGF15) in acute pancreatitis: potential consequences for bacterial translocation and infection risk

R.M. Nijmeijer[1], L.M.A. Akkermans[1], F.G. Schaap[2], P.L. Jansen[2], J. Terlinde[3], A. Verheem[1], A.B.A. Kroese[1,4], M.G.H. Besselink[1], M. Schipper[5], H.G. Gooszen[1], K. van Erpecum[3], [1]Dept of Surgery, University Medical Center Utrecht, The Netherlands, [2]Dept of Gastroenterology and Hepatology, AMC Liver Center, University of Amsterdam, The Netherlands, [3]Dept of Gastroenterology, University Medical Center Utrecht, The Netherlands, [4]Institute for Risk Assessment Sciences, Utrecht, The Netherlands, [5]Dept of Pathology, University Medical Center Utrecht, The Netherlands

Intestinal bile salts protect against bacterial overgrowth and translocation. The underlying mechanism of this beneficial effect resides in activation of the ileal bile salt nuclear receptor Farnesoid X Receptor (FXR) and upregulation of target genes angiogenin 1 (ANG1), iNOS, CAR12 and IL-18 that are involved in antibacterial defense. Additionally, FXR activation leads to expression and secretion of the ileal hormone fibroblast growth factor 15 (FGF15; human orthologue FGF19), which probably signals the end of postprandial state with inhibition of pancreatic secretion. Since in acute pancreatitis (AP), the enterohepatic bile salt circulation may be altered, we explored potential changes of the FXR-FGF15 axis in complementary mouse and human models. AP was induced in male C57BL/6 mice by hourly intraperitoneal injections of cerulein (50 µg/kg, for 10 hours). Control mice (n=10) were injected with saline. Mice were terminated 24 hours (early phase, n=10) or 72 hours after start of induction (late phase, n=10). To confirm AP, histology of pancreas samples was done. Decreased integrity of the mucosal barrier in the ileum was assessed by Ussing chamber experiments. Ileum mRNA expression of FXR and FXR-target genes was assessed by real-time PCR. Plasma FGF19 levels were determined by ELISA in 15 predicted severe AP patients during continuous enteral nutrition and compared to 28 healthy volunteers. In the mouse model, both FGF15 and FXR-intermediate SHP expression were decreased more than twofold (P=0.004 and P=0.009 respectively) in the early but not late phase of AP. Also ANG1 was downregulated in early phase (P=0.001). No change in expression of FXR was found. ASBT, iNOS, IL18, and CAR12 did not show any differences in both early and late phase of AP. Histology confirmed AP in the early phase, but in the late phase there were clear signs of recovery. Electrical resistance of the ileum was decreased in the early phase (22 ± 7 vs. controls: 44 ± 8 Ω/cm^2, P<0.001). Plasma levels of FGF19 in AP patients were significantly lower than in healthy volunteers in the postprandial state (0.39ng/ml vs. 0.71ng/ml, P=0.001). In the mouse model, ileal FGF15, SHP and ANG1 are decreased in the early phase of acute pancreatitis. Similarly, FGF19 plasma levels are decreased in AP patients. These results indicate a potential role of FXR and FXR target genes in severity of AP and the occurrence of bacterial translocation and subsequent infectious complications in AP.

β-Klotho acts as a chaperone regulating FGFR4 glycosylation and activity

V. Triantis[1], E. Saeland[2], N. Bijl[3], R.P. Oude-Elferink[1], P.L.M. Jansen[1], [1]AMC Liver Centre, Amsterdam, [2]Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, [3]Dept of Biochemistry, Academic Medical Center, Amsterdam, the Netherlands

Endocrine fibroblast growth factors (FGF19, FGF21 and FGF23) have been shown to behave more as circulating hormones (regulating bile acid, lipid and phosphate homeostasis respectively) than as canonical growth factors. All three of them bind to the same receptors as classical FGFs, however the outcome of the activation is shifted towards metabolism. Endocrine FGF activity is regulated at multiple levels, including growth factor expression, receptor binding affinity but most importantly by the presence of two proteins, namely Klotho and β-Klotho.

The proposed model incorporates these two proteins as co-receptors in the FGF signaling pathway. The Klothos interact with various FGF receptors (FGFRs) to enhance signaling from FGF19, 21 and 23. The action of the Klotho proteins seems to be redundant since they can substitute for each other. This hints towards a more universal role of the Klothos in FGF signaling. Therefore, we wanted to investigate in detail the role of the β-Klotho in FGF19 signaling.

Transfections in 293 T HEK cells show that β-Klotho is an Endoplasmic Reticulum (ER) resident protein that affects the glycosylation pattern of FGFR4, and acts more as a chaperone rather than a co-receptor for FGFRs on the plasma membrane. β-Klotho seems to bind and lead the core glycosylated form of FGFR4 from the ER to proteosomal degradation, leaving only the terminally glycosylated form to reach the cell membrane. Terminally glycosylated FGFR4 seems to be the active form during FGF19 signaling, as shown by FGFR4 phosphorylation studies but also by employing terminal glycosylation inhibitors. When 293 T HEK cells were transfected with FGFR4 constructs and treated with FGF19, only the terminal glycosylated FGFR4 was phosphorylated upon triggering. In addition, when HepG2 cells were treated with Brefeldin A or Deoxymannojirimycin (inhibitors of terminal glycosylation), they lost responsiveness to FGF19 as shown by CYP7A1 levels. Blocking proteasome degradation reversed the effect of β-Klotho on the glycosylation pattern of FGFR4, showing that β-Klotho-FGFR4 binding results in FGFR4 proteosomal degradation.

Conclusively, we show that terminal receptor glycosylation is the key determinant of FGF19 activity and β-Klotho serves as a chaperone, eliminating the inactive, core glycosylated form of FGFR4 from within the cell, rather than acting as a co-receptor on the plasma membrane.

Experimental steatosis treated with omega 3 fatty acids detected by ^{1}H-magnetic resonance spectroscopy

H.A. Marsman[1], S. Nienhuis[1], J. van Werven[2], A.J. Nederveen[2], F.J.W. ten Kate[3], M. Heger[1], J. Stoker[2], T.M. van Gulik[1], Dept of Surgery[1], Radiology[2], and Pathology[3], Academic Medical Center, University of Amsterdam, The Netherlands

Due to the obesity epidemic, NAFLD is becoming the most common chronic liver disease in the Western world. In patients undergoing major liver resection steatosis has been identified as an important risk factor. Furthermore, progression to NASH and ultimately cirrhosis poses a significant burden on liver donor waiting lists. Omega-3 fatty-acids decrease hepatic fatty-acid synthesis, by downregulating sterol element binding protein, and stimulate hepatic fatty-acid degradation, by upregulating peroxisome proliferator-activated receptors. To date, experimental studies have investigated prevention, but not reversal of steatosis by omega-3 fatty acids. The aim of this study was to treat hepatic steatosis in rats with omega-3 fatty acids and evaluate therapeutic response in vivo using 1H-magnetic resonance spectroscopy (1H-MRS). Steatosis was induced in male Wistar rats using a methionine/choline deficient diet during 3 weeks. Subsequently, rats received per gavage, either omega-3 (Omegaven), isocaloric normal fatty acids (Lipofundin), or 0.9% NaCl (n=5/group). Directly before, as well as 1 and 2 weeks after treatment, in vivo measurement of hepatic fat content was performed using a clinical 3.0 Tesla 1H-MRS. After 2 weeks treatment, histopathological steatosis percentage and lobular inflammation were evaluated and lipodemic analysis of livers was performed by gas chromatography. Blood samples were drawn for liver damage parameters (AST,ALT) and bilirubin levels. No differences in basal 1H-MRS measurements were found, whereas after 1 and 2 weeks of omega-3 treatment, hepatic fat content (1.3 ppm) was significantly decreased compared to rats receiving NaCl ($p=0.016$ and $p=0.032$, resp.) or control fatty acids ($p=0.029$ and $p=0.016$, resp.). Histopathological assessment of macrovesicular steatosis confirmed these results (%±SD): Omega-3 (31±15%) vs. control fatty acids (76±21%, $p=0.015$) and NaCl (80±16%, $p=0.008$). Liver-to-body weight ratio was significantly lower in omega-3-treated rats and an improved steatosis degree was associated with decreased lobular inflammatory foci. Furthermore, plasma AST:ALT ratio and bilirubin levels were significantly lower ($p<0.05$) in the omega-3 group. Lipodemic analysis of omega-3-treated livers showed significantly ($p<0.05$) decreased total hepatic fatty acids content, omega-6:3 fatty acids ratio, omega-3 product:precursor ratio and de novo lipogenesis (C16:0, C16:1-n7,C16:1n-9).
Conclusion: Omega-3 fatty acid treatment significantly reverses the histopathological degree of hepatic steatosis and improves the hepatic lipodemic profile in a rat model of steatosis. These results were corroborated non-invasively using clinical 3.0 Tesla 1H-MRS.

Vitamin A deficiency strongly aggravates liver damage during obstructive cholestasis; acute vitamin A therapy is the cure.

M.O. Hoeke, J. Heegsma, A.U. Rehman, H. Moshage and K.N. Faber, Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, the Netherlands

Background: Vitamin A is an essential nutrient compound that mammals obtain from dietary carotenoids and retinyl esters. Vitamin A is a fat-soluble vitamin and intestinal absorption requires bile salts. Bile salts are synthesized in the liver and maintained in an enterohepatic circulation. During cholestatic liver disease, bile salt cycling is disturbed and leads to malabsorption of fat-soluble vitamins, including vitamin A. Chronic cholestasis may ultimately lead to full depletion of the vitamin A stores in the liver. Vitamin A is an antioxidant. In addition, vitamin A-derivatives are crucial signalling molecules for the Retinoid X receptor (RXRα) that, together with the Farnesoid X receptor (FXR), regulates bile salt homeostasis. Vitamin A supplementation of cholestatic patients is, however, a controversial issue. We studied the effect of vitamin A deficiency (VAD) and retinyl-palmitate therapy in an animal model of obstructive cholestasis.Methods: Rats were made VAD by omitting vitamin A from their diet for 16 weeks, followed by ligation of the common bile duct (BDL). 7 days later, the animals were sacrificed. During the final 7 days, half of the animals received daily IP injections with retinyl-palmitate. Bile salt concentrations and liver damage markers (AST/ALT) were determined in serum. Quantitative real time PCR, Western blotting and histochemistry were performed on liver samples.Results: BDL induced a dramatic weight loss (-15 to -20% in 7 days) in VAD rats and serum liver damage markers (AST/ALT) were approximately 10-fold increased compared to BDL rats receiving a vitamin A-sufficient (VAS) diet. Markers for oxidative stress (Ho-1), inflammation (iNOS), fibrosis (α-Sma/collagen) were strongly increased. Large regions of necrotic hepatocytes were observed in VAD-BDL rats together with strong proliferation of ductular cells. Importantly, all these liver disease markers were efficiently reversed by retinyl-palmitate therapy to the level observed in VAS-BDL rats. Only minor changes in hepatic transcriptional regulation of bile salt homeostasis were detected.
Conclusions: We conclude that vitamin A deficiency dramatically aggravates liver damage caused by obstructive cholestasis. Acute vitamin A supplementation is, however, a very efficient therapy. These data urge a close monitoring of the vitamin A status in patients with chronic cholestasis.

Dietary soy phytoestrogens cause infertility in UDP-glucuronyltransferase deficient rats

J. Seppen, AMC Liver Center, Amsterdam, the Netherlands

Phytoestrogens are plant metabolites with mild estrogenic action. Soy contains high concentrations of the phytoestrogens genistein and daidzein and is the main dietary source of these compounds. Although their health benefits are controversial, a large market for soy and phytoestrogen supplements exists. Phytoestrogens are inactivated through glucuronidation by UDP glucuronyltransferases (UGT) and excretion into urine.The Gunn rat has no UGT1 activity and is the model of Crigler-Najjar disease. After 15 years of successful maintenance, our colony of Gunn rats suddenly ceased breeding. The cause of this problem was a change in animal food; back on the old chow fertility was restored. Examination of the different chow compositions revealed that the new food contained much higher levels of soy protein, an abundant source of phytoestrogens. Liquid chromatography and mass spectometry analysis of urine from normal Wistar rats fed the old and new chow confirmed that the new chow contained much higher levels of phytoestrogens. A cross-over feeding experiment was designed to test the hypothesis that dietary phytoestrogens can cause infertility in the absence of UGT1 activity.During a three month follow up, two control Gunn rat breeding pairs receiving normal chow produced two litters each. Two Gunn rat breeding pairs, composed of litter mates of the control group, but fed chow containing 300 mg/kg genistein did not produce any litters. After cross over, the fertile control breeding pairs were fed genistein chow and did not produce litters in a three month follow up. The animals that first received genistein food were subsequently fed control food; one of the breeding pairs produced two litters. Weights of control and genistein fed males were identical whereas the weight gain of females fed genistein was markedly reduced as compared to control fed females. This indicates that genistein has a strong estrogenic effect in female Gunn rats. Control Wistar rats were fertile on chow containing 300 mg/kg genistein. Daidzein containing chow had no effect on fertility of Gunn rats.
ConclusionsOur results suggest that dietary genistein causes infertility in UGT1 deficient Gunn rats. Because 10% of the population has reduced expression of the major genistein UGT isoform (Gilberts syndrome), these findings might have implications for fertility of woman taking soy or phytoestrogen supplements.

Plattegrond expositie

Alfabetische lijst van standhouders B = Beneluxhal K = Kempenhal	*Standnummer*
Abbott B.V.	B 15
Acertys B.V.	B 13
AstraZeneca B.V.	B 22
Baxter	K 20
Boston Scientific Nederland B.V.	B 4
Bristol Myers Squibb	K 15
Cobra Medical B.V.	K 4
Covidien Nederland B.V.	B 6
Crohn en Colitis Ulcerosa Ver. Nederland	B 21
Danone Nederland BV	K 10
ECCE Dutoit	K 16
Endomed B.V.	K 6
Endotechniek	B 2
Erbe Benelux B.V.	K 5
Ferring B.V.	B 1
FMH Medical B.V.	B 9
Fresenius Kabi Nederland B.V.	B 8
Getinge B.V.	K 17
Gilead Sciences Netherlands B.V.	K 14
Hitachi Medical Systems	K 7
Janssen-Cilag B.V.	K 13
Lans Medical B.V.	B 12
Medical Measurements Systems B.V.	K 19
Medicor	B 23
Minntech B.V.	B 24
Nationaal Hepatitis Centrum	B 17
Nederlandse Stomavereniging	B 18
Norgine B.V.	B 7
Nycomed B.V. Afd. Pantozol	B 14
Olympus Nederland B.V.	K 11
Orphan Europe	B 25
Pelvitec	B 3
Pentax Medical	K 8
Schering Plough B.V.	K 18
Shire Pharmaceuticals Benelux	B 11
Solvay Pharma B.V.	K 12
Stichting Opsporing Erfelijke Tumoren	B 20
Stichting Vreemde Kronkels	B 19
Stöpler Instrumenten & Apparaten B.V.	B 26
Surgical Technologies B.V.	K 9
TMI	B 5
Tramedico B.V.	K 1
Tramedico B.V.	K 2
Vereniging Ziekte van Hirschsprung	B 16
Wassenburg Medical Devices B.V.	B 10
Zambon Nederland B.V.	K 3

Nederlandse Vereniging voor Gastroenterologie

Aanmeldingsformulier lidmaatschap *(doorhalen wat niet van toepassing is)*

naam en voorletters		m / v
voornaam		geb. datum:
titel		
specialisme / functie		
doctoraal examen	neen / ja d.d.	zo ja, studierichting:
arts examen	n.v.t. / ja d.d.	
assistent i.o. voor		einde opleiding:
inschrijving MSRC	neen / ja d.d.	BIG registratie nr.
huisadres		
postcode en plaats		
telefoonnummer		
werkinstelling		
afdeling		
adres		
postcode en plaats		
telefoonnummer		
e-mail adres		
Toezending verenigingspost aan huis- / werkadres		

Tevens wil ondergetekende zich aansluiten bij:

□ Sectie Gastrointestinale Endoscopie*
□ Netherlands Society of Parenteral and Enteral Nutrition*
□ Sectie Neurogastroenterologie en Motiliteit*
□ Sectie Experimentele Gastroenterologie*
□ Sectie Kindergastroenterologie*
□ Nederlandse Vereniging voor Gastrointestinale Chirurgie *(combinatielidmaatschap)*
contributiebedragen: graag aankruisen wat voor u van toepassing is
□ Specialisten € 90,00 (totaal € 125,00 incl. lidmaatschap NVGE € 35,00)
□ Assistenten i.o. € 25,00 (totaal € 60,00 incl. lidmaatschap NVGE € 35,00)

*Aanvullende lidmaatschappen van met * aangegeven secties zijn kosteloos*

□ Hierbij machtig ik de penningmeester van de Nederlandse Vereniging voor Gastroenterologie om de verschuldigde contributie tot wederopzegging automatisch van mijn bank-/girorekening af te laten schrijven. Betaling geschiedt nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen. Indien u geen machtiging tot incasso geeft ontvangt u automatisch een factuur. Voor verzending van facturen worden vanaf volgend jaar administratiekosten in rekening gebracht.

Bank- / girorekening:

Datum en handtekening:

_____

Dit ondertekende formulier per post of fax (023 – 5513087) sturen naar: Secretariaat NVGE, Postbus 657, 2003 RR Haarlem

Aanvullende informatie: De contributie van de Nederlandse Vereniging voor Gastroenterologie bedraagt € 35,00 per jaar. Na toetreding als lid ontvangt u een factuur (conform de regels is volledige contributie verschuldigd in het jaar van toetreding). Het lidmaatschap loopt per kalenderjaar. Opzeggen dient daarom vóór 1 december te gebeuren.

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

Aanmeldingsformulier lidmaatschap

naam en voorletters		m / v
voornaam		geb. datum:
titel		
specialisme / functie		
doctoraal examen	neen / ja d.d.	zo ja, studierichting:
arts examen	n.v.t. / ja d.d.	
assistent i.o. voor		einde opleiding:
inschrijving MSRC	neen / ja d.d.	BIG registratie nr.
huisadres		
postcode en plaats		
telefoonnummer		
werkinstelling		
afdeling		
adres		
postcode en plaats		
telefoonnummer		
e-mail adres		
* Toezending verenigingspost aan huis- / werkadres		

** Doorhalen wat niet van toepassing is.*

□ Hierbij machtig ik de penningmeester van de Nederlandse Vereniging voor Hepatologie om de verschuldigde contriutie tot wederopzegging automatisch van mijn bank-/girorekening af te laten schrijven. Betaling geschiedt nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen. Indien u geen machtiging tot incasso geeft ontvangt u automatisch een factuur. Voor verzending van facturen worden vanaf volgend jaar administratiekosten in rekening gebracht.

Bank- / girorekening: Datum en handtekening:

Dit ondertekende formulier per post of fax (023 – 5513087) sturen naar:
Secretariaat NVH, Postbus 657, 2003 RR Haarlem

Aanvullende informatie: De contributie van de Nederlandse Vereniging voor Hepatologie bedraagt € 25,00 per jaar. Na toetreding als lid ontvangt u een factuur (conform de regels is volledige contributie verschuldigd in het jaar van toetreding). Het lidmaatschap loopt per kalenderjaar. Opzeggen dient daarom vóór 1 december te gebeuren.

SECTIE ENDOSCOPIE VERPLEEGKUNDIGEN EN ASSISTENTEN VAN DE NVGE

aanmeldingsformulier lidmaatschap

naam en voorletters			m / v
Evt. meisjesnaam			
voornaam			geb. datum:
titel			
specialisme / functie		BIG registratie nr.	
huisadres			
postcode en plaats			
telefoonnummer			
werkinstelling			
afdeling			
adres			
postcode en plaats			
telefoonnummer			
e-mail adres			

geeft zich hierbij op als lid van de Sectie Endoscopie Verpleegkundigen en Assistenten van de Nederlandse Vereniging voor Gastroenterologie tot schriftelijke wederopzegging.
Let wel, het lidmaatschap is persoonsgebonden en niet overdraagbaar. Verenigingspost zal uitsluitend naar uw huisadres worden gestuurd.

Datum:…… Handtekening:……

** aangeven wat van toepassing is.*

☐ Hierbij machtig ik de penningmeester van de Sectie Endoscopie Verpleegkundigen en Assistenten om het bedrag van de jaarlijkse contributie ad € 20,00, tot wederopzegging automatisch van mijn bank-/girorekening af te laten schrijven. Betaling geschiedt pas nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen.

Indien u geen machtiging tot incasso geeft ontvangt u automatisch een factuur.

(Post)bankrekeningnummer Handtekening

N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient dus vóór 1 januari te gebeuren.

Dit ondertekende formulier per post of fax sturen naar:
Centraal Secretariaat NVGE (ledenadministratie SEVA)
Postbus 657 2003 RR Haarlem fax: 023-5513087

VERENIGING
MAAG
DARM
LEVER
VERPLEEGKUNDIGEN

VMDLV

NEDERLANDSE VERENIGING VOOR MAAG-DARM-LEVER VERPLEEGKUNDIGEN

Aanmeldingsformulier lidmaatschap

naam en voorletters			m / v
Evt. meisjesnaam			
voornaam			geb. datum:
titel			
specialisme / functie		BIG registratie nr.	
huisadres			
postcode en plaats			
telefoonnummer			
werkinstelling			
afdeling			
adres			
postcode en plaats			
telefoonnummer			
e-mail adres			

Geeft zich op als lid van de Vereniging Maag Darm Lever Verpleegkundigen van de Nederlandse Vereniging voor Gastroenterologie tot schriftelijke wederopzegging. *Let wel, het lidmaatschap is persoonsgebonden en niet overdraagbaar. Verenigingspost zal uitsluitend naar uw huisadres worden gestuurd.*

Datum:…… Handtekening:…….

☐ Hierbij machtig ik de penningmeester van de Vereniging Maag Darm Lever Verpleegkundigen om de verschuldigde contributie, ad. € 27,50 per jaar, tot wederopzegging automatisch van mijn bank-/girorekening af te laten schrijven. Betaling geschiedt pas nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen.

Indien u geen machtiging tot incasso geeft ontvangt u automatisch een factuur.

(Post)bankrekeningnummer

Handtekening

……

N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient volgens de statuten vier weken voor het aflopen van het kalenderjaar **schriftelijk** te gebeuren.

Dit ondertekende formulier per post of fax sturen naar:
Centraal Secretariaat NVGE (ledenadministratie VMDLV)
Postbus 657, 2003 RR Haarlem, fax: 023-5513087