Programma voorjaarsvergadering 18 en 19 maart 2010

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 18 MAART 2010

Tijdstippen diverse ledenvergaderingen donderdag:

Nederlandse Vereniging voor Gastroenterologie 18 maart, 11.30 uur – Brabantzaal
Juniorvereniging – NVMDL (mdl-artsen i.o.) 18 maart, 12.00 uur – Zaal 82/83
Nederlandse Vereniging voor Hepatologie 18 maart, 15.00 uur – Baroniezaal

INHOUDSOPGAVE **pag**

PROGRAMMA VRIJDAG 19 MAART 2010

Tijdstippen diverse ledenvergaderingen vrijdag:

Werkgroep IBD	*19 maart, 10.00 uur – Zaal 21*
Nederlandse Vereniging van Maag-Darm-Leverartsen	*19 maart, 12.00 uur – Genderzaal*
Vereniging Maag Darm Leververpleegkundigen	*19 maart, 12.00 uur – Auditorium*
Sectie Endoscopie Verpleegkundigen en Assistenten	*19 maart, 14.10 uur – Diezezaal*
Sectie Experimentele Gastroenterologie	*19 maart, 15.15 uur – Baroniezaal*

Aandachtspunt voor de sprekers:
u dient zich strikt te houden aan de beschikbare spreektijd! U vindt dit aangegeven bij de betreffende sessie. In **zaal 25** kunt u uw PowerPoint presentatie inleveren tot uiterlijk 30 minuten voor uw voordracht.

VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering die gehouden wordt op 18 en 19 maart a.s. in Congrescentrum Koningshof te Veldhoven. Zoals gebruikelijk wordt ons congres vooraf gegaan door het cursorisch onderwijs op 17 maart, waarvan u het programma aantreft op bladzijde 6 en 7.

Het programma zal donderdag 19 maart om 10.00 uur van start gaan met twee parallelle sessies van de NVGE in de Brabantzaal en het Auditorium. In de Baroniezaal start de Dutch Experimental Gastroenterology and Hepatology Meeting (DEGH), voor het derde achtereenvolgende jaar 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 van deze posters een overzicht vanaf pagina 43.

Na de lunchpauze 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, en de Nederlandse Vereniging voor Gastroenterologie. Om 17.00 uur vindt in de Brabantzaal de Frieda den Hartog Jager lecture plaats, door prof. dr. J.B.M.J. Jansen. De lezing is getiteld: '*Vroege opsporing van dikkedarmkanker: Wat gaat landelijke screening ons brengen?'* 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.

Op vrijdagochtend zijn er vanaf 08.30 uur vrije voordrachten casuïstiek in de Brabantzaal, gevolgd door het NOTES-symposium. In de Parkzaal worden vrije voordrachten gecombineerd van Nederlandse Vereniging voor Gastroenterologie en NESPEN. 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. 's Middags is er voor het eerst een gezamenlijk symposium van de Vlaamse en Nederlandse Verenigingen voor Gastroenterologie met een symposium getiteld: Digestieve oncologie. 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

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: Prof. dr. P.D. Siersema (voorzitter) (MDL-arts, UMCU)
Dr. B.B. van Elzen (aios MDL, AMC)
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 Nieuwegein)

Onderwerp: **Infecties**

Voorzitter: Dr. R. Timmer, MDL-arts, St. Antonius Ziekenhuis, Nieuwegein

15.00 – 15.15 Evaluatie toets

15.15 – 15.45 H. pylori (en andere Helicobacters)
Dr. W.A. de Boer, Ziekenhuis Bernhoven, Oss

15.45 – 16.15 Ziekte van Whipple
Prof. dr. A. von Herbay, Universitätsklinikum Münster / University of Heidelberg, Germany

16.15 – 16.45 SOA's en het maagdarmkanaal
Prof. J.F.W.M. Bartelsman, Academisch Medisch Centrum, Amsterdam

16.45 – 17.15 Pauze

Voorzitter: Dr. D.J. de Jong, MDL-arts, UMC St. Radboud, Nijmegen

17.15 – 17.45 Leverabcessen
Dr. R.A. de Man, Erasmus MC, Rotterdam

17.45 – 18.15 Clostridium difficile geïnduceerde diarree
Dr. J.J. Keller, Haga Ziekenhuis locatie Leyweg, Den Haag

18.15 – 18.45 Parasitaire darminfecties
Dr. P.J. Wismans, Havenziekenhuis, Rotterdam

18.45 – 19.45 Dinerbuffet

Cursorisch onderwijs in maag-darm-leverziekten, vervolg **Auditorium**

Voorzitter: Prof. dr. P.D. Siersema, Universitair Medisch Centrum Utrecht

19.45 – 20.15 Infectie bij immuungecompromiteerde patiënten in relatie tot gebruikte geneesmiddelen c.q. onderliggende aandoening
Dr. G. Dijkstra, Universitair Medisch Centrum Groningen

20.15 – 20.45 Acute bacteriële infectie
Dr. A. Verbon, Erasmus MC, Rotterdam

20.45 – 21.45 Paneldiscussie met J.J. Keller, P.J. Wismans, G. Dijkstra en A. Verbon aan de hand van casuïstiek

1. Clostridium diarree
   R.J.L. Stuyt, aios MDL, LUMC, Leiden

2. Diarree bij immuungecompromiteerde patiënt
   E.T.T.L. Tjwa, aios MDL, Erasmus MC, Rotterdam

3. Diarree bij de oudere patiënt met ontsteking in het colon: diverticulitis of IBD?
   F.O. The, aios MDL, OLVG Amsterdam

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 18 maart 2010

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
10.00 – 12.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie gevolgd door ledenvergadering 11.30 p. 10	DEGH-Meeting v.a. 10.30 Gastspreker: Prof. dr. M. Trauner p. 14		Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 12	Geen programma in deze zaal op donderdag
12.00 – 13.00	Lunchbuffet expositiehal	Lunchbuffet- postersessie p.			
13.00 – 15.00	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 15	DEGH-Meeting v.a. 13.30 Gastspreker: Prof. dr. J.D. Schulzke p. 26		Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit p. 21	
15.00 – 15.30	Theepauze	Theepauze		Theepauze	
15.30 – 17.00	Vrije voordrachten Ned. Ver. voor Gastroenterologie en Gastrointestinale Chirurgie p. 17	DEGH-Meeting (vervolg) p. 27	Workshop Sedatie door niet-anesthesisten p. 28	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 23	
17.00 – 17.30	Frieda den Hartog Jager Lecture Prof.dr. J.B.M.J. Jansen p.19	Einde programma in deze zaal		Vervolg programma	
17.30 – 18.30	President Select p. 19			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 19 maart 2010

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
08.30 – 09.00	Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 29	DEGH Meeting Gastspreker: Prof. dr. S.L. Friedman p. 36	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie en NESPEN p. 32		
09.00 – 10.30	Symposium NOTES p. 30	Vervolg programma DEGH	Vervolg programma	Programma Vereniging voor Maag-Darm-Lever Verpleegkundigen (10.00) p. 42	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten (10.00) p. 41
10.30 – 11.00	Koffiepauze	Koffiepauze en ledenvergadering NVH	Koffiepauze	Koffiepauze	Koffiepauze
11.00 – 12.00	Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 30	DEGH Meeting (tot 12.30) Gastspreker: Prof. dr. E. Cario p. 37	Vrije voordrachten Sectie Kinder-MDL p. 34	Programma Vereniging voor Maag-Darm-Lever Verpleegkundigen p. 42	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 41
12.00 – 13.30	Lunchbuffet expositiehal Ledenvergadering NVMDL	Lunchbuffet- postersessie p	Lunchbuffet expositiehal	Lunchbuffet expositiehal	Lunchbuffet expositiehal
13.30 – 15.30	Symposium Digestieve Oncologie i.s.m. VVGE p. 40	DEGH Meeting en prijsuitreikingen p. 38	Ledenvergadering Kinder-MDL	Programma Vereniging voor Maag-Darm-Lever Verpleegkundigen p. 42	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p.
15.30	Koffie/thee expositiehal	Koffie/thee expositiehal	Koffie/thee expositiehal	Einde programma	Einde programma

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

09.30 Inschrijving, koffie

Voorzitters: D.J. de Jong en B. Oldenburg

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

10.00 Overexpression of CARD9 caused by a deletion polymorphism could explain the associated with Inflammatory Bowel Disease (p. 50)

S. van Sommeren[1,2], E.A.M. Festen[1,2], C. Wijmenga[2], R.K. Weersma[1], [1]Dept. of Gastro-enterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, [2]Dept. of Genetics, University Medical Centre Groningen and University of Groningen, Groningen, The Netherlands

10.10 MLDS-voordracht
Psychological distress after genetic risk assessment shortly following a diagnosis of colorectal cancer (p. 51)

K.M. Landsbergen[1], J.B. Prins[2], H.G. Brunner[1], P. van Duijvendijk[3], F. M.Nagengast[4], M. Ligtenberg[1,5], N. Hoogerbrugge[1,6], Depts. of [1]Human Genetics, [2]Medical Psychology, [3]Surgery, [4]Gastroenterology, [5]Pathology and Hepatology and [6]Medical Oncology, Medical Centre Radboud University Nijmegen, The Netherlands

10.20 Liver histology of IBD patients who are treated with 6-thioguanine due to failure of conventional thiopurines reveals very few cases of nodular regenerative hyperplasia (p. 52)

D.P. van Asseldonk[1], B. Jharap[1], N.K.H. de Boer[1], P.E. Zondervan[2], E. Bloemena[3], G. den Hartog[4], B.D. Westerveld[5], J.J. Kolkman[6], L.G.J.B. Engels[7], A.A. van Bodegraven[1], C.J. Mulder[1], [1]Dept. of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, [2]Dept. of Pathology, Erasmus Medical Centre, Rotterdam, [3]Dept. of Pathology, VU University Medical Centre, Amsterdam, [4]Dept. of Gastroenterology and Hepatology, Rijnstate Medical Centre, Arnhem, [5]Dept. of Gastroenterology and Hepatology, Isala Clinics, Zwolle, [6] Dept. of Gastroenterology and Hepatology, Twente Medical Spectrum, Enschede, [7]Dept. of Gastro-enterology and Hepatology, Orbis Medical Centre, Sittard, The Netherlands

10.30 A meta-analysis of genome wide association scans identifies TAGAP and PUS10 as shared risk loci for Crohn's disease and celiac disease (p.53)

E.A.M. Festen[1,2], P. Goyette[3], T. Green[4], C. Beauchamp[3], G. Boucher[3], G. Trynka[2], P.C. Dubois[5], C. Lagacé[3], P.C.F. Stokkers[6], The International Inflammatory Bowel Disease Genetics Consortium (IIBDGC), D.W. Hommes[7], D. Barisani[8], O. Palmieri[9] , V. Annese[9], D.A. van Heel[5], R.K. Weersma[1], M.J. Daly[3,10], C. Wijmenga[2], J.D. Rioux[3,4] ,[1]Dept. of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, [2]Dept. of Genetics, University Medical Centre Groningen and University of Groningen, The Netherlands, [3]Université de Montréal and the Montreal Heart Institute, Research Centre, Montreal, Quebec, Canada, [4]The Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, Massachusetts, USA, [5]Centre for Digestive Diseases, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medic and Dentistry, Queen Mary University of London, London, UK, [6]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [7]Dept. of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands, [8]Dept. of Experimental Medicine, Faculty of Medicine, Univ.of Milano-Bicocca, Italy, [9]UU.OO. Gastroenterologia ed Endoscopia Digestiva, Ospedale "Casa Sollievo della Sofferenza", IRCCS, San Giovanni Rotondo, Italy, [10]Centre for Human Genetic Research, Massachusetts General Hosp., Harvard Med. School, Boston, Massachusetts, USA

10.40 Azathioprine or 6-mercaptopurine associated hepatotoxicity diminishes upon administration of 6-thioguanine in IBD patients (p. 54)
D.P. van Asseldonk, A.A. van Bodegraven, C.J.J. Mulder, VU University Medical Centre, Amsterdam, The Netherlands

10.50 10 years of Infliximab: long-term efficacy outcome of 430 Crohn's disease patients in a tertiary referral center (p. 55)
E.J. Eshuis[1,2], F te Braake[1], C.Y. Ponsioen[1], J. Bartelsman[1], W.A. Bemelman[2] , P.C.F. Stokkers[1], Depts. of [1]Gastroenterology and Hepatology and [2]Surgery, Academic Medical Centre, Amsterdam, The Netherlands

11.00 The phase I safety and feasibility results of autologous intravenous Mesenchymal Stromal Cell treatment in refractory Crohn's Disease (p. 56)
M. Duijvestein[1], M.E. Wildenberg[1], B.B. Wendrich[1], A.C.W. Vos[1], A. Verhaar[1], H.H. Fidder[1], H. Roelofs[2], J.J. Zwaginga[2], W.E. Fibbe[2], G.R. van den Brink[1], D. Hommes[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Immunohematology and Blood Transfusion, Leiden University Medical Centre, Leiden, The Netherlands

11.10 Colorectal cancer in inflammatory bowel disease: A comparison between large cohorts from referral centers and general hospitals (p. 57)
E. Mooiweer[1], J. Baars[2] , M. W.M.D. Lutgens[1] , P.D. Siersema[1] , E.J. Kuipers[2] , B. Oldenburg[1] and C.J. van der Woude[2] on behalf of The Initiative on Crohn and Colitis and the Dutch IBD/CRC working group, [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, [2]Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

11.20 Substantial increase of progression rate of flat low-grade dysplasia in inflammatory bowel disease after review by an expert panel (p. 58)
F.D.M. van Schaik[1], F.J.W. ten Kate[2], G.J.A. Offerhaus[2], M.E.I. Schipper[2], F.P. Vleggaar[1], C.J. van der Woude[3], P.C.F. Stokkers[4], D.J. de Jong[5], D.W. Hommes[6], A.A. van Bodegraven[7], P.D. Siersema[1], B. Oldenburg[1], [1]University Medical Centre Utrecht, Dept. of Gastroenterology and Hepatology, [2]University Medical Centre Utrecht, Dept. of Pathology, [3]Erasmus MC University Medical Centre Rotterdam, Dept. of Gastroenterology and Hepatology, [4]Academic Medical Centre Amsterdam, Dept. of Gastroenterology and Hepatology, [5]Radboud University Nijmegen Medical Centre, Dept. of Gastroenterology and Hepatology, [6]Leiden University Medical Centre, Dept. of Gastroenterology and Hepatology, [7]VU University Medical Centre Amsterdam, The Netherlands

11.30 Einde abstractsessie

11.30 **Ledenvergadering NVGE**

12.00 Lunchbuffet in expositiehal

Nederlandse Vereniging voor Gastroenterologie **Auditorium**

09.30 Inschrijving, koffie

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

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

10.00 The opinion of gastroenterologists towards quality assurance in endoscopy (p. 59)

V. de Jonge[1], J. Sint Nicolaas[1], M.E. van Leerdam[1], E.J. Kuipers[1,2], [1]Dept of Gastroenterology and Hepatology, [2]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

10.10 Evaluation of colonoscopy performance in daily practice in a multicenter study (p. 60)

J. Sint Nicolaas[1], V. de Jonge[1], O. van Baalen[2], F. ter Borg[3], J.T. Brouwer[4], H. Geldof[5], M. Hadithi[6], A.J.P. van Tilburg[7], E.J. Kuipers[1,8], M.E. van Leerdam[1], Dept. of Gastroenterology and Hepatology of [1]Erasmus MC University Medical Centre, Rotterdam, [2]Beatrix Hospital, Gorinchem, [3]Deventer Hospital, Deventer, [4]Reinier de Graaf Hospital Group, Delft, [5]IJsselland Hospital, Capelle aan de IJssel, [6]Maasstad Hospital, Rotterdam, [7]Sint Franciscus Gasthuis, Rotterdam, [8]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

10.20 CT-Colography After Incomplete Colonoscopy: What Is The Diagnostic Yield? (p. 61)

H.J.M. Pullens[1], M.S. van Leeuwen[2], F.P. Vleggaar[1], P.D. Siersema[1],[1]Gastroenterology and Hepatology, [2]Radiology, University Medical Centre Utrecht, The Netherlands

10.30 Expression of Proteins Involved in Carcinogenic Pathways in Patients with Primary Sclerosing Cholangitis and Colitis-associated Colorectal Cancer (p. 62)

M.M.H. Claessen[1], F.P. Vleggaar[1], M.E.I. Schipper[2], F.H.M. Morsink[2], P.D. Siersema[1], G.J.A. Offerhaus[2], Dept. of Gastroenterology and Hepatology[1] and Dept. of Pathology[2], University Medical Centre Utrecht, The Netherlands

10.40 Risk factors of adenoma recurrence at surveillance colonoscopy: a systematic literature review and pooled analysis (p. 63)

V. de Jonge[1], J. Sint Nicolaas[1], E.J. Kuipers[1,2], M.E. van Leerdam[1], S.J.O. Veldhuyzen van Zanten[3], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, [2]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands, [3]Dept. of Gastroenterology and Hepatology, University of Alberta Hospital, Edmonton, Alberta, Canada

10.50 Statin treatment of colon cancer cells leads to an overall downregulation of Receptor Tyrosine Kinase activity (p. 64)

R.J. Jacobs[1], L.L. Kodach[1], S.H. Diks[2], J. Heijmans[1], D.W. Hommes[1], G.R. van den Brink[1], M.P. Peppelenbosch[2], J.C.H. Hardwick[1], [1]Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, [2]Cell Biology, University Medical Centre Groningen, The Netherlands

11.00 Routine MSI-analysis in advanced adenomas in patients younger than 45 years leads to the identification of more patients at high risk for Lynch Syndrome (p. 65)

C.H.M. Leenen[1], M.G.F. van Lier[1], A. Wagner[2], W.N.M. Dinjens[3], H.J. Dubbink[3], M.E. van Leerdam[1], E.J. Kuipers[1,4], 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 Public Health[5] , Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

11.10 Long term results of more than 100 self-expanding metallic stent (SEMS) placements for acute malignant colonic obstruction (p. 66)

H.H. Zwaving[1], M. Ledeboer[2], F. ter Borg[2], E.H. Eddes[1], R.J.I. Bosker[1], M. Eeftinck Schattenkerk[1], [1]Dept. of Surgery, Deventer Ziekenhuis, Deventer, [2]Dept. of Gastroenterology, Deventer Ziekenhuis, Deventer, The Netherlands

11.20 Is diverticular disease in younger patients associated with increased risk for colorectal neoplasia? A cross-sectional study (p. 67)

C. le Clercq[1], E. Rondagh[1], K. Steenhuisen-van Erp[1], B. Winkens[2], S. Sanduleanu[1], A. Masclee[1], Division of Gastroenterology and Hepatology[1] and Dept. of Methodology and Statistics[2], Maastricht University Medical Centre, The Netherlands

11.30 Einde abstractsessie

11.30 Ledenvergadering NVGE in de Brabantzaal

12.00 Lunchbuffet in expositiehal

Donderdag 18 maart 2010

DEGH-Meeting **Baroniezaal**

Voorzitters: M. Trauner en S. van Mil

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

10.30 Oligomerization of the human liver Na+-dependent taurocholate cotransporting protein NTCP provides a novel mechanism to regulate bile salt uptake (p. 68)

S.F.J. van de Graaf, R.A.M Bouwmeester, L.W.J. Klomp, Dept. of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, Utrecht, The Netherlands

10.42 Bile salts exposure at different pHs to esophageal squamous epithelial cells induces expression of markers that are also found in Barrett's Esophagus (p. 69)

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

10.54 Raised hepatic bile acid concentrations during pregnancy are associated with reduced Farnesoid-X-Receptor function (p. 70)

A. Milona[1] , B.M. Owen[1] , J. Cobbold[2] , E.C.L. Willemsen[3] , J. Cox[2] , M. Boudjelal[4] , W. Cairns[4], K. Schoonjans[5], S. Taylor-Robinson[2], L.W.J. Klomp[3], M.G. Parker[1], R. White[1], C. Williamson[1], S.W.C. van Mil[5], [1]Institute of Reproductive and Developmental Biology, Division of Medicine, Imperial College London, U.K, [2]Translational MR Spectroscopy Grouping, Division of Clinical Sciences, Imperial College London, U.K., [3]Dept. of Metabolic and Endocrine Diseases and Netherlands Metabolomics Centre, University Medical Centre Utrecht, The Netherlands, [4]GlaxoSmithKl, New Frontiers Science Park, Essex, U.K. [5]Ecole Polytechnique Federale de Lausanne, Switzerland

11.06 The laxative polyethylene glycol does not affect intestinal absorption of lipids but doubles the bile salt pool size in rats (p. 71)

M.Y. van der Wulp[1, 2], F.J. Cuperus[2], J. Dekker[1] , E.H. Rings[1, 2], H.J. Verkade[1,2], [1]Top Institute Food and Nutrition, Wageningen, [2]Pediatric Gastroenterology, Dept. of Pediatrics Centre for Liver, Digestive, and Metabolic Diseases, University Medical Centre Groningen, University of Groningen, The Netherlands

11.18 Reduced uptake of taurocholic acid in ATP8B1-depleted Caco-2 cells: an explanation for diarrhea in patients with ATP8B1 deficiency? (p. 72)

L.M. van der Velden[1], J.M. Stapelbroek[1,2], S.W.C. van Mil[1], V. Oorschot[3], J. Klumperman[3], M. van der Ham[1], M.G. de Sain-van der Velden[1], R. Berger[1], R.H.J. Houwen[2], L.W.J. Klomp[1], [1]Dept. of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, [2]Dept. of Paediatric Gastroenterology,, [3]Cell Microscopy Centre, Dept.of Cell Biology, Institute of Biomembranes, UMC Utrecht, The Netherlands

11.30 **Invited speaker: Prof. dr. M. Trauner**
Regulation and pharmacological interventions of transport systems in cholestatic and fatty liver disease

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 12.45 de mogelijkheid om u aan te sluiten bij een begeleide sessie langs de posters; u vindt een overzicht vanaf pagina 34 in dit programma.

13.30 Vervolg DEGH-programma, zie pagina 26.

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

Voorzitters: M.I. van Berge Henegouwen en W.M.U. van Grevenstein

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

13.00 Pre-operative staging with chest CT in patients with colorectal carcinoma: not as a routine procedure (p. 73)
I. Grossmann[1], J.K.A. Avenarius[2], W.J.B. Mastboom[1], J.M. Klaase[1], [1]Medisch Spectrum Twente, Department of Surgery, [2]Medisch Spectrum Twente, Department of Radiology, The Netherlands

13.10 Adjuvant Hyperthermic Intraperitoneal Chemotherapy after cytoreductive surgery for peritoneal carcinomatosis prolongs survival in the rat (p. 74)
Y.L.B. Klaver[1], T. Hendriks[2], R.M.L.M. Lomme[2], HJ.T. Rutten[1], R.P. Bleichrodt[2], I.HJ.T. De Hingh[1], [1]Dept. of Surgery, Catharina Hospital Eindhoven, [2]Dept. of Surgery, Radboud University Medical Centre Nijmegen, The Netherlands

13.20 Increased soluble CD95 and CD95ligand levels correlate with poor overall survival after surgical procedures in patients with colorectal livermetastases (p. 75)
F.J.H.Hoogwater[1], N.Snoeren[1], M.W. Nijkamp[1], A.C. Gunning[1], O. Kranenburg[1], R. van Hillegersberg[1], I.H.M.Borel Rinkes[1], University Medical Centre Utrecht, Dept. of Surgery, The Netherlands

13.30 Laparoscopic emergency colectomy for ulcerative colitis is associated with less adhesions compared to open (p. 76)
S.A.L. Bartels[1], D. Henneman[1], M.S. Vlug[1], J.F.M.Slors[1], W.A. Bemelman[1], [1]Dept. of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

13.40 Peri-operative blood pressure as a risk factor for anastomotic leakage in colorectal surgery (p. 77)
K. Noordzij, I. Grossmann, J. Klaase, J. van der Palen, M.F. Lutke Holzik, Medisch Spectrum Twente, Dept. of Surgery, Enschede, The Netherlands

Donderdag 18 maart 2010

13.50 The ileo neo rectal anastomosis (INRA): long-term follow up (p. 78)

J.T. Heikens[1], W.E. Hueting[2], H.J. Oostvogel[3], Th.J.M.V. van Vroonhoven[2], H.G. Gooszen[1], C.J.H.M. van Laarhoven[1], [1]Dept. of Surgery, Radboud University Nijmegen Medical Centre, Dept. of Surgery, [2]Meander Medical Centre Amersfoort, [3]Dept. of Surgery, St Elisabeth Hospital, Tilburg, The Netherlands

14.00 Development of a composite endpoint for randomized controlled trials in liver surgery (p. 79)

M.A.J. van den Broek[1], R.M. van Dam[1], G.J.P. van Breukelen[2], L.I. Mpabanzi[1], M.H. Bemelmans[1], C.H.C. Dejong[1,3], N. Freemantle[4], S.W.M. Olde Damink[1,3,5], [1]Dept. of Surgery, Maastricht University Medical Centre, Maastricht, [2]Dept. of Methodology and Statistics and [3]NUTRIM School for Nutrition, Toxicology and Metabolism, Dept. of Surgery, Maastricht University, Maastricht, The Netherlands, [4]Dept. of Primary Care and General Practice, University of Birmingham, Birmingham, United Kingdom, [5]Dept. of Surgery, University College London Hospital, London, United Kingdom

14.10 Prospective evaluation of endoscopic and conservative treatment of persistent symptomatic sterile pancreatic necrosis (p. 80)

R.P. Voermans[1, 3], O.J. Bakker[2], S. van Brunschot[1,7], H.C. van Santvoort[2], M.A. Boermeester[3], R. Timmer[4], V.B. Nieuwenhuijs[5], M.J. Bruno[6], H. Gooszen[7] and P. Fockens[1] for the Dutch Pancreatitis Study Group ,[1]Dept. of Gastroenterology and Hepatology & [3]Dept of Surgery, Academic Medical Centre, Amsterdam, [2]Dept of Surgery, UMCU, Utrecht, [4]Dept. of Gastroenterology and Hepatology, St. Antonius hospital, Nieuwegein, [5]Dept of Surgery, University Medical Centre Groningen, [6]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, [7]Dept of Surgery, University Medical Centre St. Radboud, Nijmegen, The Netherlands

14.20 Route of gastroenteric anastomosis in pancreatoduodenectomy and delayed gastric emptying – a retrospective analysis (p 81).

W.J. Eshuis, J.W. van Dalen, O.R.C. Busch, T.M. van Gulik, D.J. Gouma, Dept. of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

14.30 Long-term outcomes of transanal hemorrhoidal dearterilisation (THD) for grade 2-4 hemorrhoids (p. 82)

S.M.J. ter Veldhuis[1], R. Koop[1], J.M. Klaase[1], M.F. Lutke Holzik[1], [1]Dept. of Surgery, Medical Spectrum Twente, Enschede, The Netherlands

14.40 Percutaneous drainage for acute calculous cholecystitis (p. 83)

K. Kortram[1], T.S. de Vries Reilingh[1], D. Boerma[2], M.J. Wiezer[1], B. v. Ramshorst[1], [1]Dept. of Surgery, St. Antonius Hospital, Nieuwegein, [2]Dept.of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

14.50 Is sexual dysfunction in women after restorative proctocolectomy with ileal pouch anal anastomosis caused by autonomic pelvic nerve damage?
A prospective clinical trial (p. 84)

J. Wind[1], M.S.Vlug[1], E.T. Laan[2], R.H.W. van Lunsen[2], P.J. van Koperen[1], S.W.Polle[1], W.A. Bemelman[1], [1]Dept. of Surgery, Academic Medical Centre, University of Amsterdam, [2]Dept. of Sexology and Psychosomatic Gynaecology, Academic Medical Centre, University of Amsterdam, The Netherlands

15.00 Theepauze

Ned. Ver. voor Gastroenterologie en Gastrointestinale Chirurgie — Brabantzaal

Voorzitters: M.G.H. Besselink en E. van der Harst

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

15.30 Dyspeptic symptoms after laparoscopic large hiatal hernia repair and primary antireflux surgery for gastro-oesophageal reflux disease; a comparative study (p. 85)

E.J.B. Furnée[1], W.A. Draaisma[2], E.J. Hazebroek[1], N. van Lelyveld[3], A.J.P.M. Smout[4], I.A.M.J. Broeders[2], [1]Dept. of Surgery, University Medical Centre Utrecht, [2]Dept. of Surgery, Meander Medical Centre, Amersfoort, [3]Dept of Gastroenterology, Meander Medical Centre, Amersfoort, [4]Dept. of Gastroenterology, University Medical Centre Utrecht, The Netherlands

15.40 A pilot trial of endoscopic radiofrequency ablation for the eradication of esophageal squamous intraepithelial neoplasia and early squamous cell carcinoma limited to the mucosa (p. 86)

F.G.I. van Vilsteren[1], L. Alvarez Herrero[2,1], R.E. Pouw[1], C.M.T. Sondermeijer[1], F.J. ten Kate[3], M.I. van Berge Henegouwen[4], B.L. Weusten[2,1], J.J. Bergman[1], [1]Gastroenterology, Academic Medical Centre, Amsterdam, [2]Gastroenterology, St Antonius hospital Nieuwegein, [3]Pathology, Academic Medical Centre, Amsterdam, [4]Surgery, Academic Medical Centre, Amsterdam, The Netherlands

15.50 Lymphatic micrometastases in patients with early esophageal adenocarcinoma (p. 87)

B.A. Grotenhuis[1], M. van Heijl[2], B.P.L. Wijnhoven[1], M.I. van Berge Henegouwen[2], K. Biermann[3], F.J.W. ten Kate[4,5], O.R.C. Busch[2], W.N.M. Dinjens[3], H.W. Tilanus[1], J.J.B. van Lanschot[1], [1]Erasmus Medical Centre, Rotterdam, Dept. of Surgery; [2]Academic Medical Centre, Amsterdam, Dept. of Surgery; [3]Erasmus Medical Centre, Rotterdam, Dept. of Pathology; [4]Academic Medical Centre, Amsterdam, Dept. of Pathology; [5]University Medical Centre, Dept. of Pathology, Utrecht, The Netherlands

16.00 The stromal part of adenocarcinomas of the oesophagus: does it conceal targets for therapy? (p. 88)

E.F.W. Courrech Staal[1], M.W.J.M. Wouters[1,2], J.W. van Sandick[1], V.T.H.B.M. Smit[3], T. Karsten[4], H.H. Hartgrink[2], W.E. Mesker[2], R.A.E.M. Tollenaar[2], [1]Dept. of Surgical Oncology, Cancer Institute / Antoni van Leeuwenhoek Hospital, [2]Dept. of Surgical Oncology, Leiden University Medical Centre, [3]Dept. of Pathology, Leiden University Medical Centre, [4]Dept. of Surgery, Reinier de Graaf Hospital, The Netherlands

16.10 Gastric acidity after pancreatoduodenectomy: influence of surgical technique and peri-operative medical treatment (p. 89)

M.J.M. Morak[1], T.C.K. Tran[1], M.J. Bruno[2], W.C.J. Hop[3], G. Kazemier[1], J. de Jonge[1] and C.H.J. van Eijck[1], [1]Dept. of Surgery, Erasmus Medical Centre, Rotterdam, [2]Dept. of Gastro-enterology and Hepatology, Erasmus Medical Centre, Rotterdam, [3]Dept. of Biostatistics Erasmus MC, Rotterdam, The Netherlands

16.20 Factors predicting stent patency in patients with malignant biliary strictures: a multicenter study (p. 90)

P.G.A. van Boeckel[1], F.P Vleggaar[1], E.W. Steyerberg[2], M.J.M. Groenen[3], B.J.M. Witteman[4], B. Weusten[5], H. Geldof[6], A. Tan[7], M. Grubben[8], J. Nicolai[9], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, [2]Dept of Public Health, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, [3]Dept. of Gastroenterology, Ziekenhuis Rijnstate, Arnhem, [4]Dept. of Gastroenterology, Ziekenhuis Gelderse Vallei, Ede, [5]Dept. of Gastroenterology, St. Antonius Ziekenhuis, Nieuwegein, [6]Dept. of Gastroenterology, Canisius Wilhelmina Ziekenhuis, Nijmegen, [7]Dept. of Gastroenterology, IJsselland Ziekenhuis, Capelle a/d IJssel, [8]Dept. of Gastroenterology, Elizabeth Ziekenhuis, Tilburg, [9]Dept. of Gastroenterology, Hagaziekenhuis, Den Haag, The Netherlands

16.30 Clinical outcome of a progressive stenting protocol in patients with anastomotic strictures after orthotopic liver transplantation (p. 91)

M.N. Lekkerkerker[1], J.W. Poley[1], H.J. Metselaar[1], J. Haringsma[1], G. Kazemier[2], C.H.J. van Eijck[2], E.J. Kuipers[1], M.J. Bruno[1] ,[1]Gastroenterology & Hepatology, Erasmus Medical Centre, Rotterdam, [2]Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

16.40 Low inter-observer agreement on nodular regenerative hyperplasia of the liver: an european inter-observer analysis (p. 92)

B. Jharap[1], D.P. van Asseldonk[1], K.H.N. de Boer[1], J.F. Colombel[3], J. Diebold[5], A.M. Jonker[6], E. Leteurtre[4], W. Reinisch[7], G. Vernier-Massouille[3], D. Wendum[9], F. Wrba[8], P.E. Zondervan[10], C.J.J. Mulder[1], A.A. van Bodegraven[1], E. Bloemena[2], [1]Dept. of Gastroenterology & Hepatology, VU Medical Centre, Amsterdam, [2]Dept. of Pathology, VU Medical Centre, Amsterdam, The Netherlands, [3]Dept. of Gastroenterology & Hepatology, Academic Medical Centre Lille, France, [4]Dept. of Pathology, Academic Medical Centre Lille, France, [5]Dept. of Pathology, Cantonaal Hospital, Luzern, Switzerland, [6]Dept. of Pathology, Delfzicht Hospital, Delfzijl, The Nederlands, [7]Dept. of Gastroenterology & Hepatology, Academic Medical Centre Vienna, Austeria, [8]Dept. of Pathology, Academic Medical Centre Vienna, Austria, [9]Dept. of Pathology, Saint-Antonie Hospital, Paris, France, [10]Dept. of Pathology, Erasmus Medical Centre, Rotterdam, The Nederlands

16.50 PET/CT using ^{18}F-fluoromethylcholine to differentiate focal nodular hyperplasia from hepatocellular adenoma; preliminary results (p. 93)

J.W. van den Esschert[1], M. Bieze[1], R. Bennink[2], T.M. van Gulik[1], [1]Dept. of Surgery and [2]Nuclear Medicine, Academic Medical Centre Amsterdam, The Netherlands

Voorzitter: C.J.J. Mulder

17.00 **Frieda den Hartog Jager Lecture**
door Prof. dr. J.B.M.J. Jansen, Nijmegen

Vroege opsporing van dikkedarmkanker:
Wat gaat landelijke screening ons brengen?

President Select (plenaire sessie) — Brabantzaal

Voorzitter: C.J.J. Mulder

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

17.30 Minimally invasive step-up approach versus open necrosectomy in necrotizing pancreatitis: a randomized controlled multicenter trial (p. 94)

H.C. van Santvoort[1], M.G. Besselink[1], O.J. Bakker[1], H.S. Hofker[2], M.A. Boermeester[3], C.H. Dejong[4], H. van Goor[5], A.F. Schaapherder[6], C.H. van Eijck[7], T.L. Bollen[8], B. van Ramshorst[9], V.B. Nieuwenhuijs[2], R. Timmer[10], J.S. Laméris[11], F.M. Kruyt[12], E.R. Manusama[13], E. van der Harst[14], G.P. van der Schelling[15], T. Karsten[16], E.J. Hesselink[17], C.J. van Laarhoven[18], C. Rosman[19], K. Bosscha[20], R.J. de Wit[21], A.P. Houdijk[22], M.S. van Leeuwen[23], E. Buskens[24] and H.G. Gooszen[1] for the Dutch Pancreatitis Study Group ,[1]Dept. of Surgery, University Medical Centre Utrecht, Utrecht, [2]Dept. of Surgery, University Medical Centre Groningen, [3]Dept. of Surgery, Academic Medical Centre, Amsterdam, [4]Dept. of Surgery and NUTRIM, Maastricht University Medical Centre, Maastricht, [5]Dept. of Surgery, Radboud University Nijmegen Medical Centre, Nijmegen, [6]Dept. of Surgery, Leiden University Medical Centre, Leiden, [7]Dept. of Surgery, Erasmus Medical Centre, Rotterdam, Depts. of [8] Radiology, [9]Surgery, and [10]Gastroenterology, St. Antonius Hospital, Nieuwegein, [11]Dept. of Radiology, Academic Medical Centre, Amsterdam, [12]Dept. of Surgery, Gelderse Vallei Hospital, Ede, [13]Dept. of Surgery, Leeuwarden Medical Centre, [14]Dept. of Surgery, Maasstad Hospital, Rotterdam, [15]Dept. of Surgery, Amphia Medical Centre, Breda, [16]Dept. of Surgery, Reinier de Graaf Hospital, Delft, [17]Dept. of Surgery, Gelre Hospital, Apeldoorn, [18]Dept. of Surgery, St. Elisabeth Hospital, Tilburg (currently: Dept. of Surgery, Radboud University Nijmegen Medical Centre, Nijmegen), [19]Dept. of Surgery, Canisius Wilhelmina Hospital, Nijmegen, [20]Dept. of Surgery, Jeroen Bosch Hospital, Den Bosch, [21]Dept. of Surgery, Medisch Spectrum Twente, Enschede, [22]Dept. of Surgery, Medical Centre Alkmaar, [23]Dept. of Radiology, University Medical Centre Utrecht, [24]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, (currently: Dept of Epidemiology, University Medical Centre Groningen), The Netherlands

17.45 Interobserver agreement between experienced, semi-experienced and non-experienced endosonographers for features and specific diagnosis of pancreatic cysts (p. 95)

K. de Jong[1], T. Verlaan[1], M. Dijkgraaf[2], J.W. Poley[3], H. van Dullemen[4], M.J. Bruno[3], P. Fockens[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Biostatistics and Epidemiology, Academic Medical Centre, Amsterdam, [3]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, [4]Dept. of Gastroenterology and Hepatology, University Medical Centre Groningen, The Netherlands

18.00 Neoadjuvant radiochemotherapy in esophageal carcinoma: a high incidence of complete pathological response (p. 96)

R.L.G.M. Blom[1], W. Schreurs[2], G. Lammering[3], R.F.A. Vliegen[4], L.E. Oostenbrug[5], M. Nap[6], M.N. Sosef[1], [1]Dept. of Surgery, [2]Dept. of Nuclear Medicine Atrium Medical Centre, Heerlen, [3]Dept. of Radiation Oncology (MAASTRO), University Medical Centre Maastricht, Dept. of Radiology, [5]Dept.of Internal Medic and Gastroenterology, [6]Dept. of Pathology, Atrium Medical Centre, Heerlen, The Netherlands

Donderdag 18 maart 2010

18.15 Lysophosphatidic acid is a potential mediator of cholestatic pruritus (p. 97)

A.E. Kremer[1], J.J. Martens[1], W. Kulik[2], C. Williamson[3], W.H. Moolenaar[4], J. Kondrackiene[5], U. Beuers[1], R.P.J. Oude Elferink[1] ,[1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, University of Amsterdam, [2]Laboratory Genetic Metabolic Diseases, Academic Medical Centre, University of Amsterdam, The Netherlands; [3] Maternal and Fetal Disease Group, Institute of Reproductive and Developmental Biology, Imperial College London, United Kingdom; [4]Division of Cellular Biochemistry, Centre for Biochemical Genetics, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [5]Dept. of Gastroenterology, Kaunas University of Medicine , Kaunas, Lithuania

18.30 Einde programma, congresborrel in de expositiehallen

19.30 Diner in de Genderzaal

Sectie Neurogastroenterologie en Motiliteit **Auditorium**

Voorzitters: A.J. Bredenoord en A.J.P.M. Smout

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

13.00 Is visceroperception influenced by meal ingestion in irritable bowel syndrome (IBS)? (p. 98)
S. Ludidi, J.M. Conchillo, C.J. Koning, S. Vanhoutvin, D. Jonkers, A.A. Masclee , Division of Gastroenterology and Hepatology, Dept. of Internal Medicine , Maastricht University Medical Centre, Maastricht, The Netherlands

13.10 Ano-reservoir function after ileal neorectal anastomosis for ulcerative colitis; a comparison with the ileal pouch anal anastomosis (p. 99)
J.T. Heikens[1], W. Hopmans[2], D.J. de Jong[2], C.J.H.M. van Laarhoven[1], [1]Dept. of Surgery, Radboud University Nijmegen Medical Centre, [2]Dept. of Gastroenterology, Radboud University Nijmegen Medical Centre, The Netherlands

13.20 Which clinical symptoms reflect postoperative recovery of gastrointestinal motility? (p. 100)
S.H. van Bree[1], L.E. Nijhuis[1], M.S. Vlug[2], W.A. Bemelman[2], W.J. de Jonge[1], S.A. Snoek[1], E.P. van der Zanden[1], F.O. The[1], M.W. Hollmann[3], R.J. Bennink[4], G.E. Boeckxstaens[1,5], Dept. of [1]Gastroenterology, [2]Surgery, [3]Anesthesiology, [4]Nuclear Medicine, Academic Medical Centre, Amsterdam, The Netherlands, [5]Dept. of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium

13.30 The effect of laparoscopy and/or fast track multimodal management on postoperative gastrointestinal motility after colonic surgery (p. 101)
S.H. van Bree[1], M.S. Vlug[2], W.A. Bemelman[2], M.W. Hollmann[3] , W.J. de Jonge[1], S.A. Snoek[1], E.P. van der Zanden[1], F.O. The[1], R.J. Bennink[4], G.E. Boeckxstaens[1,5], Depts. of [1]Gastroenterology, [2]Surgery, [3]Anesthesiology, [4]Nuclear Medicine, Academic Medical Centre, Amsterdam, The Netherlands, [5]Dept. of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium

13.40 Functional Nonretentive Fecal Incontinence, do enemas help? (p. 102)
R. Burgers, C.J.C. Hoppenbrouwers, M.E.J. Bongers, F. de Lorijn, W.P. Voskuijl, M.M. van den Berg, N. Bekkali, O. Liem. B. Peeters, C.M. Loots, M.P. van Wijk, M.A. Benninga, Emma Kinderziekenhuis AMC, Amsterdam, The Netherlands

13.50 IgE immunoglobulins and mast cells in colonic mucosa of patients with Irritable Bowel Syndrome (p. 103)
B.Braak[1], S.A. van Diest[2], T.K. Klooker[1], O. Welting[2], C.M. van der Loos[3], R.M. van den Wijngaard[2], G.E.E. Boeckxstaens[1,4], [1]Gastroenterology and Hepatology, AMC, Amsterdam, [2]Tytgat Institute of Liver and Intestinal Research, AMC, Amsterdam, [3]Pathology, AMC, Amsterdam, The Netherlands, [4]Gastroenterology, University Hospital Leuven, Catholic University Leuven, Belgium

Donderdag 18 maart 2010

14.00 Free immunoglobulin light chains may be involved in stress-induced visceral hypersensitivity in maternal separated rats (p. 104)

S.A. van Diest[1], O.I. Stanisor[1], O. Welting[1], W.J. de Jonge[1], A.D. Kraneveld[2], F.A. Redegeld[2], G.E. Boeckxstaens[1,3], R.M. van den Wijngaard[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, [2]Division of Pharmacology & Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands, [3]Dept. of Gastroenterology, Catholic University of Leuven, Belgium

14.10 The peripheral Histamine 1-receptor antagonist fexofenadine effectively reverses stress-induced visceral hypersensitivity in a rat model of maternal separation (p. 105)

O.I. Stanisor[1], S.A. van Diest[1], O. Welting[1], C. Cailotto[1], J. van der Vliet[1], W.J. de Jonge[1], G.E. Boeckxstaens[2], R.M. van den Wijngaard[1], [1]Tytgat Institute for Liver and Intestinal Research, (former AMC Livercenter), Academic Medical Centre, The Netherlands, [2]Gastroenterology, Katholieke Universiteit , Leuven, Belgium

14.20 ApoA-IV and CCK signalling is enhanced in the duodenum of GERD patients (p. 106)

O.S. van Boxel, J.J.M. ter Linde, J. Oors, A.J.P.M. Smout, P.D. Siersema, Dept. of Gastro-enterology and Hepatology, University Medical Centre Utrecht, The Netherlands

14.30 High Resolution Esophageal Topography is superior to conventional sleeve manometry for the detection of TLESRs associated with reflux (p. 107)

W.O.A. Rohof[1], G.E.E. Boeckxstaens[1,2], D.P. Hirsch[1],[1]Dept of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands[2], Dept of Gastroenterology, University Hospital, Leuven, Belgium

14.40 Prevalence of gastrointestinal symptoms in diabetics is related to psychological factors (p. 108)

S. de Kort[1], J. Kruimel[1], I. Arts[3], J. Sels[2], N. Schaper[2], A. Masclee[1], Division of Gastroentero-logy[1] and Endocrinology[2], Dept. of Internal Medicine and Dept. of Epide-miology[3], Maastricht University Medical Centre, The Netherlands

14.50 Impedance recording and high resolution manometry help to better define rumination episodes (p. 109)

B.F. Kessing, F. Govaert, A.A. Masclee, J.M. Conchillo, Division of Gastroenterology and Hepa-tology, Dept. of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

15.00 Theepauze

Voorzitters: J.Ph. Kuyvenhoven en A.A.M. Masclee

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

15.30 High cumulative and relative cancer risk and increased mortality in patients with Peutz-Jeghers syndrome (p. 110)

M.G.F. van Lier[1], A.M. Westerman[2], A. Wagner[3], C.W.N. Looman[4], J.H.P. Wilson[2], F.W.M. de Rooij[2], V. Lemmens[5], E.J. Kuipers[1,2], E.M.H. Mathus-Vliegen[6], M.E. van Leerdam[1], Dept. of Gastroenterology and Hepatology[1] , Internal Medicine[2], Clinical Genetics[3] and Public Health[4], Erasmus MC, University Medical Centre, Rotterdam, Dept. of Research[5], Comprehensive Cancer Centre South, Eindhoven, Dept. of Gastroenterology and Hepatology[6], Academic Medical Centre, Amsterdam, The Netherlands

15.40 High intussusception risk at young age in patients with Peutz-Jeghers syndrome: time to update surveillance guidelines? (p. 111)

M.G.F. van Lier[1], E.M.H. Mathus-Vliegen[2], A. Wagner[3], M.E. van Leerdam[1], E.J. Kuipers[1,4], Depts. of Gastroenterology and Hepatology[1], Clinical Genetics[3] and Internal Medicine[4], Erasmus MC, University Medical Centre, Rotterdam, Dept. of Gastroenterology and Hepatology[2] , Academic Medical Centre, Amsterdam, The Netherlands

15.50 The European Achalasia trial: a randomized multi-centre trial comparing endoscopic pneumodilation and laparoscopic Heller myotomy as primary treatment of idiopathic achalasie (p. 112)

G.E. Boeckxstaens[1,2], V. Annese[3], S. Bruley des Varannes[4], S. Chaussade[5], M. Costantini[6], I. Elizalde[7], U. Fumagalli[8], M. Gaudric[5], E.H. Metman[9], J. Pérez de la Serna[10] , W.O. Rohof[1], A.J. Smout[11], J. Tack[2], G. Zaninotto[6], O.R. Busch[12], [1]Dept. of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, University Hospital, catholic University, Leuven, Belgium, [3]Ospedale Casa Sollievo della Sofferenza, S. Giovanni Rotondo, Italy, [4]Gastroenterology, Centre Hospitalier Universitaire, Nantes, France, [4]Cochin University Hospital, Paris, France, [6]Surgery, S Giovanni e Paolo Hospital, Venice, Italy, [7]Gastroenterology, University of Barcelona, Barcelona, Spain, [8]Surgery, Istituto Clinico Humanitas, Milan, Italy, [9]Gastroenterology, Hôpital Trousseau, Tours, France,[10]Gastro-enterology, Hospital Universitario San Carlos, Madrid, Spain, [11]Gastroenterology, University Medical Centre, Utrecht, The Netherlands, [12] Surgery, Academic Medical Centre, Amsterdam, The Netherlands

16.00 Laparoscopic Nissen (posterior total) versus Toupet (posterior partial) Fundoplication for Gastro-oesophageal Reflux Disease A meta-analysis of randomised trials (p. 113)

J.A. Broeders[1], F.A. Mauritz[1], U. Ahmed Ali[1], W.A. Draaisma[1], J.P. Ruurda[1], H.G. Gooszen[1], A.J. Smout[2], I.A. Broeders[3] , E.J. Hazebroek[1], [1]Dept. of Surgery, Gastrointestinal Research Centre of the University Medical Centre Utrecht, Utrecht, [2]Dept. of Gastroenterology, Gastrointestinal Research Centre of the University Medical Centre, Utrecht, [3]Dept. of Surgery, Meander Medical Centre, Amersfoort, The Netherlands

Donderdag 18 maart 2010

16.10 Concomitant use of a proton pump inhibitor does not increase the risk of recurrent myocardial infarction among clopidogrel users (p. 114)

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

16.20 Proton pump inhibitor use is associated with an increased risk for microscopic colitis: a case-control study (p. 115)

D. Keszthelyi[1], S. Jansen[1], B. Scholtes[2], L.G. Engels[2], A.A.M. Masclee[1], [1]Division of Gastroenterology-Hepatology, Dept. of Internal Medical, Maastricht University Medical Centre, Maastricht, [2]Division of Gastroenterology, Dept. of Internal Medical, Orbis Medical Concern, Sittard, The Netherlands

16.30 New clopidogrel users on PPIs are at an increased risk of cardiovascular and gastrointestinal complications - results of a large Dutch cohort study (p. 116)

O.S. van Boxel[1], M.G.H. van Oijen[2], M.P. Hagenaars[3], A.J.P.M. Smout[1], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, [2]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, [3]Achmea Health Insurance, Leiden, The Netherlands

16.40 Proton pump inhibitor use and health-related quality of life in patients with gastroesophageal reflux disease and functional dyspepsia (p. 117)

O.S. van Boxel[1], B.L.A.M. Weusten[2], P.D. Siersema[1], A.J.P.M. Smout[1], [1]Dept. of Gastroentero-logy and Hepatology, University Medical Centre Utrecht, [2]Dept. of Gastroenterology, Saint Antonius Hospital, Nieuwegein, The Netherlands

16.50 The interval between the diagnosis of long segment Barrett's esophagus and symptommatic esophageal adenocarcinoma as found in an observational cohort followed up for 35 years (p. 118)

C.M. den Hoed[1], M. van Blankenstein[1], J. Dees[1], E.J. Kuipers[1,2], Depts. of Gastroenterology and Hepatology[1] and Internal Medicine[2], Erasmus Medical Centre, Rotterdam, The Netherlands

17.00 Prevalence of esophagitis and Barrett's esophagus patients undergoing routine colonoscopy; a cohort study (p. 119)

C.M. den Hoed[1], B.C. van Eijck[1], P.D. Siersema[1], E.J. Kuipers[1,2], Dept. of Gastroenterology and Hepatology[1] and Internal Medicinec[2], Erasmus Medical Centre, Rotterdam, The Netherlands

17.10 Covered self-expandable stents for the treatment of benign esophageal perforations and anastomotic leaks (p. 120)

P.G.A. van Boeckel[1], K.S. Dua[2], R.J.H. Schmits[1], N. Surapaneni[2], F.P. Vleggaar[1], P.D. Siersema[1], [1]Dept. of Gastroenterology & Hepatology, University Medical Centre Utrecht, The Netherlands[2], Dept. of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, USA

17.20 Endoscopic extraction of self-expandable metal stents from the esophagus: outcome and complications in 107 procedures (p. 121)
N.C.M. van Heel, J. Haringsma, E.J. Kuipers, Dept. of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, The Netherlands

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

18.30 Borrel in expositiehallen

19.30 Diner Genderzaal

Donderdag 18 maart 2010

DEGH-Meeting **Baroniezaal**

Voorzitters: J.D. Schulzke en R. van Tol

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

13.30 Intestinal bile salt nuclear receptor FXR protects from inflammatory bowel disease: potential therapeutic implications (p. 122)

R.M.Gadaleta[1,2,3], K.J. van Erpecum[1], B. Oldenburg[1], E.C.L. Willemsen[2], S. Murzilli[3], L.W.J.Klomp[2], P.D. Siersema[1], A. Moschetta[3], S.W.C. van Mil[2], [1]Dept. of Gastroenterology and Hepatology, [2]Laboratory of Metabolic and Endocrine Diseases and Netherlands Metabolomics Centre, UMC Utrecht, The Netherlands, [3]Laboratory of Lipid Metabolism and Cancer, Consorzio Mario Negri Sud, S.ta Maria Imbaro (Ch), Italy

13.42 Development of colitis in Muc2-deficient mice: diet matters! (p. 123)

N. Burger-van Paassen[1], P.J. Puiman[1], P. Lu[1], N. Le Polles[1], J. Bouma[1], A.M. Korteland-van Male[1], G. Boehm[1,2], J.B. van Goudoever[1], I.B. Renes[1], [1]Erasmus MC-Sophia, Lab.[1]Pediatrics, Neonatology,, Rotterdam, The Netherlands, [2]Danone Research, Friedrichsdorf, Germany

13.54 Lipid-rich nutrition inhibits mast cell activation via the vagal anti-inflammatory pathway (p. 124)

J. de Haan[1], M. Hadfoune[1], T. Lubbers[1], W.A. Buurman[1], J.W.M. Greve[2,1], [1]Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, [2]Surgery, Atrium Medisch Centre, Heerlen, The Netherlands

14.06 Functional splanchnic hypoperfusion precedes intestinal epithelial cell damage during strenuous exercise (p. 125)

K. van Wijck[1,2,3], K. Lenaerts[1,2,3], L.J.C. van Loon[1,2,4], J.M. Senden[1,2,4], C.H.C. Dejong[1,2,3], W.A. Buurman[1,2,3], [1]Top Institute Food and Nutrition, Wageningen, [2]NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht, [3]Dept. of Surgery, [4]Dept. of Human Movement Sciences, Maastricht University Medical Centre, Maastricht, The Netherlands

14.18 Increasing intestinal threonine metabolism improves gut barrier function and resistance to necrotizing enterocolitis in preterm pigs fed colostrum (p. 126)

P.J. Puiman[1], M.L. Jensen[2], B. Stoll[3], K. Dorst[1], I. Renes[1], P. Sangild[2], J.B. van Goudoever[1], [1]Pediatrics, Neonatology, Erasmus MC-Sophia, Rotterdam, The Netherlands, [2]Dept. of Human Nutrition, University of Copenhagen, Denmark, [3]Pediatrics, Children's Nutrition Research Centre, Houston, Texas, U.S.

14.30 Vagus nerve released acetylcholine can inhibit intestinal inflammation via cross talk with vasoactive intestinal peptide (p. 127)

E.P. van der Zanden[1], C. Cailotto[1], L.E.J. Nijhuis[1], G. Boeckxstaens[1,2] , W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, Catholic University of Leuven, Leuven, Belgium

14.42 Intestinal integrity is preserved and inflammation is reduced by lipid-rich enteral nutrition in a rat hemolysis model (p. 128)
J. de Haan[1], B. Hanssen[1], I. Vermeulen Windsant[1], T. Lubbers[1], M. Hadfoune[1], W.A. Buurman[1], J.W.M. Greve[2], [1]Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University MC, [2]Surgery, Atrium MC, Heerlen, The Netherlands

14.56 Theepauze en Ledenvergadering NVH

DEGH-Meeting **Baroniezaal**

Voorzitters: J.P.H. Drenth en G. Bouma

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

15.30 **Invited speaker: Prof. dr. J.D. Schulzke**
Regulation of tight-junctions in the intestinal epithelium and their role in the development of GI disease

16.00 Hepatitis B virus impairs the interaction between natural killer cells and plasmacytoid dendritic cells (p. 129)
C.C. Shi[1,2], E.T.T.L. Tjwa[1], P.J. Biesta[1], Q. Xie[2], H.L.A. Janssen[1], A.M. Woltman[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands, [2]Dept. of Infectious Disease, Rujin Hospital, Shanghai, China

16.12 Novel semi-synthetic flavonoid monoHER prevents monocrotaline induced sinusoidal obstruction syndrome in rats (p. 130)
M.A.J. van den Broek[1], D.K. Dhar[2], T.M. Ezzat[2], N.A. Davies[3], A. Bast[4], M. Malagó[2], S.W.M. Olde Damink[1,2], [1]Dept. of Surgery, Maastricht University Medical Centre, The Netherlands, [2]HPB Research Group, Dept. of Surgery, University College London, United Kingdom, [3]Liver Failure Group, Institute of Hepatology, University College London, United Kingdom, [4]Dept. of Toxicology and Pharmacology, Maastricht University Medical Centre, The Netherlands

16.24 BMI1 is a marker of activated liver progenitor cells (p. 131)
B.A. Schotanus[1], B. Spee[1,2], H.S. Kruitwagen[1], B. Brinkhof[1], T.S.G.A.M. van den Ingh[3], J. Rothuizen[1], L.C. Penning[1], T. Roskams[2], [1]Dept. of Clinical Sciences of Companion Animals, Utrecht University, The Netherlands, [2]Dept. of Morphology and Molecular Pathology, University Hospitals Leuven, Leuven, Belgium, [3]TCCI-consultancy, Utrecht, The Netherlands

16.36 Regulation of hCTR1-dependent cellular copper uptake by heteromerization with the homologous hCTR2 copper transporter (p. 132)
P.V.E van den Berghe, L.W.J. Klomp, Dept. of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, The Netherlands

Donderdag 18 maart 2010

16.48 Changes in transmembrane lipid distribution in human erythrocytes as a possible cause for Ribavirin-induced anemia (p. 133)
K. Mast[1], M-C Kleinegris[1], J.M. Balk[2], G.R.M.M. Haenen[2], A.Bast[2], G.H. Koek[1], E.M. Bevers[3], [1]Dept. Internal Medicine, Maastricht University Medical Centre, [2]Dept. Pharmacology and Toxicology and [3]Dept.of Biochemistry, Maastricht University

17.00 Einde programma.
Voor de Frieda den Hartog Jager Lecture en de President Select kunt u zich begeven naar de Brabantzaal

18.30 Borrel in expositiehallen

19.30 Diner Genderzaal

Workshop **Parkzaal**

Voorzitter: J.D. van Bergeijk

Workshop Sedatie door niet-anesthesisten

15.30 Sedatie en bewaking
anesthesist

16.00 Propofol bij endoscopisch onderzoek
Dr. J.J. Kolkman, maag-darm-leverarts,
Medisch Spectrum Twente, Enschede

16.30 Concept richtlijn Sedatie
Dr. S.J. van den Hazel, maag-darm-leverarts,
Slingeland Ziekenhuis, Doetinchem

17.00 Einde programma

Sectie Gastrointestinale Endoscopie — Brabantzaal

Voorzitters: M.A.J.M. Jacobs en B.L.A.M. Weusten

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

8.30 Multi-Band Mucosectomy in Barrett Esophagus: a prospective registration of 1060 resections in 243 procedures (p. 134)

L. Alvarez Herrero[1, 2], R.E. Pouw[2], B.L. Weusten[1], J.J. Bergman[2], [1]Dept. of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

8.40 Safety outcomes of balloon-based circumferential radiofrequency ablation after focal endoscopic resection of early Barrett's neoplasia in 118 patients: results of an ongoing European multicenter study (p. 135)

R.E. Pouw[1], R. Bisschops[2], O. Pech[3], K. Ragunath[4], B.L. Weusten[5], B. Schumacher[6], B. Rembacken[7], A. Meining[8], H. Messmann[9], E.J. Schoon[10], L. Gossner[11], J. Mannath[4], C.A. Seldenrijk[12], M. Visser[13], A. Lerut[14], J. Devière[15], T. Rösch[16], S. Seewald[16], F.J. ten Kate[13], C. Ell[3], H. Neuhaus[3], J.J. Bergman[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology and Endoscopy, University Hospitals Leuven, Leuven, Belgium, [3]Dept. of Internal Medicine II, Dr. Horst-Schmidt-Kliniken, Wiesbaden, Germany, [4]Division of Gastroenterology, Wolfson Diges-tive Diseases Centre, Nottingham, UK, [5]Dept. of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, The Netherlands, [6]Dept. of Gastroenterology, Evangelisches Krankenhaus Düsseldorf, Düsseldorf, Germany, [7]Dept. of Gastroenterology, The General Infirmary at Leeds, United Kingdom, [8]Second Medical Department, Technical University of Munich, Munich, Germany, [9]Third Medical Clinic, Klinikum Augsburg, Augsburg, Germany, [10]Dept. of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands, [11]Dept. of Medicine I, Klinikum Karlsruhe, Karlsruhe, Germany, [12]Dept. of Pathology, St. Antonius Hospital, Nieuwegein, The Netherlands, [13]Dept. of Pathology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands, [14]Dept. of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium, [15]Dept. of Gastro-enterology and Hepatology, Erasme University, Brussels, Belgium, [16]Dept. for Interdisciplinary Endoscopy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

8.50 Simultaneous (same session) radiofrequency ablation and endoscopic resection is feasible, safe and effective for selected cases of early neoplasia in Barrett's esophagus (p. 136)

F.G.I. van Vilsteren[1], R.E. Pouw[1], L. Alvarez Herrero[2,1], M. Visser[3], F.J. ten Kate[3], B.L. Weusten[2,1], J.J. Bergman[1], [1]Gastroenterology, Academic Medical Centre, Amsterdam, [2]Gastroenterology, St Antonius hospital, Nieuwegein, [3]Pathology, Academic Medical Centre, Amsterdam, The Netherlands

09.00 Einde abstracts, vervolg symposium NOTES

Symposium NOTES — Brabantzaal

Chairman: P. Fockens en W. Hameeteman

09.00 Current status of NOTES in the Netherlands
P. Fockens, Dept. of Gastroenterology, Academic Medical Centre Amsterdam

09.10 Hybrid procedures in laparoscopy and NOTES
W. Bemelman, Dept of Surgery, Academic Medical Centre Amsterdam

09.30 Endoscopic transmural necrosectomy for organized pancreatic necrosis
H. Seifert, Dept of Internal Medicine, Oldenburg Municipal Hospital, Germany

09.50 New technical developments for NOTES
M.I. van Berge Henegouwen, Dept of Surgery, Academic Medical Centre Amsterdam

10.10 Q & A

10.30 Coffee / tea, exhibition hall

Sectie Gastrointestinale Endoscopie — Brabantzaal

Voorzitters: M.A.M.J. Jacobs en B.L.A.M. Weusten

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

11.00 A prospective, group sequential study evaluating a new type of fully covered self expandable metal stent with a proximal retrieval lasso for the treatment of benign biliary strictures (p. 137)
J.W. Poley[1], D. Cahen[1], G. Kazemier[2], H.J. Metselaar[1], J. Haringsma[1], C.H.J. van Eijck[2], E..J. Kuipers[1], M.J. Bruno[1], Dept. of Gastroenterology & Hepatology[1] and Surgery[2], Erasmus MC, University Medical Centre Rotterdam, The Netherlands

11.10 A multi-centre randomized cross-over trial comparing Endoscopic Trimodal Imaging (ETMI) with standard endoscopy (SE) for the detection of dysplasia in Barrett's esophagus (BE) in patients with a confirmed diagnosis of low-grade dysplasia (LGD) performed in a non-university setting (p. 138)

W.L. Curvers[1], F.G.I. van Vilsteren[1], L.C. Baak[2], C. Böhmer[3], R.C. Mallant-Hent[4], A.H. Naber[5], A. van Oijen[6], C.Y. Ponsioen[1], P. Scholten[7], E. Schoon[8], E. Schenk[9], G.A. Meijer[10] , F.J. ten Kate[11], J.J.G.H.M. Bergman[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [2]Dept. of Gastroenterology and Hepatology, OLVG, Amsterdam, [3]Dept. of Gastroenterology and Hepatology, Spaarne Hospital, Hoofddorp, [4]Dept. of Internal Medicine, Flevohospital, Almere, [5]Dept. of Internal Medicine, Tergooi Hospitals, Hilversum, [6]Dept. of Gastroenterology and Hepatology, Medical Centre Alkmaar, [7]Dept. of Gastroenterology and Hepatology, St Lucas Andreas Hospital, Amsterdam, [8]Dept. of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, [9]Dept. of Gastroenterology and Hepatology, Isala Clinics, Zwolle, [10]Dept of Pathology, Free University Medical Centre, Amsterdam, [11]Dept. of Pathology, Academic Medical Centre, Amsterdam, The Netherlands

11.20 Endoscopic Tri-modal Imaging (ETMI) for the detection and classification of early colorectal neoplasia; a multi-centre randomized controlled trial (p.139)

T. Kuiper[1], F.J.C. van den Broek[1], A. H. Naber[2], E. J.van Soest[3], P. Scholten[4], R.Ch. Mallant - Hent[5], J. van den Brande[2], J.M. Jansen[6], A.H.A.M. van Oijen[7], W.A. Marsman[3], J.J.G.H.M. Bergman[1], P. Fockens[1], E. Dekker[1], [1]Academic Medical Centre, Dept of Gastroenterology, Amsterdam, [2]Tergooi hospitals, Hilversum, [3]Kennemer Gasthuis, Haarlem, [4]St Lucas Andreas Hospital, Amsterdam, [5]Flevohospital, Almere, [6]OLVG, Amsterdam, [7]Medical Centre Alkmaar, The Netherlands

11.30 Post-polypectomy surveillance practice of adenoma patients – considerable room for improvement (p. 140)

E.M.B. van Heijningen[1], I. Lansdorp-Vogelaar[1], E.J. Kuipers[2], M. van Ballegooijen[1], [1]Dept. of Public Health, Erasmus MC, Rotterdam, [2]Dept. of Gastroenterology and Hepatology and Dept. of Internal Medicine , Erasmus MC, Rotterdam, The Netherlands

11.40 Nurse endoscopists performing colonoscopy: a prospective study on quality and patient experiences (p. 141)

P.G. van Putten[1], F. ter Borg[2], R.P.R. Adang[3], M.E. van Leerdam[1], and E.J. Kuipers[1, 4], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, [2]Dept. of Gastroenterology and Hepatology, Deventer Hospital, [3]Dept. of Gastroenterology and Hepatology, Viecuri Medical Centre, Venlo, [4]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

11.50 Self-assessment in Colonoscopy, a Novel Tool for Assessment of Skills (p. 142)

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

Nederlandse Vereniging van Maag-Darm-Leverartsen **Genderzaal**

12.00 Ledenvergadering *(met lunchbuffet in de zaal)*

NVGE en NESPEN **Parkzaal**

Voorzitters: C.F. Jonkers en G. Wanten

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

08.30 MLDS-voordracht:
Genomic and signal transduction events promoting insulinoma (p. 143)
E-J.M Speel, Dept. of Molecular Cell Biology, GROW-School for Oncology & Developmental Biology, Maastricht University Medical Centre, The Netherlands

08.40 MLDS-voordracht:
Reduced small intestinal function in essential fatty acid (EFA) deficiency (p. 144)
S. Lukovac, E.H.H.M. Rings, H.J. Verkade, Pediatric Gastroenterology, Dept. of Pediatrics, Beatrix Children's Hospital, Groningen University Institute for Drug Exploration (GUIDE), Centre for Liver, Digestive and Metabolic Diseases, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

08.50 Food matrix effects on bio-accessibility of β-carotene can be measured in an in-vitro gastrointestinal model (p. 145)
C.A. van Loo-Bouwman[1], T.H.J. Naber[1,2], M.M Kus[3], R.B. van Breemen[4], T. van Roekel- Jansen[5], P.J.M. Hulshof[5], G. Schaafsma[5,6], [1]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, [2]Dept. of Internal Medicine, Tergooi Hospitals, Hilversum, [3]TNO Quality of Life, Zeist, The Netherlands, [4]Dept. of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois, Chicago, IL, USA, [5]Division of Human Nutrition, Wageningen University, Wageningen, [6]Research group on Sports, Nutrition and Lifestyle, HAN University, Nijmegen, The Netherlands

09.00 Multiple common genetic variants for coeliac disease influencing immune gene expression (p. 146)
G. Trynka[1], P.C.A. Dubois[2], L. Franke[1], C.J. Mulder[3], G.J. Tack[3], W.H.M. Verbeek[3], V.M. Wolters[4], R.H.J. Houwen[4], M.L. Mearin[5], Coeliac Disease Genetics Consortium[6], R. McManus[7], D. Barisani[8], P. Saavalan[9], D.A. van Heel[2], C. Wijmenga[1], [1]Genetics Dept. University Medical Centre and Groningen University, The Netherlands, [2]Centre for Gastroenterology, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, UK, [3]Dept. of Gastroenterology, VU Medical Centre, Amsterdam, [4]Dept. of Paediatric Gastroenterology, University Medical Centre Utrecht, Utrecht, [5]Dept. of Paediatric Gastroenterology, Leiden University Medical Centre, Leiden, [6]The Celiac Disease Genetics Consortium, Groningen, The Netherlands and London, United Kingdom, [7]Dept. of Clinical Medicine, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland, [8]Dept. of Medical Sciences, University of Milan, Italy, [9]Dept. of Medical Genetics, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland

09.10 Survival in Enteropathy Associated T-cell lymphoma: type of lymphoma is not a prognostic factor (p. 147)
L.R. de Baaij[1], J.M.W. van de Water[1], W.H.M. Verbeek[1] and C.J.J. Mulder[1], [1]Gastro-enterology and Hepatology, VU University Medical Centre Amsterdam, The Netherlands

09.20 Prediction model for the diagnosis chronic upper gastrointestinal ischemia: diagnostic value of symptoms, radiological imaging and gastrointestinal tonometry (p. 148)

A. Sana[1], D. van Noord[1], Y. Vergouwe[2], L.M.G. Moons[1], H.J.M. Verhagen[3], P.M.T. Pattynama[4], E.J. Kuipers[1], P.B.F. Mensink[1], Dept. of Gastroenterology and Hepatology[1], Centre for Medical Decision Sciences[2], Vascular Surgery[3], Interventional Radiology[4] Erasmus MC - University Medical Centre, Rotterdam, The Netherlands

09.30 Loss of the guardians at the intestinal barrier: paneth cell apoptosis as a new phenomenon in human intestinal ischemia-induced bacterial translocation (p. 149)

J. Grootjans[1], C. Hodin[1], J.J. de Haan[1], K. Lenaerts[1], M. Hadfoune[1], J. Derikx[2], A.P. de Bruïne[3], R. van Dam[1], C.H.C. Dejong[1], W. Buurman[1], [1]Surgery, Maastricht University Medical Centre, Maastricht, [2]Surgery, Orbis Medical Centre, Sittard, [3]Pathology, VieCuri Medisch Centrum, Venlo, The Netherlands

09.40 Vitamin B_{12} deficiency in Patients with Chronic Pancreatitis: Not as rare a previously thought (p. 150)

R.C.G. Biesmans[1], A.G.H. Kessels[2], J.H.M. Brouns[3], P.P.C.A. Menheere[4], A.A.M. Masclee[1], Y.C.A. Keulemans[1], [1]Gastroenterology, [2]Epidemiology, Maastricht University Medical Centre, Maastricht, [3]Dietetics and Nutrition, Maastricht University Medical Centre, [4]Clinical Chemistry, Maastricht University Medical Centre, Maastricht, The Netherlands

09.50 Endoglin as indicator of metastatic neuroendocrine tumors of the pancreas (p. 151)

P. Kuiper[1], H.W. Verspaget[1], E.S.M. de Jonge-Muller[1], L.J.A.C. Hawinkels[2], I. Biemond[1], C.B.H.W. Lamers[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Molecular Cell Biology and Centre for Biomedical Genetics, Leiden University Medical Centre, Leiden, The Netherlands

10.00 Smoking induces pancreatic fibrosis in humans (p. 152)

E.J.M. van Geenen[1,2], M.M. Smits[1], T.C.M.A. Schreuder[1,5], D.L. van der Peet[4], E. Bloemena[3], C.J.J. Mulder[1], [1]Dept. of Gastroenterology & Hepatology, VU University Medical Centre, Amsterdam, [2]Dept. of Gastroenterology & Hepatology, Bronovo Teaching Hospital, The Hague, [3]Dept. of Pathology, VU University Medical Centre, Amsterdam, [4]Dept. of Gastrointestinal Surgery, VU University Medical Centre, Amsterdam, [5]Dept. of Gastroenterology & Hepatology, Slingeland Ziekenhuis, Doetinchem, The Netherlands

10.10 Does consultation of a dietician in chronic pancreatitis patients with exocrine insufficiency make a difference? a Dutch national survey (p. 153)

E.C.M. Sikkens[1], D. Cahen[1], C.H. van Eijk[2], E.J. Kuipers[1], M.J. Bruno[1],[1]Dept. of Gastroentero-logy, Erasmus Medical Centre, Rotterdam, [2]Dept. of Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

10.20 Lipid-rich nutrition reduces enterocyte damage and controls inflammation in murine gram-negative sepsis (p. 154)

T. Lubbers[1], J.J. De Haan[1], M. Hadfoune[1], Y. Zhang[4], M.D. Luyer[1,2], D. Grundy[4], W.A. Buurman[1], J.W. Greve[1,3], [1]Dept. of Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, [2]Dept. of surgery, Maasland Hospital, Sittard, [3]Dept. of Surgery, Atrium Medical Centre, Heerlen, The Netherlands, [4]Dept. of Biomedical Science, University of Sheffield, Sheffield, United Kingdom

10.30 Koffie/thee in de expositiehal

NVGE Sectie Kinder-MDL — Parkzaal

Voorzitters: J.C. Escher en R.H.J. Houwen

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

11.00 Long-term efficacy of infliximab treatment in pediatric Crohn's disease in The Netherlands (p. 155)

C.I. de Bie[1], T.Z. Hummel[2], A. Kindermann[2], F.T.M. Kokke[3], G.M. Damen[4], C.M.F. Kneepkens[5], P.F. van Rheenen[6], J.J. Schweizer[7], J.H. Hoekstra[8], O.F. Norbruis[9], W.E. Tjon a Ten[10], A.C. Vreugdenhil[11], J.M. Deckers-Kocken[12], C. Gijsbers[13], J.C. Escher[1], L. de Ridder[1], [1]Dept. of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, [2]Dept. of Pediatric, Gastroenterology, Emma Children's Hospital/Academic Medical Centre, Amsterdam, [3]Dept. of Pediatric Gastroenterology, Wilhelmina Children's Hospital/Utrecht Medical Centre, Utrecht, [4]Dept. of Pediatric Gastroenterology, University Medical Centre St Radboud, Nijmegen, [5]Dept. of Pediatric Gastroenterology, VU University Medical Centre, Amsterdam, [6]Dept. of Pediatric Gastroenterology, Beatrix Children's Hospital/University Medical Centre Groningen, Groningen, [7]Dept. of Pediatric Gastroenterology, Leiden University Medical Centre, Leiden, [8]Dept. of Pediatric Gastroenterology, Hieronymus Bosch Hospital, 's-Hertogenbosch, [9]Dept. of Pediatric Gastroenterology, Isala Klinieken, Zwolle, [10]Dept. of Pediatric Gastroenterology, Maxima Medical Centre, Veldhoven, [11]Dept. of Pediatric Gastroenterology, University Hospital Maastricht, [12]Dept. of Pediatric Gastroenterology, Flevoziekenhuis, Almere, [13]Dept. of Pediatric Gastroenterology, Juliana Children's Hospital, The Hague, The Netherlands

11.10 Multichannel intraluminal impedance baseline values in infants before and during proton pump inhibitor therapy (p. 156)

C.M. Loots[1,3], M.J. Smits[1], M.P. van Wijk[1,3], T.G. Wenzl[2], M.A. Benninga[1], T.I. Omari[3], [1]Paediatric Gastroenterology and Nutrition, Emma Children's Hospital/Academic Medical Centre, Amsterdam, The Netherlands, [2]Klinik für Kinder- und Jugendmedizin, Univer-sitätsklinikum der RWTH , Aachen, Germany, [3]Centre for Paediatric and Adolescent Gastro-enterology, CYWHS, Women's and Children's Hospital, Adelaide, SA, Australia

11.20 The Role of Endoscopy of the Upper Gastrointestinal Tract in the diagnostic assessment of Childhood Inflammatory Bowel Disease (p. 157)

T.Z. Hummel[1], F.J.W. ten Kate[2], M.A. Benninga[1], A. Kindermann[1], Dept. of Pediatric Gastroenterology[1], Dept. of Pathology[2] Amsterdam Medical Centre, The Netherlands

11.30 Sacral nerve neuromodulation therapy; a promising new treatment for children with refractory functional constipation (p. 158)

B. Peeters[1], B.P.W. van Wunnik[2], W. van Gemert[2], M.A. Benninga[1], C.G.M.I. Baeten[2], [1]Dept. of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre Amsterdam, [2]Dept. of Surgery, University Medical Centre Maastricht, The Netherlands

11.40 A novel mouse model for celiac disease reveals that gluten feed does not abide the rules of oral tolerance (p. 159)

M.F. du Pré[1], L..A. van Berkel[1], M.N. ter Borg[1], L. Torp Jensen[2], Y. Kooy-Winkelaar[3], F. Koning[3], L.M. Sollid[4], E.E.S. Nieuwenhuis[1], L.A. Fugger[5], J.N. Samsom[1], [1]Dept. of Pediatrics, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands, [2]Clinical Institute, Aarhus University Hospital, Skejby Sygehus, Denmark, [3]Dept. Blood Transfusion and Immunohematology, Leiden University Medical Centre, Leiden, The Netherlands, [4]Institute of Immunology, University of Oslo, Rikshospitalet-Radiumhospitalet Medical Centre, Norway, [5]Dept. of Clinical Neurology & MRC Human Immunology Unit, Weatherall Institute of Molecular Medicinec, John Radcliffe Hospital, University of Oxford, UK

11.50 A biopsy is not always necessary to diagnose celiac disease (p. 160)

A. Mubarak[1], V.M. Wolters[1], S.A.M. Gerritsen[1], F.H.J. Gmelig-Meyling[2], F.J.W. ten Kate[3], R.H.J. Houwen[1], [1]Dept. of Paediatric Gastroenterology, [2]Immunology and [3]Pathology, University Medical Centre Utrecht, The Netherlands

12.00 Lunch in de expositiehal

13.30 Vergadering Kinder-MDL

DEGH-Meeting **Baroniezaal**

Voorzitters: S.L. Friedman en K.N. Faber

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

08.30 Constitutive Hedgehog signaling impairs maturation and migration of esophageal epithelial precursor cells (p. 161)

W.A. van Dop[1,2], A. Uhmann[3], V. Jaks[4], J. Offerhaus[5], M.A. van den Bergh Weerman[6], J. Heijmans[7], D.W. Hommes[7], J.C. Hardwick[7], R. Toftgård[4], H. Hahn[3], G.R. van den Brink[7,1], [1]CEMM, Academic Medical Centre, Amsterdam, [2]Dept. of Gastroenterology & Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [3]Institute of Human Genetics, Georg August University of Göttingen, Germany, [4]Dept. of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden, [5]Dept. of Pathology, University Medical Centre, Utrecht, [6]Dept. of Pathology, Academic Medical Centre, Amsterdam, [7]Dept. of Gastroenterology & Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

08.42 Human polycystic liver cyst fluid disturbs cholangiocyte cyclic AMP signaling and proliferation, both processes are normalized by lanreotide treatment in a somatostatin receptor 5 and phosphodiesterase 4D dependent mechanism (p. 162)

J. Woudenberg, M.J. Janssen, I. Worm, R.H. te Morsche, M. Chrispijn, J.P.H. Drenth, Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

08.54 Characterization of the liver progenitor cell niche in liver diseases: potential involvement of Wnt and Notch signaling (p. 163)

B. Spee[1], G. Carpino[2], B.A. Schotanus[3], A. Katoonizadeh[1], S. van der Borght[1], E. Gaudio[4], and T. Roskams[1], [1]Dept. of Morphology and Molecular Pathology, University Hospitals Leuven, Leuven, Belgium, [2]Dept. of Health Sciences, University of Rome "Foro Italico", Rome, Italy, [3]Dept. of Clinical Sciences of Companion Animals, Faculty of Veterinary Medic, Utrecht University, The Netherlands, [4]Dept. of Human Anatomy, Sapienza University of Rome, Rome, Italy

09.06 Conditional loss of intestinal Hedgehog signaling results in a regenerative response and subsequently in loss of villi and the spontaneous development of chronic enteritis (p. 164)

W.A. van Dop[1,2], E.A. Wassenberg[1], B. Lanske[3], A.R. Clarke[4], J. Offerhaus[5], D.W. Hommes[6], J.C. Hardwick[6], I. Biemond[6], G.R. van den Brink[1,6], [1]CEMM, Academic Medical Centre, Amsterdam, [2]Dept. of Gastroenterology & Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [3]Dept. of developmental biology, Harvard School of Dental Medicine, Boston, MA, USA, [4]School of Biosciences, University of Cardiff, United Kingdom, [5]Dept. of Pathology, University Medical Centre, Utrecht, [6]Dept. of Gastroenterology & Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

09.18 In autosomal dominant polycystic liver disease (PCLD) cysts develop through a cellular recessive mechanism involving loss of heterozygosity and somatic mutations (p. 165)

M.J. Janssen[1], E. Waanders[1,2], H.B. Dijkman[3], R.H.M. te Morsche[1], J. Woudenberg[1], J.P.H. Drenth[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Human Genetics and [3]Dept. of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

09.30 Evaluation of the human hepatoma cell HepaRG for bioartificial liver application (p. 166)
G.A.A. Nibourg[1,2], T.V. van der Hoeven[1,2], M.T. Ackermans[3], R.P.J. Oude Elferink[2], T.M. van Gulik[1], R.A.F.M. Chamuleau[2], R. Hoekstra[1,2], [1]Surgical Laboratory, [2]Tytgat Institute for Liver and Intestinal Research, [3]Laboratory of Endocrinology, Academic Medical Centre, Amsterdam, The Netherlands

09.42 **Invited speaker: Prof. dr. S.L. Friedman**
Molecular mechanisms involved in the development of liver fibrosis

10.15 Uitreiking Distinguished Hepatologist en Young Hepatologist

10.30 Koffiepauze

DEGH-Meeting — Baroniezaal

Voorzitters: E. Cario en A.A. te Velde

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

11.00 Role of IL-1R-MyD88 signaling in the pathogenesis of postoperative ileus (p. 167)
S.A Snoek[1], S.H. van Bree[1], F.W. Hilbers[1], O. Welting[1], R.M. van den Wijngaard[1], G.E. Boeckxstaens[1,2], W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, University Hospitals Leuven, Leuven, Belgium

11.12 ATG16L1 and IRGM contribute to the regulation of immune responses (p. 168)
M.E. Wildenberg, A.C.W. Vos, M. Duijvestein, A.P. Verhaar, C. Strisciuglio, G.R. van den Brink, D.W. Hommes, Dept. of Gastroenterology and Hepatology, Leiden University Medical Centre, The Netherlands

11.24 Anti-TNF induced inhibition of T cell proliferation in a mixed lymphocyte reaction is Fc receptor dependent (p. 169)
A.C.W. Vos[1], M.E. Wildenberg[1], M. Duijvestein[1], A.P. Verhaar[1], J. Heijmans[1], G.R. van den Brink[1], D.W. Hommes[1], [1]Dept. of Gastroenterology and Hepatology, Leiden Univeristy Medical Centre, Leiden, The Netherlands

11.36 Immunoglobulin A: FcαRI interactions induce neutrophil migration through release of leukotriene B4 (p. 170)
L. van der Steen[1], C. W. Tuk[1], J.E. Bakema[1], G. Kooij[1], A. Reijerkerk[1], G. Vidarsson[4], G. Bouma[2], G. Kraal[1], H.E. de Vries[1], R.H.J. Beelen[1], M. van Egmond[1,3], [1]Dept. of Molecular Cell Biology and Immunology, [2]Dept. of Gastroenterology, [3]Dept. of Surgery, VU University Medical Centre, Amsterdam, [4]Dept. of Experimental Immunohematology, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands

11.48 6-thioguanine increases human innate immunity via inhibition of the Rac1 signaling path-way (p. 171)
L. Zhou[1,2], G. Dijkstra[2], K. Parikh[1], L. Visser[3], A. Regeling[2], G.M. Fuhler[1], M.P. Peppelenbosch[1], K.N. Faber[2], [1]Dept. of Gastroenterology, [2]Dept. of Cell biology, [3]Dept. of Pathology, University Medical Centre Groningen, The Netherlands

12.00 **Invited speaker: Prof. dr. E. Cario**
Toll-like receptors in inflammatory bowel disease

Postersessies DEGH **Meierij en Limburg Foyer**

12.30 De postersessie van de DEGH vindt plaats tussen 12.30 en 13.30 uur met vanaf 12.45 de mogelijkheid om u aan te sluiten bij een begeleide sessie langs de posters; u vindt een overzicht vanaf pagina 43 in dit programma.

DEGH-Meeting **Baroniezaal**

Voorzitters: C.C. Paulusma en E.H.H.M. Rings

Voordrachten in het Engels, spreektijd 8 minuten, discussietijd 4 minuten

13.30 Monocytes from chronic HCV patients are functionally altered with distinct regulation of bacterial and viralrecognition pathways (p. 172)
B. Liu, H.L.A. Janssen, A. Boonstra, Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

13.42 Potent in vivo inhibition of hepatitis C virus replication by mycophenolic acid in mice (p. 173)
P. de Ruiter[1], Q. Pan[2], H.J. Metselaar[2], J. Kwekkeboom[2], G. Kazemier[1], H.W. Tilanus[1], H.L.A. Janssen[2], L.J.W. van der Laan[1], Depts. of [1]Surgery and [2]Gastroenterology & Hepatology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

13.54 5-Aminosalicylic acid induces colorectal cancer cell death in vitro and in vivo (p. 174)
P.J. Koelink, A.I.M.J. Langers, W.H. De Vos tot Nederveen Cappel, M.A.C. Mieremet-Ooms, D.W. Hommes, C.B.H.W. Lamers, H.W. Verspaget, Dept. of Gastroenterology-Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

14.06 Preoperative calorie restriction reduces hepatic tumour load after exposure to circulating coloncarcinoma tumorcells in a mouse model (p. 175)
T.M. van Ginhoven[1], J.W. van den Berg[1,2], W.A. Dik[2], J.N.M. IJzermans[1], R.W.F. de Bruin[1], [1]Dept. of Surgery, Erasmus MC, Rotterdam, [2]Dept. of Immunology, Erasmus MC, Rotterdam, The Netherlands

14.18 Distinct pathways leading to colorectal cancer are prevalent in hyperplastic polyposis syndrome (p. 176)

K.S. Boparai[1], E. Dekker[1], M. Polak[2], A. Musler[2], S. van Eeden[2], C.J.M. van Noesel[2], [1]Dept. of Gastroenterology & Hepatology, Academic Medical Centre, Amsterdam, [2]Dept. of Pathology, Academic Medical Centre, Amsterdam, The Netherlands

14.30 Successful prevention of surgery-induced liver metastases development after anti- tumor monoclonal antibody therapy is mediated by the innate mononuclear phagocyte network (p. 177)

S.Grewal[1], M. Bögels[2], G.J. Van der Bij[1,2], M.A. Otten[1], S.J. Oosterling[2], S. Meijer[2], R.H.J. Beelen[1], M. van Egmond[1,2], [1]Dept. of Molecular Cell Biology and Immunology, [2]Dept. of Surgical Oncology, VU University Medical Centre, Amsterdam, The Netherlands

14.42 C-terminal phosphorylation of β-catenin increases its downstream signaling and contributes to intestinal carcinogenesis (p. 178)

W. van Veelen[1], N.H. Le[2], W. Helvensteijn[1], L. Blonden[2], M. Theeuwes[1], E. Bakker[1], L. van Gurp[3], F. Meijlink[3], E.J. Kuipers[1], R. Fodde[2], R. Smits[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, [2]Dept. of Pathology, Joseph Nefkens Institute, Erasmus Medical Centre, Rotterdam, The Netherlands

14.54 **Prijsuitreiking beste presentaties en beste posters**

15.15 Closing

Vrijdag 19 maart 2010

NVGE en VVGE **Brabantzaal**

Symposium Digestieve Oncologie
Georganiseerd door de Vlaamse en Nederlandse Verenigingen voor Gastroenterologie

Voorzitters: H. Boot en M. Peeters

13.30 Organisatie van screening voor colorectaal carcinoom in België
Prof. dr. G. Van Hal, medisch socioloog
Universiteit van Antwerpen

13.55 Behandeling van het maagcarcinoom: meer dan chirurgie
Dr. H. Boot, maag-darm-leverarts,
NKI Antoni van Leeuwenhoekhuis, Amsterdam

14.20 Brachytherapie bij het rectumcarcinoom - wat de MDL-arts moet weten
Mevr. prof. dr. C.A.M. Marijnen, radiotherapeut,
Leids Universitair Medisch Centrum

14.45 Identificatie van (non)-responders in de behandeling van gastrointestinale tumoren
Mevr. prof dr. N. Van Roy, Centre for Medical Genetics
Universitair Ziekenhuis Gent

15.10 De rol van MDL-artsen in de oncologie:
Prof. dr. M. Peeters, maag-darm-leverarts,
Universitair Ziekenhuis Antwerpen

15.35 Einde symposium

Sectie Endoscopie Verpleegkundigen en Assistenten **Diezezaal**

10.00	Opening door de voorzitter
10.15	Pre-assessment zinvol? *Mw. M.L.C. Kooijman-Spierings, endoscopie-assistente,* *Kennemer Gasthuis, Haarlem*
10.35	Nurse endoscopie, *Drs. P. van Putten, arts-onderzoeker,* *Erasmus MC, Rotterdam*
11.05	Kwaliteit op de endoscopieafdeling *Drs. V. de Jonge, onderzoeksmedewerker,* *Erasmus MC, Rotterdam*
11.35	Diagnostiek IBD volgens de CBO-richtlijnen. *Mw. N. Ipenburg, IBD consulent,* *Kennemer Gasthuis, Haarlem*
12.00	Lunchbuffet in de Kempenhal
13.45	Mevr. dr. M. Kaljouw, bestuursvoorzitter Verpleegkundigen & Verzorgenden Nederland
14.10	Ledenvergadering, stemming en toetreding tot de V&VN *Niet SEVA leden zijn welkom*
14.30	Inschrijving en Champagne?!
15.30	Einde programma

Vrijdag 19 maart 2010

Vereniging Maag Darm Leververpleegkundigen **Auditorium**

09.30	Ontvangst en infomarkt
10.00	Welkomstwoord, *W.H. Goverde, voorzitter VMDLV*
10.05	Motoriekstoornissen van slokdarm en maag *Prof. dr. A.J.P.M. Smout, maag-darm-leverarts,* *Academisch Medisch Centrum, Amsterdam*
11.00	Koffiepauze en infomarkt
11.30	Endoscopische behandeling bij slokdarmtumoren en maagpathologie *Dr. J.J.G.H.M. Bergman, maag-darm-leverarts,* *Academisch Medisch Centrum, Amsterdam*
12.00	Ledenvergadering en presentatie V&VN W. Goverde / M. Kaljouw
13.00	Lunch en infomarkt
14.00	Radiotherapie bij slokdarmcarcinoom met Brachy therapie *T. Rozema, radioloog,* *Dr. Bernard Verbeeten Instituut, Tilburg*
14.30	Chirurgische interventies bij slokdarm- en maagcarcinoom *Drs. A.A.P.M. Luijten, chirurg, Máxima Medisch Centrum*
15.00	Voeding bij radiotherapie van slokdarm en hoofd-hals tumoren *Mevr. M. Lassche, diëtist voedingsteam* *Medisch Centrum Alkmaar*
15.30	Einde programma

ZonMw

Theme 1. Cancer *(Limburg Foyer),* chairs: E.H.H.M. Rings en J.P.H. Drenth

Time *Poster* *Title*

12:45 **1** MicroRNA-145 is highly expressed in Barrett's esophagus, induces a decrease in cell proliferation and targets GATA6 in esophageal squamous epithelial cells
J.W.P.M. van Baal[1] , F.P. Vleggaar[1] , P.D. Siersema[1] ,[1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, The Netherlands

2 Methylation of the suppressor of cytokine signaling (SOCS)3 promoter region in ulcerative colitis-related carcinogenesis
A .C. de Haar[1], Y. Li[1], J. Deuring[1], B. Xia[2], EJ. Kuipers[1], CJ. van der Woude[1], [1]Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands, [2]Internal Medicine, Zhongnan Hospital, Wuhan, China

3 Candidate driver genes in focal chromosomal aberrations of stage II colon cancer
J.C. Haan[2], R.P.M. Brosens[1,4], B. Carvalho[2], F. Rustenburg[2], H. Grabsch[3], A.F. Engel[4], M.A. Cuesta[1], M. Flens[5], G.A. Meijer[2], B. Ylstra[2], [1]Dept. of Surgery, VU University Medical Centre, Amsterdam, [2]Dept. of Pathology, VU University Medical Centre, Amsterdam, The Netherlands, [3]Pathology and Tumour Biology, Leeds Institute of Molecular Medicine, University of Leeds, UK, [4]Dept. of Surgery, [5]Dept. of Pathology, Zaans Medical Centre, Zaandam, The Netherlands

4 Copy number profiles from small bowel adenocarcinomas are more similar to profiles from colorectal cancer than gastric cancer
J.C. Haan[1], T.E. Buffart[1], M.A. van de Wiel[1,2,3], B. Carvalho[1], C. Postma[1], N.C.T. van Grieken[1], I.D. Nagtegaal[4], C.J. Mulder[5], K. Maude[6], P. Howdle[6], P. Quirke[7], H. Grabsch[7], B. Ylstra[1], G.A. Meijer[1],[1]Dept. of Pathology, VU University medical centre, Amsterdam, [2]Dept. of Biostatistics (KEB), VU University medical centre, Amsterdam, [3]Dept. of Mathematics, Free University, Amsterdam, [4]Dept. of Pathology, University Medical Centre, Nijmegen, [5]Dept. of Gastroenterology, VU University medical centre, Amsterdam, The Netherlands, [6]Section of Medicine, Surgery and Anaesthesia, [7]Pathology and Tumour Biology, Leeds Institute of Molecular Medicine, University of Leeds, UK

5 Surgery-induced inflammation stimulates liver metastasis development
N. Gül[1], M. Bögels[2], R.H.J. Beelen[1], M. van Egmond[1,2], [1]Dept. of Molecular Cell Biology and Immunology, [2]Dept. of Surgical Oncology, VU University Medical Centre, Amsterdam, The Netherlands

Theme 2. Metabolism *(Limburg Foyer),* chairs: S. van Mil en K.N. Faber

Poster *Title*

11 Regulation of hepatic triglyceride content in bile salt deficient mice
C. Kunne, A. Acco, S. Duijst, D.R. de Waart, C.C. Paulusma, R.P.J. Oude Elferink, Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands

12 Fatty hepatocytes are not more susceptible to bile acid-induced apoptosis: involvement of PPAR-alpha activation

G. Karimian, M. Buist-Homan, U.J.F. Tietge[1], K.N. Faber, H. Moshage, Dept. Gastroenterology and Hepatology, [1]Dept. Pediatrics, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

13 Westernized high-fat diet accelerates development of dextran sulfate sodium-induced colitis in mice and supplementation of heme aggravates the disease course

E.M.J. van der Logt[1], T. Blokzijl[1], R. van der Meer[2], M.P. Peppelenbosch[3], K.N. Faber[1], G.Dijkstra[1], [1]Gastroenterology & Hepatology, University Medical Centre, Groningen, [2]Dietetics and Nutrition, NIZO, Ede, [3]Gastroenterology & Hepatology, Erasmus MC, Rotterdam, The Netherlands

14 Lactose malabsorption during methotrexate-induced gastrointestinal mucositis in a rat model

M. Fijlstra[1,3,4], E.H.H.M. Rings[1,3], J.F.W. Baller[1], T.H. van Dijk[1], T. Boer[1], F. Stellaard[1], A.R.H. van der Molen[2], H.J. Verkade[1,3], W.J.E. Tissing[4], Laboratory of Pediatrics, Centre for Liver, Digestive and Metabolic Diseases[1] and Laboratory Medicine[2] , University Medical Centre Groningen. Depts. of Pediatric Gastroenterology[3] and Pediatric Oncology[4], Beatrix Children's Hospital, University Medical Centre Groningen, The Netherlands

15 Hepatic transport mechanisms of Cholyl-L-Lysyl-Fluorescein

D.R. de Waart[1], S. Häusler[2], M.L.H. Vlaming[3], C. Kunne[1], E. Hänggi[2], H.J. Grass[4], R.P.J. Oude Elferink[1], B. Stieger[2], [1]AMC Liver Centre, Academic Medical Centre, Amsterdam, The Netherlands, [2]Division of Clinical Pharmacology and Toxicology, University Hospital, Zurich, Switzerland, [3]Division of Experimental Therapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [4]Norg , Norg International Ltd., Harefield, UK

Theme 3. Immunology *(Meierij Foyer)*, chairs: R. van Tol en G. Bouma

Poster Title

21 Kinetics of direct pathway allo-reactive T-cells after liver transplantation using a novel assay

Ö. Tapirdamaz[1], H.J. Metselaar[1], S. Mancham[1], L.J.W. van der Laan[2], K. Thielemans[3], J. Kwekkeboom[1],[1]Depts. of Gastroenterology & Hepatology and [2]Surgery, Erasmus MC, Rotterdam, The Netherlands, [3]Lab. of Molecular and Cellular Therapy, Free University Brussel, Belgium

22 Role for liver CD4+CD25+FoxP3+ Treg after IFN-α and ribavirin induced hepatitis C virus eradication

M.A.A. Claassen, R.J. de Knegt, H.L.A. Janssen, A. Boonstra, Dept. of Gastro-enterology and Hepatology, Erasmus MC – University Medical Centre Rotterdam, The Netherlands

23 Formation of tertiary lymphoid structures in dextran sodium sulphate colitis is partially dependent on lymphotoxin-alpha

B.J. Olivier[1,2], M. Knippenberg[1], M.J. Greuter[1], G. Goverse[1], E.D. Keuning[1], A.A. te Velde[2], G. Bouma[3], R.E. Mebius[1], [1]Dept. of Molecular Cell Biology and Immunology, VU University Medical Centre, Amsterdam, [2]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, [3]Dept. of Gastroenterology, VU University Medical Centre, Amsterdam, The Netherlands

24 Ribavirin improves Pegylated-interferon-α 2a-induced dendritic cell modulation in chronic hepatitis B

A. Boltjes[1], M.L. op den Brouw[1], P.J. Biesta[1], R.S. Binda[1], D. Turgut[1], M. Raptopoulou-Gigi[2], R.G. van der Molen[1], H.L.A. Janssen[1], A.M. Woltman[1],[1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands, [2]Clinical Immunology Unit, 2nd Medical Dept. Aristotelian University of Thessaloniki, Thessaloniki, Greece

25 Lithium, a glycogen synthase kinase 3beta inhibitor, does not have beneficial effects on dextran sulfate sodium-induced colitis, but shows intestinothrophic potential

E.M.J. van der Logt[1], T. Blokzijl[1], K.N. Faber[1], M.P. Peppelenbosch[2], G. Huls[3], G. Dijkstra[1], [1]Gastroenterology & Hepatology, [3]Hematology, University Medical Centre, Groningen, [2]Gastroenterology & Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands

Theme 4. Cell Biology *(Meierij Foyer)*, chairs: C.C. Paulusma en A.A. te Velde

Poster Title

31 The mechanism of intestinal barrier dysfunction induced by bowel manipulation in a model for postoperative ileus

S.A Snoek[1], O.I. Stanisor[1], F.W. Hilbers[1], S.H. van Bree[1], E.P. van der Zanden[1], C. Verseijden[1], A. Koeman[2], R.M. van den Wijngaard[1], C.J. Zuurbier[2], G.E. Boeckxstaens[1,3], W.J. de Jonge[1],[1]Tytgat Institute for Liver and Intestinal Research, [2]Dept. of Anaesthesiology, Academic Medical Centre, Amsterdam, The Netherlands, [3]Dept. of Gastroenterology, University Hospitals Leuven, Belgium

32 Butyrate attenuates deoxycholate-induced increase in permeability of human colonic tissue

S. Vanhoutvin[1,2], F. J. Troost[1,2], M. Geraedts[3], A. Bodelier[1], D. Jonkers[1,2], K. Venema[1,4], R.J.M. Brummer[5], A. Masclee[1,2], [1]TI Food and Nutrition, Wageningen, [2]Internal Medicine, Div. Gastroenterology & Hepatology, Maastricht University Medical Centre, Maastricht, [3]Human Biology, Maastricht University Medical Centre, Maastricht, [4]Biosciences, TNO Quality Of Life, Zeist, The Netherlands, [5]School of Health and Medical Sciences, Orebro University, Orebro, Sweden

33 Barrett's esophagus is characterized by a predominant intestinal immunological microenvironment

A. Lind[1,2], L. Koenderman[2], P.D. Siersema[1], [1]Dept. Gastroenterology and Hepatology and [2]Respiratory Medicine, University Medical Centre Utrecht, The Netherlands

34 Decreased expression of Paneth cell antimicrobial peptides coincides with bacterial translocation after starvation

C.M. Hodin[1], K. Lenaerts[1], J.J. de Haan[1], J. Grootjans[1], M. Hadfoune[1], E. Heineman[1,2], W.A. Buurman[1], [1]NUTRIM School for Nutrition, Toxicology and Metabolism, Dept. of Surgery, Maastricht University Medical Centre, Maastricht, [2]Dept. of Surgery, University Medical Centre Groningen, The Netherlands

35 Effects of ethanol and acetaldehyde on epithelial integrity in a three dimensional (3D) epithelial cell culture model

E. Elamin[1, 2], D. Jonkers[1,2], F. Troost[1,2], K. Juuti-Uusitalo[1,3], S. van IJzendoorn[1,3], H. Duimel[4], J. Broers[4], F. Verheyen[4], J. Dekker[1], A. Masclee[1,2], [1]Top Institute Food and Nutrition (TIFN), Wageningen, [2]Div. of Gastroenterology-Hepatology, Dept. of Internal Medicine, Maastricht University Medical Centre, Maastricht, [3]University Medical Centre Groningen, [4]Dept. of Molecular Cell Biology, Maastricht University Medical Centre, The Netherlands

Theme 1. Cancer *(Limburg Foyer),* chairs: E.H.H.M. Rings en J.P.H. Drenth

Time *Poster* *Title*

12.45 **6** MicroRNA-143, 145, 192, 194, 215 and components of the miRNA processing apparatus and gene silencing complex are preferentially expressed in Barrett's esophagus compared to normal squamous epithelium 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 Centre Utrecht, The Netherlands

7 High Resolution Array Comparative Genomic Hybridization in Sporadic and Celiac Disease-Related Small Bowel Adenocarcinomas

B. Diosdado[1], T.E Buffart[1], R. Watkins[2], B. Carvalho[1], B. Ylstra[1], M. Tijssen[1], J.S Bolijn[1], F. Lewis[2], K. Maude[3], C. Verbeke[4], I.D. Nagtegaal[5], H. Grabsch[2], C.J.J. Mulder[6], P. Quirke[2], P. Howdle[2], G.A. Meijer[1], [1]Dept. of Pathology, VU University Medical Centre Amsterdam, The Netherlands, [2]Pathology and Tumour Biology, Leeds Institute of Molecular Medicine, University of Leeds, UK, [3]Medicine, Surgery and Anaesthesia, Leeds Institute of Molecular Medicine, University of Leeds, UK, [4]Dept. of Histopathology and Molecular Pathology, St James's University Hospital, Leeds, UK, [5]Dept. of Pathology, University Medical Centre, Nijmegen, [6]Dept. of Gastroenterology, VU University Medical Centre Amsterdam, The Netherlands

8 Generation of an inducible Wnt5a transgenic mouse model to study the contribution of increased Wnt5a expression to intestinal tumor growth

E. Bakker[1], W. Helvensteijn[1], W. van Veelen[1], E.J. Kuipers[1,2], R. Smits[1],[1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

9 Differential expression and activity of Toll-Like receptor 2 and 4 in Barrett's esophagus and esophageal adenocarcinoma

R.E. Verbeek[1], F.J. ten Kate[2], F.P. Vleggaar[1], P.D. Siersema[1], J.W.P.M. van Baal[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Pathology, University Medical Centre Utrecht, The Netherlands

10 DNA copy number alterations in flat colorectal adenomas

Q.J.M. Voorham[1], B. Carvalho[1], A.J. Spiertz[2], N.C.T. van Grieken[1], H.I. Grabsch[3], B. Rembacken[4], M. Kliment[5], M.A. van de Wiel[6], B. Ylstra[1], A.P. de Bruïne[2], C.J.J. Mulder[7], M. van Engeland[2], G.A. Meijer[1], [1]Dept. of Pathology, VU University Medical Centre, Amsterdam, [2]Dept. of Pathology, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands, [3]Pathology and Tumour Biology, Leeds Institute of Molecular Medicine, University of Leeds, [4]Centre for Digestive Diseases, Leeds General Infirmary, Leeds, UK, [5]Gastroenterology, Hospital Vitkovice, Ostrava, Czech Republic, [6]Dept. of Epidemiology and Biostatistics, [7]Dept. of Gastroenterology, VU Medical Centre, Amsterdam, The Netherlands

Theme 2. Metabolism *(Limburg Foyer),* chairs: S. van Mil en K.N. Faber

Poster Title

16 Luminal preservation or preservation with a tailored preservation medium attenuates ischemia-reoxygenation-injury (IRI) in rat intestine, ex vivo

A.M. Roskott[1], G. Dijkstra[2], I.A.M. de Graaf[3], G.M.M Groothuis[3], H.G.D. Leuvenink[1], R.J. Ploeg[1], V.B. Nieuwenhuijs[1], [1]Dept. of Surgery, [2]Dept. of Gastroenterology,, [3]Dept. of Pharmacy, Division of Pharmacok tics, Toxicology and Targeting, University Medical Centre Groningen, The Netherlands

17 Overfeeding leads to CHOPped mouse liver and steatohepatitis

I.C. Gaemers, J.M. Stallen, C. Kunne, W.H. Lamers.,AMC, Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

18 Mrp1 is not required for hepatocyte- and hepatic progenitor cell-dependent liver regeneration in mice

A. van Steenpaal, M. Geuken, H. Moshage, K.N. Faber, Dept. of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, The Netherlands

19 Expression profiling of intestinal ischemia/reperfusion: first human in vivo findings

K. Lenaerts, J. Grootjans, J.P. Derikx, R.M. van Dam, C.H.C. Dejong, W.A. Buurman , Dept. of Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, The Netherlands

20 Liver-specific MicroRNA-122 is a serum biomarker for hepatic injury

W.R.R. Farid[1], Q. Pan[2], J. Kwekkeboom[2], H.W. Tilanus[1], G. Kazemier[1], H.L.A. Janssen[2], L.J.W. van der Laan[1], Depts. of [1] Surgery and [2] Gastroenterology & Hepatology, Erasmus MC - University Medical Centre, Rotterdam, The Netherlands

Theme 3. Immunology *(Meierij Foyer)*, chairs: R. van Tol en G. Bouma

Poster Title

26 The zebrafish; a novel model to study bacterial-host interactions in health and disease

S. Brugman, S. Middendorp, E.E.S. Nieuwenhuis, Laboratory of Translational Immunology, Pediatric Immunology, Wilhelmina Children's Hospital UMC Utrecht, The Netherlands

27 Abundant numbers of regulatory T cells localize to the liver of chronic hepatitis C infected patients and limit the extent of fibrosis

M.A.A. Claassen, R.J. de Knegt, H.L.A. Janssen, A. Boonstra, Dept. of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre Rotterdam, The Netherlands

28 Viral load reduction improves activation andfunction of natural killer cells in patients with chronic hepatitis B

E.T.T.L. Tjwa[1], G.W. van Oord[1], J.P. Hegmans[2], H.L.A. Janssen[1], A.M. Woltman[1], [1]Dept. of Gastroenterology and Hepatology and [2]Dept. of Pulmonary Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

29 Flow cytometric identification and functional analysis of 2 subpopulations of mouse Kupffer cells based on F4/80 expression

D. Movita, H. Janssen, A. Boonstra, Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre Rotterdam, The Netherlands

30 Cholinergic agonists and neuropeptides interact to reduce peritoneal macrophage activity

E.P. van der Zanden[1], K. Michel[2], M. Schemann[2], G.E. Boeckxstaens[1,3], W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Human Biology, Technical University Munchen, Freising, Germany, [3]Dept. of Gastroenterology , University Hospitals Leuven, Belgium

Theme 4. Cell Biology *(Meierij Foyer)*, chairs: C.C. Paulusma en A.A. te Velde

Poster Title

36 Portal vein embolization: the effect of different embolic agents on the hypertrophy response

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

37 Smoking leads to an overall downregulation of T-cell and intestinal epithelial cell kinase activity: identification of possible therapeutic targets for smoking patients with IBD

E.M.J. van der Logt[1], T. Blokzijl[1], K.N. Faber[1], M.P. Peppelenbosch[2], G. Dijkstra[1], [1]Dept. of Gastroenterology & Hepatology, University Medical Centre, Groningen, [2]Dept. of Gastroenterology & Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands

38 TLR signaling affects barrier function of intestinal epithelial cells

I.H. Hiemstra[1], G. Bouma[2], G. Kraal[1], J. den Haan[1], [1]Dept. of Molecular Cell Biology and Immunology, VU University Medical Centre, Amsterdam, [2]Dept. of gastroenterology, VU University Medical Centre, Amsterdam, The Netherlands

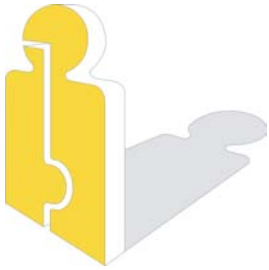
39 Effects of smoking and smoking cessation on dextran sulfate sodium-induced colitis in mice

E.M.J. van der Logt[1], T. Blokzijl[1], M.P. Peppelenbosch[2], K.N. Faber[1], G. Dijkstra[1], [1]Dept. of Gastroenterology & Hepatology, University Medical Centre, Groningen, [2]Dept. of Gastroenterology & Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands

40 Neuroanatomical evidence for activation of vagal motor neurons by intestinal inflammation in a model of postoperative ileus

C. Cailotto[1], J. van der Vliet[1], S van Bree[1,2], R.M. van den Wijngaard[1], W.J. de Jonge[1], G.E. Boeckxstaens[3], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, [2]Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [3]Gastroenterology, Katholieke Universiteit, Leuven, Belgium

Abstracts

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Overexpression of CARD9 caused by a deletion polymorphism could explain the associated with Inflammatory Bowel Disease

S. van Sommeren[1,2], E.A.M. Festen[1,2], C. Wijmenga[2], R.K. Weersma[1], [1]Dept. of Gastro-enterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, [2]Dept. of Genetics, University Medical Centre Groningen and University of Groningen, Groningen, The Netherlands

The Inflammatory Bowel Diseases (IBD) are chronic gastrointestinal inflammatory disorders with a partly genetic aetiology. The CARD9-region has recently been shown to be associated with ulcerative colitis (UC) and Crohn's disease (CD). CARD9 is a likely candidate, because it is a link in the innate immune response against fungi and bacteria. The most associated marker has a correlation with expression of CARD9: individuals homozygous for the risk allele have a higher expression level of CARD9 than individuals homozygous for the wildtype allele. Higher expression of CARD9 could cause UC and CD through a more extensive immune response in reaction to pathogens. In the search for the explanation of both the association of the region with UC and CD and the difference in expression level, we fine-mapped the association signal. We genotyped several single nucleotide polymorphisms (SNPs) in the CARD9-region in 534 IBD patients and 600 controls. In addition, 43 UC samples were fine-mapped on an Illumina Human 670Quad slide also containing copy number variation (CNV) markers. In the signals for the fine-mapping SNPs and the CNV markers we found signs for a deletion upstream of CARD9, containing the genes INPP5E and SDCCAG3. This deletion influences expression level of all three genes: it is correlated with a higher expression of CARD9 and a lower expression of INPP5E and SDCCAG3.
Conclusion: A deletion in the CARD9-region, which influences the expression levels of several genes including CARD9, could be the explanation for the association of this region with UC and CD. Further genotyping of this deletion in cases en controls is necessary to confirm this.

Psychological distress after genetic risk assessment shortly following a diagnosis of colorectal cancer

K.M. Landsbergen[1], J.B. Prins[2], H.G. Brunner[1], P. van Duijvendijk[3], F. M.Nagengast[4], M. Ligtenberg[1,5], N. Hoogerbrugge[1,6], Depts. of [1]Human Genetics, [2]Medical Psychology, [3]Surgery, [4]Gastroenterology,[5] Pathology and Hepatology and [6]Medical Oncology, Medical Centre Radboud University Nijmegen, The Netherlands

According to the Dutch Guideline Hereditary Colorectal Cancer 2008 pathologists test for high risk of a hereditary cause (MSI-testing) immediately after tumour resection in patients diagnosed with colorectal cancer (CRC) below 50 years. An MSI positive CRC indicates high risk for hereditary CRC, Lynch syndrome, previously called HNPCC. The aim of the present study is to determine psychological distress and effects on family communication in recently diagnosed patients with CRC below 50 years or with two Lynch syndrome associated tumours below 70 years after MSI testing. From March 2007 until September 2009, 400 newly diagnosed patients with CRC from 30 Dutch hospitals whose CRC had been tested for MSI were identified by the researcher and invited to participate by surgeons. Response rates of patients at high (MSI+) and at low (MSI-) risk for hereditary CRC were 30% (n=23/77) and 18% (n=57/323), respectively. Patients received questionnaires immediately after MSI-test disclosure, about 3 months after surgery (T1) and 6 months later (T2). MSI+ patients and MSI- patients did not differ regarding age, gender, educational level, marital status or having children. At T1, mean levels of cancer specific distress (Impact of Event Scale-cancer) of MSI+ patients and MSI- patients were high but not statistically significant different, 25.1 (SD 9.4) and 26.2 (SD 4.7), respectively (*P*=0.6). Levels of cancer specific distress reached post traumatic stress disorder levels (IES cut off score >26) in 49% of this newly diagnosed patient group of who 9 MSI+ patients and 30 MSI- patients (*P*=0.16). At T1, mean levels of general psychological distress (Symptom Checlist-90) of MSI+ patients and MSI- patients were 137.0 (SD 43.9) and 128.7 (SD 36.2), respectively (*P*=0.4). Only a small group, 2 MSI+ patients and 3 MSI- patients, reported many psychoneurotic symptoms (SCL-90 cut off score >200). MSI+ patients reportead statistically significant less family communication (Openness to Discuss Hereditary Cancer-Scale) compared to MSI- patients, 12.8 (SD 5.5) and 15.9 (SD 4.5), respectively (*P*=0.01). Results of T2 are expected in the spring of 2010.
Conclusion: Newly diagnosed patients at high risk for hereditary CRC report similar levels of psychological distress, but less open family communication as compared to patients who are at low risk for hereditary CRC.

Liver histology of IBD patients who are treated with 6-thioguanine due to failure of conventional thiopurines reveals very few cases of nodular regenerative hyperplasia

D.P. van Asseldonk[1], B. Jharap[1], N.K.H. de Boer[1], P.E. Zondervan[2], E. Bloemena[3], G. den Hartog[4], B.D. Westerveld[5], J.J. Kolkman[6], L.G.J.B. Engels[7], A.A. van Bodegraven[1], C.J. Mulder[1], [1]Dept. of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, [2]Dept. of Pathology, Erasmus Medical Centre, Rotterdam, [3]Dept. of Pathology, VU University Medical Centre, Amsterdam, [4]Dept. of Gastroenterology and Hepatology, Rijnstate Medical Centre, Arnhem, [5]Dept. of Gastroenterology and Hepatology, Isala Clinics, Zwolle, [6]Dept. of Gastroenterology and Hepatology, Twente Medical Spectrum, Enschede, [7]Dept. of Gastroenterology and Hepatology, Orbis Medical Centre, Sittard, The Netherlands

6-Thioguanine (6-TG) has been proposed as a rescue drug in patients with inflammatory bowel disease (IBD) who fail to tolerate or are refractory to conventional thiopurines. However, the use of 6-TG has mainly been discarded due to previous reported hepatotoxicity, which may be class or dose-dependent. The aim of this study was to assess short-term hepatotoxicity of 6-TG therapy in a large population of IBD patients previously failing conventional thiopurines. A national prospective cross-sectional multi-Centre cohort study was performed including IBD patients who were treated with 6-TG in an aimed dose of 0.3mg/kg for at least six months and who underwent a liver biopsy for safety assessment according to European consensus guidelines. The liver specimens were stained with H&E, trichrome and reticuline and were scored by experienced liver pathologists. From 99 patients with a mean age of 43.8 years (SD 12.0) a total of 99 liver biopsy specimens were obtained. Thirty six patients (36%) were male. Sixty-one patients (62%) had Crohn's disease and 38 (38%) had ulcerative colitis. Median duration of IBD before initiation of 6-TG was 9 years (range 1-54). Except for two patients, all were pretreated with azathioprine and/or 6-mercaptopurine. Ninety-three percent of these patients had been intolerant to previous thiopurine treatment, of which the median treatment duration was six weeks (range 1-780). Mean 6-TG dose was 0.28mg/kg (SD 0.07) and median 6-TG treatment duration, from initiation up to the first liver biopsy, was 25 months (range 6-65). Liver histology revealed no abnormalities in 51 specimens (51.5%); mild steatosis in 14 (14.1%); mild fibrosis in 3 (3.0%); severe steatosis in 2 (2.0%); steatohepatitis in 2 (2.0%) sinus dilatation in 8 (8.1%); cholangitis/PSC in 4 (4.0%); aspecific regeneration in 11 (11.1%) and nodular regenerative hyperplasia (NRH) in 4 (4.0%).
Conclusion: this large, prospective study reveals very few cases of NRH (4%) in a specific IBD population who had been failing conventional thiopurine therapy and were subsequently treated with 6-TG. This is in contrast to some previous studies (up to 62%), but corresponding with the prevalence of NRH in thiopurine naïve IBD patients (6%). Aspecific findings with unknown clinical implications were observed in about half of the patients.

A meta-analysis of genome wide association scans identifies TAGAP and PUS10 as shared risk loci for Crohn's disease and celiac disease

E.A.M. Festen[1,2], P. Goyette[3], T. Green[4], C. Beauchamp[3], G. Boucher[3], G. Trynka[2], P.C. Dubois[5], C. Lagacé[3], P.C.F. Stokkers[6], The International Inflammatory Bowel Disease Genetics Consortium (IIBDGC), D.W. Hommes[7], D. Barisani[8], O. Palmieri[9], V. Annese[9], D.A. van Heel[5], R.K. Weersma[1], M.J. Daly[3,10], C. Wijmenga[2], J.D. Rioux[3,4], [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, [2]Dept. of Genetics, University Medical Centre Groningen and University of Groningen, Groningen, The Netherlands, [3]Université de Montréal and the Montreal Heart Institute, Research Centre, Montreal, Quebec, Canada, [4]The Broad Institute of Massachusetts Institute of Technology and Harvard, Cambridge, Massachusetts, USA, [5]Centre for Digestive Diseases, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medic and Dentistry, Queen Mary University of London, London, UK, [6]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [7]Dept. of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands, [8]Dept. of Experimental Medic , Faculty of Medic , University of Milano-Bicocca, Italy, [9]UU.OO. Gastroenterologia ed Endoscopia Digestiva, Ospedale "Casa Sollievo della Sofferenza", IRCCS, San Giovanni Rotondo, Italy, [10]Centre for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Crohn's disease (CD) and celiac disease (CelD) are chronic intestinal inflammatory diseases, involving both genetic and environmental factors in their pathogenesis. Similarities in disease localization and pathogenesis between the diseases and the observation that the two diseases often co-occur within families suggest a common genetic background. Indeed, three shared genetic risk loci have already been identified for CelD and CD. The aim of our study was to identify additional shared risk loci for these two diseases. We analyzed genetic data from the two diseases as a single unified disease phenotype against healthy controls. Such an analysis should dilute disease-specific genetic associations, but increases the power for finding shared genetic risk loci of small effect in the individual diseases. Results from two genome-wide association study (GWAS) datasets from CelD (768 cases, 1422 controls) and CD (3230 cases, 4829 controls) were combined in a meta-analysis. The 15 most associated single nucleotide polymorphisms (SNPs) were selected for replication in independent samples of 3149 CelD cases (4714 controls) and 1835 CD samples (1669 controls). Three loci clearly showed significant association and replication in a combined study of CelD and CD cohorts. The TAGAP and PUS10 loci were firmly established as shared risk loci of genome-wide significance (respectively, $p = 1,3 \times 10^{-11}$ and $p = 5,0 \times 10^{-12}$ in the overall meta-analysis); while a third locus, on 17p13, did not formally reach genome-wide significance ($p = 4,0 \times 10^{-7}$ in the overall meta-analysis), showing strong association in the CD replication cohort ($p = 1,3 \times 10^{-5}$) and a trend toward association in CelD ($p = 5,1 \times 10^{-3}$). A fourth locus, SH2B3 was confirmed as a CelD risk locus in the replication phase ($p = 8.1 \times 10^{-8}$) but did not show association in CD (p = 0,056).

Conclusion: Through a meta-analysis of GWAS data from CD and CelD, we have identified three novel shared risk loci: TAGAP, PUS10 and 17p13. The combined analysis of the two datasets provided the power, lacking in the individual GWAS for single diseases, to detect shared loci with a relatively small effect. For many diseases with overlapping phenotypic characteristics GWAS data is available; joint analysis of GWAS datasets of these related diseases could lead to the identification of many new shared susceptibility loci.

Azathioprine or 6-mercaptopurine associated hepatotoxicity diminishes upon administration of 6-thioguanine in IBD patients

D.P. van Asseldonk, A.A. van Bodegraven, C.J. Mulder, VU University Medical Centre, Amsterdam, The Netherlands

Azathioprine (AZA) and 6-mercaptopurine (6-MP) are of pivotal importance in the treatment of the inflammatory bowel diseases (IBD) Crohn's disease (CD) and ulcerative colitis (UC). Unfortunately, a substantial proportion of patients withdraws thiopurine therapy due to adverse events (AE). A skewed metabolism with subsequently high levels of 6-methylmercaptopurine nucleotides (6-MMP) upon administration of AZA or 6-MP has previously been related with hepatotoxicity. We hypothesized that 6-thioguanine (6-TG) therapy, which is not accompanied by the formation of these 6-MMP, could ameliorate or avoid hepatotoxicity. From a cohort of IBD patients which has been treated with 6-TG, those patients who previously failed AZA or 6-MP as a result of a skewed metabolism, indicated by a 6-MMP/6-TGN ratio above 15, were selected. Both patients with and without liver test abnormalities were eligible. Liver test abnormalities were defined as any of the following above the upper limit of the normal range: ASAT, ALAT, gamma-GT and alkaline phosphatase. Disease activity scores, laboratory test and therapy specific data were collected at baseline (just prior to 6-TG initiation) and during follow-up. Eleven patients (three males) with a mean age of 50.2 (SD 12.6) were included in the analysis. Five had Crohn's disease and six had ulcerative colitis. All were pretreated with AZA , 6-MP or both. Just prior to the initiation of 6-TG the median 6-MMP/6-TGN ratio was 48 (19-124). Median 6-TG dosage was 21mg (10-24) daily and the median time to follow-up was 2.5 months (1.4-18.2). Both at baseline and during follow-up all but one patient were in clinical remission. At follow-up only two out of 11 had liver test abnormalities as compared with eight out of 11 at baseline (p=0.014). Mean ALAT and ASAT concentrations decreased from 34 to 22 U/l (p=0.038) and 75 to 27 U/l (p=0.014), respectively. The median 6-TGN concentration was 300 (170-830) at baseline, whereas at follow-up during 6TG therapy this was 1070 pmol/8x108 RBC (390-2100) (p=0.001).
Conclusion: 6-thioguanine reduces hepatotoxicity, expressed as elevated liver tests, in IBD patients with a skewed thiopurine metabolism who developed hepatotoxicity during AZA or 6-MP treatment. This may be owed to the absence of 6-MMP upon 6-TG administration. In addition, 6-TG therapy was able to maintain clinical remission.

10 years of Infliximab: long-term efficacy outcome of 430 Crohn's disease patients in a tertiary referral Centre

EJ Eshuis[1,2], F te Braake[1], C.Y. Ponsioen[1], J. Bartelsman[1], W.A. Bemelman[2], P.C.F. Stokkers[1], Depts. of [1]Gastroenterology and Hepatology and [2]Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Ten years after approval of infliximab (IFX) for treatment of Crohn's disease (CD), time has come to analyse the long-term outcome of this revolutionary agent. Aim was to assess the long-term efficacy of CD patients treated with IFX in a single referral center cohort. All patients treated with IFX were assessed from our CD patients' database. Medical charts were retrospectively reviewed. Primary endpoint was efficacy. Patients qualified as responders when using IFX during follow up or when IFX was stopped not due to treatment failure but because of remission, pregnancy, patients' wish, trial protocol or predetermined therapy plan. Patients who stopped IFX because of primary non response, loss of response, side effects or requirement of surgery were considered failures. Secondary endpoint was the number of IFX episodes and response rates per episode.
Four hundred and thirty CD patients (280 female (65.1%)) received IFX. Mean ages at diagnosis and at time of start with IFX were 24.0 and 33.0, respectively. Of 366 patients (85%) it was possible to assess effectiveness, with a median follow-up of 4.5 years (IQR 2.7 - 6.7). Of those, 219 patients (59.8%) responded well on the first IFX episode. Mean duration of therapy in responders was 29.2 months with a mean of 16.7 infusions. One hundred and forty patients (38.3 %) were considered failure (mean episode duration 9.8 months, mean number of infusions 8.8). Seven patients were considered neither responder nor failure, since co morbidity required them to stop IFX therapy irrespective of (lack of) response. One hundred and 9 patients received a second episode of IFX. Of those, 65 experienced response (59.6%); 38 patients showed treatment failure (34.9%) and of the remaining 6 patients, 3 had co morbidity requiring them to stop IFX and from 3 patients data were lacking. Of these 109 patients receiving a second episode of IFX, 58.8 % of patients were responders in the first episode and 41.2 % were failures. However, response and failure during the second episode was equally distributed amongst the responders and failures from the first episode. Eighteen patients received a total of 3 IFX episodes (13 (72.2%) response and 5 (27.8%) failure); seven patients had 4 episodes (100% response) and one patient had 5 episodes of IFX treatment (100% response).
Conclusion: In our cohort, failure of IFX treatment defined as cessation of IFX therapy due to non-response, loss of response, adverse events or surgical intervention is noted in 1 out of 3 treated patients. Similar failure rates were noted in patients retreated with IFX in a second episode. Previous failure was not predictive for failure in later episodes.

The phase I safety and feasibility results of autologous intravenous Mesenchymal Stromal Cell treatment in refractory Crohn's Disease

M Duijvestein[1], M.E. Wildenberg[1], B.B. Wendrich[1], A.C.W. Vos[1], A. Verhaar[1], H.H. Fidder[1], H. Roelofs[2], J.J. Zwaginga[2], W.E. Fibbe[2], G.R. van den Brink[1], D. Hommes[1], [1]Dept. of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, [2]Dept. of Immunohematology and Blood Transfusion, Leiden University Medical Centre, Leiden, The Netherlands

Background: Mesenchymal Stromal Cell (MSC) transplantation is being explored as therapy for various indications, including graft versus host disease, myocardial infarction and Crohn's Disease (CD). Aim: The aim of this study was to determine the safety and feasibility of autologous bone marrow derived MSC therapy in patients with refractory CD. Methods: Nine adult patients (7 females/2 males) underwent bone marrow aspiration under local anesthesia. Mononuclear cells were isolated and MSCs were expanded and tested for phenotype and functionality in vitro. 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. Results: MSC isolated from CD patients showed similar morphology, phenotype and growth potential as those of healthy donors as well as similar differentiation along the adipogenic and osteogenic lineages. Importantly, immunomodulatory capacity was intact, as both healthy donor and CD MSC reduced lymphocyte proliferation in vitro up to 70%. Baseline median CDAI was 317 (224-378). MSC infusion was successful and without side effects, besides 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. Despite an initial drop in CDAI, she was operated upon due to poor general condition and persistent rectal blood loss before primary endpoint was met. The other patients showed an average decrease in median CDAI of 59 points 6 weeks post transplant. Endoscopic improvement was seen in two patients with extensive CD localized in the colon whereas no significant improvement was seen in two patients with ileal CD.
Conclusions: Administration of autologous bone marrow derived MSCs appears safe and feasible in the treatment of refractory CD, no serious adverse events were detected during harvesting and study follow up. In addition, possible clinical and endoscopic efficacy was observed.

Colorectal cancer in inflammatory bowel disease: A comparison between large cohorts from referral Centres and general hospitals

E. Mooiweer[1], J. Baars[2], M. W.M.D. Lutgens[1], P.D. Siersema[1], E.J. Kuipers[2], B. Oldenburg[1] and C.J. van der Woude[2] on behalf of The Initiative on Crohn and Colitis and the Dutch IBD/CRC working group, [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, [2]Dept. of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

The increased risk of colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD) is well established in literature. The prevalence of IBD-related CRC, however, differs markedly between cohorts from referral Centres and population-based studies. The CRC cases in population-based studies might even be predominantly sporadic and not IBD-associated. In the present study we aimed to identify differences in demographic and disease-specific parameters between IBD-related CRC cohorts from tertiary referral Centres (TRC's) and general hospitals (GH's). PALGA, a nationwide pathology network and registry in the Netherlands, was used to search for patients with IBD-associated CRC for the time period of 1990 until 2006. Patients from seven university medical Centres (TRC's) and from 78 GH's were included. Demographic and disease specific parameters were collected retrospectively using patient charts.The search resulted in 328 patients with IBD-associated CRC. 203 Patients had UC, 122 patients had Crohn's colitis and 3 patients were diagnosed with indeterminate colitis. 131 TRC patients were compared with 197 GH patients. TRC patients were found to have a lower mean age at diagnosis of IBD (29 years versus 35 years (p=0.001)), while having a more severe course of the disease before CRC diagnosis (3.9 exacerbations vs. 1.5 in GH patients (p=0.000)). Furthermore, 68 (59%) of TRC patients had severe inflammation at some point during follow-up compared to 60 (43%) of the GH patients (p=0.01). In TRC patients CRC was diagnosed at a younger age (47 years compared to 50 years (p=0.03)). Remarkably, interval between IBD and CRC diagnosis was shorter in GH patients (15 years compared to 18 years (p=0.01)) CRC related mortality and other parameters were comparable in both groups. IBD patients visiting tertiary referral Centres represent a subgroup with a more aggressive phenotype. Although CRC is diagnosed at an earlier age, interval between IBD and CRC diagnosis is longer in these patients.

Substantial increase of progression rate of flat low-grade dysplasia in inflammatory bowel disease after review by an expert panel

F.D.M. van Schaik[1], F.J.W. ten Kate[2], G.J.A. Offerhaus[2], M.E.I. Schipper[2], F.P. Vleggaar[1], C.J. van der Woude[3], P.C.F. Stokkers[4], D.J. de Jong[5], D.W. Hommes[6], A.A. van Bodegraven[7], P.D. Siersema[1], B. Oldenburg[1], [1]University Medical Centre Utrecht, Dept. of Gastroenterology and Hepatology, [2]University Medical Centre Utrecht, Dept. of Pathology, [3]Erasmus MC University Medical Centre Rotterdam, Dept. of Gastroenterology and Hepatology, [4]Academic Medical Centre Amsterdam, Dept. of Gastroenterology and Hepatology, [5]Radboud University Nijmegen Medical Centre, Dept. of Gastroenterology and Hepatology, [6]Leiden University Medical Centre, Dept. of Gastroenterology and Hepatology, [7]VU University Medical Centre Amsterdam, The Netherlands, Dept. of Gastroenterology and Hepatology

Flat mucosa low-grade dysplasia (fLGD) and abnormalities indefinite for dysplasia (IND) are frequently detected in patients with Inflammatory Bowel Disease (IBD). The rate of progression to advanced neoplasia (dysplasia-associated lesion or mass (DALM), high-grade dysplasia (HGD) or colorectal cancer (CRC)) of fLGD and IND is important, as this could affect the therapeutic management of these patients. Our aim was to assess the progression rates of fLGD and IND to advanced neoplasia in a large cohort of patients with IBD before and after a blinded review by a panel of expert GI pathologists. A nationwide pathology database was used to identify patients diagnosed with IBD-associated dysplasia in six university Centres in the Netherlands between 1990 and 2006. Medical records, endoscopy, pathology and surgery reports of patients with recorded fLGD or IND were reviewed. Histological slides from three university Centres were blindly reviewed by a panel of three expert GI pathologists. The progression rates of fLGD and IND to advanced neoplasia were assessed before and after review of the histological slides. Before histological review, 113 fLGD patients (92 UC, 18 CD, 3 IBD-unclassified (IBDU); 60 male; median age at fLGD diagnosis 41 [12-78] yrs) and 26 IND patients (21 UC, 4 CD, 1 IBDU; 19 male; median age at IND diagnosis 37 [18-73] yrs) were identified. Advanced neoplasia was found in 19 fLGD (16.8%) patients (1 DALM, 11 HGD of which 5 with subsequent CRC, 5 CRC, 2 HGD with concurrent CRC) after a median follow-up of 48 months resulting in a 5-yr progression rate of 12.5%. Five (19.2%) IND patients developed advanced neoplasia (3 HGD, 1 HGD with subsequent CRC, 1 HGD with concurrent CRC) after a median follow-up of 24 months resulting in a 5-yr progression rate of 21.4%. Histological review of 1551 histological slides from three university Centres reduced the total number of fLGD patients from 78 to 25 (15 CU, 8 CD, 2 IBDU; 12 male), while the number of IND patients increased from 18 to 38 (32 UC, 5 CD, 1 IBDU; 17 male). After review the 5-year progression rate to advanced neoplasia increased to 37% for fLGD patients, whereas this rate decreased to 8.5% in IND patients ($p<0.05$, log-rank test).

Conclusions: When a diagnosis of IBD-associated dysplasia is reviewed by a panel of expert GI pathologists, the number of patients with fLGD is lower, whereas that with IND is higher than before review. When a diagnosis of fLGD is confirmed by an expert GI pathologist panel, the rate of progression to advanced neoplasia increases to 37% in 5 years, while confirmed IND is associated with a low rate of progression to advanced neoplasia.

The opinion of gastroenterologists towards quality assurance in endoscopy

V. de Jonge[1], J. Sint Nicolaas[1], M.E. van Leerdam[1], E.J. Kuipers[1,2], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, [2]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

Quality assurance (QA) in endoscopy has become an important issue. Reasons for the increasing interest in QA are rising costs, increasing demand for endoscopies and more accepted standards of care. Many societies are adopting QA programs in order to monitor and improve the quality of care. Optimal uptake depends on acceptance and enforcement strategies. Aim of this study was to assess the opinion of gastroenterologists towards a comprehensive QA program on the endoscopy department. For this purpose a survey was sent to all registered gastroenterologists (n=319) in the Netherlands. Participants could complete the survey on or send it back by mail. The survey assessed the general opinion to the implementation of a QA program for endoscopy units. Additionally, questions were included about the design, logistics, and the content of a QA program. A 5-point Likert-scale was used to score the opinion from very positive to very negative. A total of 200 gastroenterologists (63%) completed the questionnaire (80% males, mean age 47 yrs, mean endoscopy experience 16 yrs). The majority of gastroenterologists (95%) had a positive opinion towards the implementation of a nation-wide QA program for endoscopy units. Twenty percent of respondents assumed a positive impact on the time available for patient contact by introducing a QA program, while 28% foresaw a negative impact. Ten percent expected that the capacity of the endoscopy department would increase, while 35% thought the capacity would decline. Overall, 67% supposed the quality of delivered care would increase and only 1% thought it would decrease by a QA program. A negative attitude towards sharing the results with health authorities (15%), insurance companies (22%) and media (53%) was reported. Of the respondents, 73% thought involvement of nurses in QA was of importance, and 60% thought managers should be involved. Concerning the content of a QA program, clinical quality was deemed to be an important aspect by 94% and patient-Centreed care by 91% of the respondents. Most important quality measurements were standardized reporting and assessment of complications (97%), completeness of procedures (92%) and endoscopy reports (96%), adequate patient information (95%), adequate aftercare (94%) and adherence to follow-up recommendations (93%).
Conclusion: Endoscopists have a positive attitude towards QA and the implementation of a comprehensive QA program. However, concerns do exist about time investment and disclosure of results to others. Information provision (both to the patient as well as to the referrer) and procedure characteristics were considered the most important aspects of a QA program.

Evaluation of colonoscopy performance in daily practice in a multiCentre study

V. de Jonge[1], J. Sint Nicolaas[1], O. van Baalen[2], F. ter Borg[3], J.T. Brouwer[4], H. Geldof[5], M. Hadithi[6], A.J.P. van Tilburg[7], E.J. Kuipers[1,8], M.E. van Leerdam[1], Dept. of Gastroenterology and Hepatology of [1]Erasmus MC University Medical Centre, Rotterdam, [2]Beatrix Hospital, Gorinchem, [3]Deventer Hospital, Deventer, [4]Reinier de Graaf Hospital Group, Delft, [5]IJsselland Hospital, Capelle aan de IJssel, [6]Maasstad Hospital, Rotterdam, [7]Sint Franciscus Gasthuis, Rotterdam, [8]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

Colonoscopy demand rises among others because of the introduction of colorectal cancer screening. Various studies have reported large differences in the quality of colonoscopy. International assessment of this issue is of importance to allow optimal patient benefits, improvement of training and international comparison of data. Therefore we aimed to evaluate the performance of colonoscopy procedures in daily clinical practice. Consecutive colonoscopy reports from 7 endoscopy units (1 academic, 6 general hospitals, 200 reports per site) were retrospectively reviewed from March to April 2009. Data captured included patient characteristics, indication, sedation and outcomes. A total of 1,442 procedures were included (1,425 patients, 46% males, mean age: 58 yrs, ±16) from 55 endoscopists (mean: 25 procedures, ±17). Gastroenterologists referred 39% of patients, general practitioners 28%, internists 16% and others 17%. The most frequent indications were lower abdominal symptoms (28%), rectal blood loss (15%) and CRC surveillance (12%). Bowel preparation was not optimal in 30% of procedures. No association was found between inadequate bowel preparation and gender and age in multivariate regression. In 94% of procedures conscious sedation was applied by means of midazolam in 28%, fentanyl in 1% and the combination in 68%. Unadjusted cecal intubation rate was 90%. Most frequent reasons for failure of cecal intubation were looping and anatomic variations of the colon (21%), stenosis (19%), poor bowel preparation (19%) and pain (17%). Multivariate logistic regression showed that failure of cecal intubation was associated with insufficient bowel preparation (OR: 3.23, 95%CI: 2.04-5.10) and age ≥60 yrs (OR: 1.84, 95%CI: 1.15-2.96). Neoplasia was detected in 23% of patients including tubular adenomas in 55%, tubulovillous adenomas in 21%, villous adenomas in 4% and carcinoma in 20%. Advanced adenomas were found in 13% of all patients and 3% had ≥3 adenomas. Multivariate logistic regression showed that male gender (OR: 1.73, 95%CI: 1.25-2.37), bowel complaints (OR: 1.53, 95%CI: 1.11-2.12) and age ≥60 yrs (OR: 3.93, 95%CI: 2.80-5.52) were associated with the presence of neoplasia. One perforation was reported (0.07%) and 15 patients had minor bleeding after polypectomy (1%).

In conclusion, the technical quality of colonoscopy in daily practice in the Netherlands does reach the international standards, i.e. >90% cecal intubation, >20% adenoma detection and <0.1% perforation. However, improvement can be achieved among others with respect to bowel preparation. The quality indicators are helpful to assess quality of colonoscopy in daily clinical practice.

CT-Colography After Incomplete Colonoscopy: What Is The Diagnostic Yield?

H.J.M. Pullens[1], M.S. van Leeuwen[2], F.P. Vleggaar[1], P.D. Siersema[1], [1]Gastroenterology and Hepatology, [2]Radiology, University Medical Centre Utrecht, The Netherlands

Introduction: CT-colography (CTC) is a relatively new diagnostic tool to examine the colon. It is increasingly being used as a screening modality for colorectal cancer (CRC). CTC can also be used when the colon is not completely intubated during colonoscopy or when colonoscopy is contra-indicated. In addition, CTC may give additional information, on extracolonic lesions.
Aims & Methods: We reviewed 96 consecutive CTCs, performed after incomplete colonoscopy. All intra- and extracolonic findings on CTC were recorded, and evaluated for relevance for further diagnostic or therapeutic work-up. Results: Indications for colonoscopy included iron deficiency anemia (24%), change in bowel habits (19%), rectal bleeding (18%), CRC screening or surveillance (12%), diarrhea (7%), constipation (8%), abdominal pain (5%), suspicion of CRC on abdominal ultrasound (2%) or other (5%). Reasons for incomplete colonoscopy were a fixated sigmoid colon (33%), strong angulation of the sigmoid colon (18%), intractable pain during colonoscopy (7%), spastic or atonic colon (7%), obstructive CRC (4%), dolichocolon (3%), abdominal wall herniation (3%), undetermined colonic stricture (2%), other (12%) or unreported reasons (9%). Introduction of the colonoscope was limited to the left-sided colon in 51% of cases. Colonoscopy detected 6 (6%) patients with CRC and 19 (20%) with polyps. CTC revealed additional polyps in 5 (5%) patients and additional CRC in 2 (2%). Both CRCs were located proximally to a fixated sigmoid. Colonoscopy in these patients had been performed for suspicion of CRC on preceding abdominal ultrasound. Of the 5 patients with polyps, a polyp in one patient was found to harbor CRC at second colonoscopy. This polyp was located in a colon part that had been inspected at prior colonoscopy (missed CRC). In addition, CTC found extracolonic abnormalities with clinical consequences in 5 (5%) patients, i.e. fistulizing diverticulitis (n=2), gastric lymphoma (n=1), liver abscess (n=1) and infected embolisms in the renal arteries (n=1).
Conclusion: CTC revealed 12 relevant additional lesions (both intra- and extracolonic) in 11 of 96 (11%) patients with incomplete colonoscopy. When the patients with CRC found during colonoscopy, for whom a staging CT was already indicated, are also considered, CTC yielded additional information in another 7 patients (6 CRCs found with colonoscopy + 1 missed CRC), making a total of 18 (19%) patients with clinically relevant additional findings.

Expression of Proteins Involved in Carcinogenic Pathways in Patients with Primary Sclerosing Cholangitis and Colitis-associated Colorectal Cancer

MMH Claessen[1], F.P. Vleggaar[1], M.E.I. Schipper[2], F.H.M. Morsink[2], P.D. Siersema[1], G.J.A. Offerhaus, [2]Dept. of Gastroenterology and Hepatology[1] and Dept. of Pathology[2], University Medical Centre Utrecht, The Netherlands

Background: The molecular background of colitis-associated carcinogenesis differs from the sporadic pathway in frequency and moment of underlying genetic mutations. Patients with IBD and concurrent primary sclerosing cholangitis (PSC) have a significantly higher risk of developing colorectal cancer (CRC) than patients without PSC. Although the molecular background behind colorectal carcinogenesis is gradually elucidated, still little is known about this specific subgroup of tumors. Aim: To compare the expression of proteins involved in different carcinogenic mechanisms in PSC-IBD-related CRC with other subtypes of colorectal tumors, such as IBD-CRC, sporadic CRC and Lynch syndrome-related CRC, and to determine differences in the molecular background of inflammatory- and noninflamma-tory-associated CRCs.Methods: A tissue micro-array was constructed with colonic samples from 7 groups: (1) healthy subjects, (2) IBD-patients, (3) IBD-related CRC, (4) PSC-IBD-related CRC, (5) Lynch syndrome- related CRC, (6) sporadic left-sided CRC, and (7) sporadic right-sided CRC. Each group consisted of 8-20 patients. Immunohistochemistry was performed using monoclonal antibodies against β-catenin, Cylin D1, CD44V6, p53, SMAD4, and COX2. Results: Median age of all patients was 55 years (range 12-92 years), with 61% of cases being male. Of all cases in groups 2-4, ulcerative colitis was present in 53% of cases. In groups 3, 4 and 5, 29%, 60%, and 50% of CRCs, respectively, were proximally located, (p=0.3). In 55.4% of all tumors, CRC had metastasized to regional lymph nodes or distant sites. Overexpression of p53 was found in the majority of all tumors (60%), except the Lynch-CRC group (12.5%) (p=0.44). Expression of Cyclin D1 was found in 56% and 88% of the inflammatory-related tumors and sporadic tumors, respectively (p=0.002). After correction for tumor stages and age this difference remained significant. No statistical differences were found in expression of nuclear ß-catenin, CD44V6, and COX-2. Loss of expression of SMAD4 was twice as high in the inflammatory-related tumor groups compared to the sporadic tumors, 26% and 9%, respectively (p=0.09). No association was found between the expression of ß-catenin and CyclinD1.
Conclusion: Cyclin D1 expression is significantly less in the inflammatory-related tumor group than in the sporadic CRCs and there appears to be loss of SMAD4 expression as well: this suggests a difference in colorectal carcinogenesis between these two groups.

Risk factors of adenoma recurrence at surveillance colonoscopy: a systematic literature review and pooled analysis

V. de Jonge[1], J. Sint Nicolaas[1], E.J. Kuipers[1,2], M.E. van Leerdam[1], S.J.O. Veldhuyzen van Zanten[3], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, [2]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands, [3]Dept. of Gastroenterology and Hepatology, University of Alberta Hospital, Edmonton, Alberta, Canada

Colorectal cancer screening guidelines recommend surveillance after adenoma removal. However, various guidelines vary considerable in advised surveillance intervals. This reflects the lack of comprehensive evidence of adenoma recurrence after base colonoscopy. This variation also affects adherence. Surveillance intervals need to be based on the risk of adenoma recurrence in the individual patient. We therefore aimed to assess the risk factors of adenoma recurrence. A systematic search was performed up to October 2008, using MedLine. Studies including base and follow-up colonoscopy, at least 6 months apart and with stratification for base findings, were included. Exclusion criteria were studies on high-risk patients and prevention trials with a significant effect. A Data Quality Score assessed study quality using inclusion criteria and data specification as main parameters. Pooled relative risks were calculated using random effects analysis. Twenty-three studies met the inclusion criteria (8 high quality (HQ), 15 non-HQ). A pooled RR for adenoma recurrence was calculated for presence of advanced adenomas (3 HQ, 2 non-HQ), adenomas ≥10 mm (5 HQ, 8 non-HQ), ≥3 adenomas (4 HQ, 11 non-HQ), villous adenomas (VA; 4 HQ, 6 non-HQ), high grade dysplasia (HGD; 2 HQ, 6 non-HQ), proximal location of adenomas (3 HQ, 2 non-HQ), age ≥60 yrs (3 HQ, 3 non-HQ) and gender (6 HQ, 8 non-HQ). Most important risk factors for adenoma recurrence were base presence of advanced adenomas (pooled RR: 2.27, 95%CI: 1.09-4.75, I^2: 94%), age ≥60 yrs (pooled RR: 1.84, 95%CI: 1.34-2.54, I^2: 17%), HGD (pooled RR: 1.67, 95%CI: 1.24-2.24, I^2: 60%) and ≥3 adenomas (pooled RR: 1.60, 95%CI: 1.32-1.94, I^2: 62%). The pooled RR for adenoma recurrence with other base characteristics were less increased: ≥10 mm (pooled RR: 1.70, 95%CI: 1.32-2.18, I^2: 78%), VA (pooled RR: 1.44, 95%CI: 1.12-1.87, I^2: 77%), proximal location of adenomas (pooled RR: 1.72, 95%CI: 0.99-2.99, I^2: 90%) and male gender (pooled RR: 1.19, 95%CI: 1.07-1.32), I^2: 6%).

In conclusion, convincing evidence exist that patients with advanced, ≥3 adenomas, HGD or age ≥60 yrs have an increased risk of adenoma recurrence. The evidence for other base findings for an increased risk of adenoma recurrence is inconclusive. Marked variation in study design and substantial heterogeneity between studies was observed and non-HQ studies reported lower RR's, which emphasizes the necessity of well-performed and reported studies. Given the high impact of surveillance on patients and service providers, there is a marked need for further assessment of these parameters and subsequent development of targeted surveillance regimens.

Statin treatment of colon cancer cells leads to an overall downregulation of Receptor Tyrosine Kinase activity

R.J. Jacobs[1], L.L. Kodach[1], S.H. Diks[2], J. Heijmans[1], D.W. Hommes[1], G.R. van den Brink[1], M.P. Peppelenbosch[2], J.C.H. Hardwick[1], [1]Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, [2]Cell Biology, University Medical Centre, Groningen, The Netherlands

Introduction: Colorectal cancer (CRC) is one of the leading causes of death by cancer in the Western world. Unfortunately, successful treatment is dependent still on early diagnosis and surgical resection. Epidemiological studies suggest that Statins have powerful chemopreventive properties with respect to colon cancer, but the mechanism of action of Statins in colon cancer is unknown. Most research has focused on the post-translational prenylation of proteins, but several studies have shown that statins also have additional effects. A limited number of well characterized signal transduction pathways allow cells to react to their environment and are regulated by phosphorylation. By generating a comprehensive description of the phosphoproteome we aimed to investigate the mechanism of action of statins in colon cancer cells in an unbiased fashion. Aims & Methods: Aim: To elucidate the molecular mechanism of action of Statins in colorectal cancer. Methods: We used arrays containing 1024 different kinase substrates spanning the entire human kinome. The peptide arrays were incubated with cell lysates plus radioactive ATP, exposed to a phospho-imaging screen and scanned. The density of the spots was measured and analyzed with array software. Western blotting was used to independently validate the results. Results: To analyze the changes in the phosphoproteome we determined the number of significantly phosphorylated substrates for each condition. Statin treatment for 24 hours leads to a substantial down-regulation of cell signaling. Non-treated cells displayed phosphorylation of 222 substrates, and treated cells 151 substrates. While most other pathways remained unaffected the activity of multiple Receptor Tyrosine Kinases (RTKs) was significantly decreased with down regulation of their downstream targets. As RTKs play a well known role in cell cycle progression, growth and metabolism control, their inhibition by statins may provide a new insight into the chemopreventive properties of this drug.
Conclusion: Treatment of colon cancer cells with Statins alters intracellular signaling by downregulation of the activity of multiple Receptor Tyrosine Kinases and its downstream pathways. This insight could help to identify a group of patients with CRC where Statins can be successfully used as chemotherapeutic and chemopreventive drugs.

Routine MSI-analysis in advanced adenomas in patients younger than 45 years leads to the identification of more patients at high risk for Lynch Syndrome

C.H.M. Leenen[1], M.G.F. van Lier[1], A. Wagner[2], W.N.M. Dinjens[3], H.J. Dubbink[3], M.E. van Leerdam[1], E.J. Kuipers[1,4], 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 Public Health[5], Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

Lynch Syndrome (LS) is caused by germline mutations in mismatch repair (MMR) genes and is responsible for at least 3% of all colorectal carcinomas (CRC). Colorectal adenomas are thought to occur at a relatively young age in LS patients. Diagnostic strategies for LS include assessment for microsatellite instability (MSI) and immunohistochemical analysis (IHC) of tumor tissue. Although identification of LS is important, the detection is far from optimal.The aim of this study was to evaluate a new diagnostic strategy for LS by performing routine molecular analysis of advanced adenomas (AA) in patients ≤45 years.In 9 hospitals all consecutive patients ≤45 yrs with AA were included (May 2007–Nov 2009) as part of a population based study. AA were defined as ≥10 mm and/or with a villous component and/or high grade dysplasia. Additionally, patients with ≥3 synchronous adenomas were included. All AA were analyzed for MSI and IHC of MMR proteins MLH1**,** MSH2, MSH6, and PMS2**.** AA were classified as 1)suspect for LS if MSI-high (MSI-H) and simultaneously showing absent MMR protein expression with exclusion of *MLH1*-promoter hypermethylation in case of absent MLH1 expression, 2)sporadic if microsatellite stable (MSS/MSI-L) or MSI-H and absent MLH1 expression with *MLH1* promoter methylation. A total AA of 69 patients were analyzed (57% males), median age 40 yrs (range 22-45). AA were located left-sided in 51 patients (73%), right-sided in 30 patients (17%), in 9% the location in the colon was not further specified. In 45% the adenoma size was ≥10mm (range 10-27mm). A villous component was observed in 58%. 15% of AA showed high grade dysplasia. In 7 patients (10%) ≥3 adenomas were removed during colonoscopy. Molecular analyses revealed 3/69 AA (4.3%;95%CI 3.5-5.1) suspect for LS (all other AA were MSS). Mean age of these 3 male patients was 40 yrs (range 34-44). All MSI-H adenomas were located in the left hemicolon (2/3 in the rectum). The MSI-H adenomas showed villous histology in 2/3 and a size ≥10 mm in 2/3 cases. IHC was compatible with lack of MLH1 expression in 2/3 patients, and lack of MSH6 in 1 patient. In 2 cases MMR gene germline mutations were confirmed by DNA analysis (*MLH1* and *MSH6*). DNA analysis in the third patient is pending. 2/3 families did not fulfil the Amsterdam II criteria.In conclusion, molecular screening for LS in young patients presenting with AA leads to early identification of a profile pathognomic for LS in 4.3% of patients. The routine use of molecular screening of AA thus may contribute to detect more LS patients, which is of major relevance in order to decrease CRC-related mortality by surveillance colonoscopy.

Long term results of more than 100 self-expanding metallic stent (SEMS) placements for acute malignant colonic obstruction

H.H. Zwaving[1], M. Ledeboer[2], F. ter Borg[2], E.H. Eddes[1], R.J.I. Bosker[1], M. Eeftinck Schattenkerk[1], [1]Dept. of Surgery, Deventer Ziekenhuis, Deventer, [2]Dept. of Gastro-enterology, Deventer Ziekenhuis, Deventer, The Netherlands

Since 2003 all patients with an acute malignant colonic obstruction has been treated with placement of a SEMS in our teaching hospital. Before or immediately after placement of the SEMS further investigations are performed. For patients with evidence of diffuse metastatic disease or severe co-morbidity SEMS was decided to be the definitive treatment. All other patients were scheduled for curative resection within some weeks after SEMS placement. In this study we describe our results of 97 patients treated with a SEMS in the period 2003-2009.In this period, 103 SEMS placements were performed. In 47 patients the SEMS was used as bridge to surgery (BTS)(median age 75 years),in 50 patients as definitive treatment (median age 76 years).In the BTS-group no SEMS related complications occurred. The clinical and technical success rate was 96 percent. In one patient only partial relief of symptoms was achieved. One tumor obstruction could not be passed. These two patients were operated within 24 hours after stent procedure. The median time between SEMS placement and operation was 25 days (range 1-89). Resection types were right hemicolectomy (10), transverse colectomy (7), left hemicolectomy (11), sigmoid resection (13), low anterior resection (6). One temporarily diverting colostomy was performed. In three patients a definitive colostomy was created as a Hartmann procedure. Seventy-one percent of the operated patients had no complications. Post-operative complications were only minor, no anastomotic leakage or intra-abdominal abscesses occurred. Mortality was low, one patient died 3 days after the operation from a myocardial infarction (30 day mortality rate of 2%).After a median follow-up of 25 months, local recurrence occurred in 3 patients, three patients developed a second colonic malignancy. In the palliative treated group most patients were known to have a colonic malignancy. Median placement of a SEMS was 88 days after initial diagnostic endoscopy. The median survival after initial diagnosis was 192 days. Thirty-six percent of the patients received chemotherapy. In some patients an operation was unavoidable during follow-up. At last 11 patients underwent surgery in this palliative setting. This was necessary because of tumor progression (2), dislocation (2), blow-out (2), malfunction (3) and non passable tumor (3). All patients survived operation. Eight definitive colostomies were performed. All other stents functioned well to death.
Conclusion: Mortality and morbidity of colonic resections after SEMS placement are low. In palliative setting an operation cannot be avoided in all cases. With a good follow-up the number of operations can still be low.

Is diverticular disease in younger patients associated with increased risk for colorectal neoplasia? A cross-sectional study

CMC le Clercq[1], E. Rondagh[1], K. Steenhuisen-van Erp[1], B. Winkens[2], S. Sanduleanu[1], A. Masclee[1], Division of Gastroenterology and Hepatology[1] and Dept. of Methodology and Statistics[2], Maastricht University Medical Centre, The Netherlands

Diverticular disease and colorectal neoplasia are common conditions in Western populations and their prevalences increase with age. Some studies have pointed to an association between both conditions, although this issue remains controversial. The aim of this cross-sectional study was to investigate the relationship between diverticular disease and colorectal lesions (CRLs), adjusted for age. Methods All consecutive patients referred for routine colonoscopy at our GI endoscopy unit during one year (February 2008-February 2009) were included. Colonoscopy reports and histopathology of removed CRLs were obtained. Characteristics of CRLs and diverticular disease were registered using a standardized endoscopy reporting system. Diverticular disease was defined as presence of two or more diverticula during endoscopy. CRLs were categorized into adenomatous and serrated lesions. Results A total of 2,310 patients (mean age 58.4 yrs, range 18-93 yrs and 46.1% males) were included. Seventy-nine % of patients were referred due to symptoms, while 20.7% for screening or surveillance indications. In the total population, 37% (n=855) had diverticular disease, of which 77% (n=658) left-sided, 2% (n=16) right-sided and 21% (n=181) generalized. Endoscopic signs of diverticulitis were found in 9.0% (n=77) of the patients with diverticular disease. Of all patients, 27% (n=619) had at least one adenoma and 13% (n=307) at least one serrated lesion. In patients with diverticular disease vs. those without, adenomas were found in 26.8% vs. 17.5% ($p<0.001$), serrated lesions in 9.5% vs. 6.2% ($p=0.004$) and both lesions combined in 7.0% vs. 5.2% ($p=0.08$) of patients, respectively. Multiple logistic regression analysis with interactions, showed that the relationship between diverticular disease and CRLs was affected by age ($p<0.001$). Presence of diverticular disease was associated with increased risk for CRLs in patients aged <70 yrs (OR 2.2, 95% CI 1.7–3.0, $p<0.001$), while this was not found in patients aged ≥70 yrs. Noteworthy, the association between diverticular disease and risk for CRLs gradually increased with younger age, as follows: OR 3.0 (95% CI 2.1-4.3, $p<0.001$) for age <60 yrs, OR 4.5 (95% CI 2.8-7.0, $p<0.001$) for age <50 yrs and OR 6.6 (95% CI 3.8-11.6, $p<0.001$) for age <40 yrs.
Conclusion: We found an age-dependent association between diverticular disease and colorectal lesions. In younger patients diverticular disease is an independent risk factor for simultaneous presence of colorectal lesions, while this is not the case in patients aged 70 yrs or more.

Oligomerization of the human liver Na+-dependent taurocholate cotransporting protein NTCP provides a novel mechanism to regulate bile salt uptake

SFJ van de Graaf, R.A.M Bouwmeester, L.W.J. Klomp, Dept. of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, Utrecht, The Netherlands

The Na+ taurocholate cotransporting protein (NTCP) is the primary mediator of bile salt absorption from the portal circulation into the hepatocyte. NTCP (or SLC10A1) is part of the SLC10A protein family, currently consisting of seven members. SLC10A2 mediates the majority of intestinal bile salt reabsorption. With the exception of SLC10A6, which transports steroid sulfates, the substrates and physiological functions of the other SLC10A family members are unknown. The aim of the present study was to investigate the interdependence of SLC10A proteins in the regulation of bile salt uptake. Many transport proteins require oligomerization for their activity and regulation, and consistent with this notion, co-immunoprecipitation of HA- and FLAG-tagged NTCP subunits demonstrated a physical interaction between individual NTCP subunits. The oligomeric nature of NTCP was further substantiated by FRET using fluorescently labeled subunits. Chemical cross-linking and immunoblot analysis demonstrated a preference for dimeric complexes. NTCP lacking the carboxyl-terminus was poorly targeted to the plasma membrane and was retained in the endoplasmic reticulum (ER). The carboxyl-terminus is not essential for oligomerization, as was demonstrated by co-immunoprecipitation. Furthermore, co-expression of this truncated NTCP retained wild-type NTCP in the ER in a dominant fashion, suggesting that oligomerization occurs early in the secretory pathway. FRET results further demonstrated that the oligomerization persists at the plasma membrane. Together these data clearly demonstrate that NTCP adopts a dimeric structure. Next, immunoprecipitations using lysates of cells co-expressing NTCP and SLC10A6 or NTCP and SLC10A7 demonstrated that NTCP can form heteromeric complexes with its SLC10A-family members. Importantly, expression of SLC10A6 or SLC10A7 resulted in a significant reduction of NTCP-mediated taurocholate uptake. In conclusion, NTCP hetero-oligomerization with SLC10A family members provides a putative novel regulatory mechanism to fine-tune bile salt uptake.

Bile salts exposure at different pHs to esophageal squamous epithelial cells induces expression of markers that are also found in Barrett's esophagus

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

Barrett's esophagus (BE) is characterized by the replacement of squamous epithelium (SQ) by columnar epithelium due to gastroesophageal reflux. COX2 and MUC2, are known to be expressed in BE. In addition, IL-6 is secreted by BE. It is not known whether bile salts at neutral or low pH cause an increased expression of these markers on esophageal squamous epithelial cells.The aim of our study is to determine whether incubation of esophageal squamous epithelial cells with a mixture of bile salts at low or neutral pH affects cell viability and causes upregulation of markers known to be expressed in BE. Normal esophageal squamous epithelial cells (HET-1A) were exposed to a 200, 400 or 800 µM bile mixture (25% DCA, 45% GCA, and 30% TCDCA, mimicking human bile) at pH7 or pH5 for 30 min. At 24 hrs after incubation, cell viability was measured by MTT assay, and RNA was extracted. COX2 and MUC2 mRNA expression were analyzed by Q-RT-PCR (GAPDH was used for normalization). IL6 secretion was analyzed by ELISA. Incubation with the bile mixture at pH5 decreased cell viability ($p<0.001$), whereas the bile mixture at pH7 and pH7 alone had no effect on cell viability. Exposure of HET-1A cells to the bile mixture at pH7 showed increased COX2 (1.5-fold) and MUC2 (2-fold) mRNA expression compared to pH7 alone. COX2 and MUC2 expression was even higher (more than 3-fold) when HET-1A cells were incubated with the bile mixture at pH5. In addition, HET-1A cells showed a 4-fold increased IL-6 secretion upon incubation with the bile mixture at pH5 (80.49 pg/ml ± 4.85; versus pH7 alone: 18.77 pg/ml ± 0.69). Increased IL-6 secretion was not seen when cells were incubated with the bile mixture at pH7 (15.58 pg/ml ± 2.08). No upregulation of COX2 or MUC2 mRNA expression or secretion of IL6 was seen when HET-1A cells were incubated with pH5 alone.
Conclusion: Bile mixture exposure at neutral pH to the SQ cell HET-1A resulted in increased COX2 and MUC2 expression, with a further increase in an acidic environment. Bile mixture exposure in an acid environment also resulted in IL-6 secretion. As these effects were not seen upon incubation with acid alone, it is suggested that bile salts play an important role in the transition of SQ to BE. This finding may help in designing strategies for chemoprevention of BE.

Raised hepatic bile acid concentrations during pregnancy are associated with reduced Farnesoid-X-Receptor function

S.W.C. van Mil[5], A. Milona[1], B.M. Owen[1], J. Cobbold[2], E.C.L. Willemsen[3], J. Cox[2], M. Boudjelal[4], W. Cairns[4], K. Schoonjans[5], S. Taylor-Robinson[2], L.W.J. Klomp[3], M.G. Parker[1], R. White[1], C. Williamson[1], [1]Institute of Reproductive and Developmental Biology, Division of Medicine, Imperial College London, U.K, [2]Translational MR Spectroscopy Grouping, Division of Clinical Sciences, Imperial College London, U.K. [3]Dept. of Metabolic and Endocrine Diseases and Netherlands Metabolomics Centre, University Medical Centre Utrecht, The Netherlands, [4]GlaxoSmithKline, New Frontiers Science Park, Essex, U.K. [5]Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland

Intrahepatic cholestasis of pregnancy (ICP) is associated with raised maternal bile acid levels, fetal distress and unexplained intrauterine death. The etiology of ICP is poorly understood. However, heterozygous mutations in bile acid homeostasis genes together with the high estrogen and progesterone concentrations during pregnancy, are thought to unmask cholestatic disease in otherwise asymptomatic individuals. In this report, in order to obtain better insights in the etiology of ICP, we aimed to study bile acid homeostasis in pregnant mice. Therefore, bile acid concentrations in liver and serum were assayed and gene expression profiling in livers of normal and pregnant mice was conducted. We show that normal pregnant mice have raised hepatic and serum bile acid levels in the presence of pro-cholestatic gene expression profile. The bile acid sensor Farnesoid X receptor (Fxr) regulates transcription of the majority of these differentially expressed genes and we show that in Fxr null mice and in CA fed mice the accumulation of hepatic bile acids during pregnancy did not occur, suggesting that the function of Fxr is perturbed during pregnancy in wild-type mice. In subsequent in vitro experiments, serum from pregnant mice and humans repressed Fxr target gene expression in rat hepatoma-derived FAO cells. This inhibition was abolished by co-incubation with the estrogen receptor (ER) antagonist Fulvestrant (ICI 182780), suggesting that ER and estrogens circulating in pregnant serum play a role in Fxr repression in the liver. We next showed that in reporter assays, FXR transcriptional activation was repressed upon cotransfection with ER and estrogen stimulation. Finally, Fxr interacts with ERα/β in vitro in a ligand-dependent manner in GST pulldown assays, suggesting that estrogens via their receptor ER transrepress Fxr function.
In conclusion, we provide evidence that ligand-activated ERα/β inhibits Fxr function during pregnancy resulting in a pro-cholestatic gene expression profile and raised hepatic and serum bile acid concentrations. We propose that this will cause ICP in genetically pre-disposed individuals.

The laxative polyethylene glycol does not affect intestinal absorption of lipids but doubles the bile salt pool size in rats

M.Y.M. van der Wulp[1,2], F.J. Cuperus[2], J. Dekker[1], E.H. Rings[1, 2], H.J. Verkade[1,2], [1]Top Institute Food and Nutrition, Wageningen, [2]Pediatric Gastroenterology, Dept. of Pediatrics, Centre for Liver, Digestive, and Metabolic Diseases, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Polyethylene glycol (PEG) is a frequently used osmotic laxative that decreases gastrointestinal transit time (GITT). It is unknown if PEG treatment or a decreased GITT influences the absorptive function of the intestine. The absorptive function of the intestine regarding lipids involves dietary fats, cholesterol and bile salts (BS). Altered absorption of lipids can have gastrointestinal and cardiovascular consequences. The aim of this study was to determine the effects of PEG treatment on GITT, absorption of fat and cholesterol, and the enterohepatic circulation of BS in rats. Male Wistar rats were treated with PEG (Colofort® 71 g/ L, estimated daily dose ~5.5 g/ kg) in drinking water for two weeks, or were not treated (controls). GITT was defined as the interval between intragastrical administration of carmine dye and its first appearance in feces. We determined cholesterol absorption using the dual stable isotope technique (administration of IV D7- and intragastric D5-labeled cholesterol). Enterohepatic circulation of the major primary BS cholate was assessed by stable isotope dilution technique (IV ^{13}C-cholate). Intestinal fat absorption was quantified by a 48 hr fat balance. In a separate experiment, plasma kinetics of intragastrically administered labeled triglycerides and free fatty acids (tri-1-^{13}C-palmitate and 1-^{13}C-stearate) were determined. PEG decreased GITT by ~20% (from 10.1 ± 2.2 to 8.1 ± 2.7 h, $p<0.05$). Plasma appearance of 1-^{13}C-palmitate and 1-^{13}C-stearate were unchanged. In accordance, fat balance data showed no differences in fat absorption between groups. PEG treatment neither affected cholesterol absorption nor its fecal excretion. Total fecal BS excretion was reduced by ~40% (from 7.4 ± 1.2 to 4.5 ± 0.6 mmol/ 100g BW/ day, $p= 0.001$) during PEG treatment. Intestinal reabsorption of cholate (~98%) and biliary cholate secretion rates were unchanged during PEG treatment, as was the cholate synthesis rate. However, the cholate pool size was profoundly increased (+ ~85%, $p=0.01$) during PEG treatment.
Conclusion: PEG treatment in rats decreases the gastrointestinal transit time, but does not affect intestinal absorption of dietary fats, cholesterol or bile salts. PEG treatment nearly doubles the BS pool size, which increase seems predominantly confined to BS in the intestinal lumen. Given the frequent and long-term prescriptions of PEG in clinical practice, the effects of an increased intestinal BS pool need to be addressed.

Reduced uptake of taurocholic acid in ATP8B1-depleted Caco-2 cells: an explanation for diarrhea in patients with ATP8B1 deficiency?

L.M. van der Velden[1], J.M. Stapelbroek[1,2], S.W.C. van Mil[1], V. Oorschot[3], J. Klumperman[3], M. van der Ham[1], M.G. de Sain-van der Velden[1], R. Berger[1], R.H.J. Houwen[2], L.W.J. Klomp[1], [1]Dept. of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, [2]Dept. of Paediatric Gastroenterology, UMC Utrecht, [3]Cell Microscopy Centre, Dept. of Cell Biology, Institute of Biomembranes, UMC Utrecht, The Netherlands

ATP8B1 deficiency is a hereditary cholestasis syndrome, caused by mutations in the ATP8B1 gene, encoding a putative aminophospholipid translocase. Diarrhea is a common extrahepatic manifestation of ATP8B1 deficiency, and is likely associated with bile salt malabsorption in the intestine, where ATP8B1 is abundantly expressed at the apical membrane. Here, we investigated the consequences of ATP8B1 deficiency in enterocytes in vitro.The expression of ATP8B1 was targeted by shRNA constructs in the human intestinal cell Caco-2, which resulted in reduced ATP8B1 protein expression. ATPB8B1 knockdown resulted in a signifycant reduction of taurocholate uptake across the enterocyte apical membrane. Since ATP8B1 is a putative aminophospholipid translocase, it is unlikely that reduced uptake of taurocholate is a direct effect of ATP8B1 knock down. However, aminophospholipid translocases in yeast have been implicated in vesicular transport and subcellular localization of other proteins. Therefore we assessed the expression and localization of the enterocyte bile acid transport proteins by immunocytochemistry. Localization of the heterodimeric basolateral bile salt export protein (OSTα/β) was unaffected. In contrast, apical bile salt importer protein (ASBT) was hardly detected in the ATP8B1 knock down cells compared to empty vector control cells. Other enterocyte apical membrane marker proteins such as aminopeptidase N, alka phosphatase and sucrase-isomaltase all displayed reduced apical expression, as assessed by immunocytochemistry and western blot analysis. We investigated this loss of apical membrane protein expression in more detail by analyzing the overall cellular architecture. Severe perturbations in apical membrane organization of ATP8B1 depleted Caco-2 cells were observed including a disorganized apical actin cytoskeleton and a severe loss of microvilli as assessed by immunocytochemistry and transmission electron microscopy, respectively.
Conclusion: Bile salt import in ATP8B1-depleted Caco-2 cells is severely compromised due to decreased expression of ASBT at the apical plasma membrane. These in vitro observations of reduced bile acid uptake, overall reduced apical membrane protein expression and the severe loss of microvilli, provide a potential explanation for the intractable diarrhea in patients with ATP8B1 deficiency.

Pre-operative staging with chest CT in patients with colorectal carcinoma: not as a routine procedure.

I. Grossmann[1], J.K.A. Avenarius[2], W.J.B. Mastboom[1], J.M. Klaase[1], [1]Medisch Spectrum Twente, Department of Surgery, [2]Medisch Spectrum Twente, Department of Radiology, The Netherlands

Background Preoperative staging of patients with colorectal carcinoma (CRC) has the potential benefit of altering treatment options when metastases are present. The clinical value of chest CT in staging remains unclear.
Methods All patients who undergo colorectal surgery in our hospital are prospectively registered, including patient-, treatment- and histopathological characteristics, outcome and follow-up. From January 2007, routine pre-operative staging CT of chest and abdomen for patients with CRC was performed as part of our regional guidelines. In this observational cohort study an analysis on outcome was done after inclusion of 200 consecutive patients.
Results Synchronous metastases were present in 60 patients (30%). Staging chest CT revealed pulmonary metastases in 6 patients, with one false positive finding. In 50 patients indeterminate lesions were seen on chest CT (25%). These were diagnosed during follow-up as true metastases (n=8), bronchus carcinoma (n=2), benign lesions (n=25) and remaining unknown (n=15). Ultimately synchronous pulmonary metastases were diagnosed in 13 patients (7%), in 6 patients confined to the lung (3%). In none of the patients the treatment plan for the primary tumor was changed based on the staging chest CT.
Conclusion The low incidence of pulmonary metastases and minimal consequences for the treatment plan limits the clinical value of routine staging chest CT before operation. It has several disadvantages such as costs, radiation exposure and prolonged uncertainty due to the frequent finding of indeterminate lesions. Based on this study a routine staging chest CT in CRC patients is not advocated.

Adjuvant Hyperthermic Intraperitoneal Chemotherapy after cytoreductive surgery for peritoneal carcinomatosis prolongs survival in the rat

Y.L.B. Klaver[1], T. Hendriks[2], R.M.L.M. Lomme[2], HJ.T. Rutten[1], R.P. Bleichrodt[2], I.HJ.T. De Hingh[1], [1]Dept. of Surgery, Catharina Hospital Eindhoven[2], Dept. of Surgery, Radboud University Medical Centre Nijmegen, The Netherlands

Peritoneal carcinomatosis of colorectal origin has long been considered to be an untreatable condition, suitable for palliative systemic treatment only. The combination of cytoreductive surgery (CS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been shown to be an effective treatment for selected patients with peritoneal carcinomatosis of colorectal origin. The disease free interval and survival are significantly prolonged as compared to conservative treatment strategies. However, it remains to be proven whether the addition of hyperthermic chemotherapy to cytoreductive surgery is essential for the reported survival benefit. Objective of this study was to determine if HIPEC with mitomycin C can improve survival if used as an adjunct to CS for the treatment of peritoneal carcinomatosis in a preclinical model. Sixty WAG/Rij rats were inoculated intraperitoneally with the rat colon carcinoma cell CC-531. Animals were randomized into three treatment groups. The first group was treated with cytoreductive surgery only, in the second group cytoreductive surgery was followed by HIPEC (mitomycin 15 mg/m^2), and in the third group HIPEC was added to cytoreductive surgery with mitomycin in a concentration of 35 mg/m^2. Survival was the primary outcome parameter. The humane endpoint was determined by a biotechnician, blinded for the treatment regimen. Secundary outcome parameters were amount of ascites and tumor load at obduction. Median survival of rats treated with cytoreductive surgery alone was 43 days. Rats receiving HIPEC 15 mg/m^2 and HIPEC 35 mg/m^2 both had a significantly longer median survival of 80 and 100 days, respectively ($p<0.001$). In addition, rats receiving HIPEC showed a significantly lower tumor load at obduction as compared to rats treated with cytoreductive surgery only.
Conclusions: A combination of CS and HIPEC results in a delay of tumor growth and a significantly higher survival than CS alone in rats with peritoneal carcinomatosis of colorectal origin. The procedures are associated with a minor toxicity. This result provides a firm experimental basis for generally accepting HIPEC as the standard treatment for patients with peritoneal carcinomatosis.

Increased soluble CD95 and CD95ligand levels correlate with poor overall survival after surgical procedures in patients with colorectal livermetastases.

N. Snoeren[1], F.J.H.Hoogwater[1], M.W.Nijkamp[1], A.C. Gunning[1], O. Kranenburg[1], R. van Hillegersberg[1], I.H.M.Borel Rinkes[1], University Medical Centre Utrecht, Dept. of Surgery, The Netherlands*

Death from colorectal cancer is caused by metastatic disease rather than by the primary tumour. About 50% of patients with colorectal cancer are destined to develop hepatic metastases. Both resection and radiofrequency ablation are treatment options offering five year survival for patients with colorectal liver metastases. Unfortunately local or distant recurrences after liver surgery are a frequent phenomenon. CD95 is a cell surface receptor best known for its proapoptotic function upon binding with its physiological ligand (CD95L). The soluble forms of CD95 and CD95 ligand are however associated with escape mechanisms of apoptosis and could therefore be favourable for outgrowth of tumour. In the present study we determined levels of soluble CD95 and soluble CD95 ligand (sCD95/sCD95L) in 84 colorectal cancer patients with liver metastases before and after surgical intervention to see if sCD95 or sCD95L can serve as a marker for overall survival.Blood samples were obtained from 84 patients with colorectal liver metastases before and after liver surgery. Computed tomographic scans were done every 3 months to monitor recurrences. Mean follow up was 24 months. Levels of sCD95 and sCD95L were determined using Enzyme-Linked Immuno Sorbent Assays (ELISAs). A cox regression analysis was performed to determine the correlation between levels of sCD95 and sCD95L and overall survival.High preoperative and postoperative sCD95 levels are associated with poor overall survival (p=0.010, HR=1.7, 95%CI: 1.14-2.55 and p=0.032, HR=1.6, 95%CI: 1.04-2.56). Preoperative sCD95L is not associated with overall survival (p=0.744, HR= 0.853, 95%CI: 0.33-2,214), whereas postoperative CD95L is associated with overall survival (p=0.009, HR=3.56, CI:1.38-9.12). These results show that pre-operative sCD95 and postoperative levels of sCD95 and sCD95L are predictors of outcome in terms of overall survival of patients with colorectal liver metastases. The evaluation of sCD95 and sCD95 ligand serum levels may be important for the selection of therapeutic strategies. The mechanism by which these soluble factors are associated with poor prognosis needs to be elucidated.

Laparoscopic emergency colectomy for ulcerative colitis is associated with less adhesions compared to open

S.A.L. Bartels[1], D. Henneman[1], M.S. Vlug[1], J.F.M.Slors[1], W.A. Bemelman[1], [1]Dept. of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

The aim of this retrospective study is to determine whether the need for adhesiolysis during completion proctectomy and pouch creation is influenced by the approach and the hospital (referring or academic) of the initial colectomy. The incidence of Ulcerative Colitis (UC) is rising and estimated between 7-14 per 100.000 in Western countries. Thirty-two per cent of UC patients receive surgical treatment eventually. In case of refractory UC and life threatening symptoms an acute (sub)total colectomy is performed, leaving a rectal stump and ileostomy in situ. The emergency colectomy can be done laparoscopically or open. During the completion proctectomy and pouch procedure, the need for adhesiolysis can be recorded. Likewise, this can be recorded in patients that were referred and in patients that had initial surgery in our academic hospital. All patients that underwent a completion proctectomy with ileo pouch anal anastomosis (IPAA) between January 1999 to October 2009 were included in this study. All case files were reviewed, focusing on operation time, adhesiolysis, correction of incisional hernias and perioperative morbidity.Ninety-four patients underwent a completion proctectomy with IPAA, of whom 44 received their acute (sub)total colectomy in a referring Centre and 50 patients in our academic hospital. Twenty-four out of 50 patients had laparoscopic colectomy in the academic hospital, two out of 44 in a referring hospital. Median operating time of the proctectomy and pouch, morbidity, hospital stay and incisional hernia rate were similar between the open/laparoscopic and referred/academic hospital groups, although completion proctectomy took longer when the patients were referred (resp. 150.5 vs. 167 min., P=0.097). In patients that underwent acute colectomy in a referring hospital, significantly more adhesiolysis was performed during completion proctectomy (32 vs. 20, P=0.001). Significantly more adhesiolysis was performed after open compared to laparoscopic colectomy (70.6% vs. 15.4%, P<0.001). Overall morbidity, hospital stay and incisional hernia rate between patients operated in a referring or the academic hospital was not significantly different. In conclusion, laparoscopic emergency colectomy is associated with less adhesions that require lysis during the completion proctectomy. Referred patients require more operating time for their completion proctectomy and pouch procedure.

Peri-operative blood pressure as a risk factor for anastomotic leakage in colorectal surgery

M.F. Lutke Holzik, K. Noordzij, I. Grossmann, J. Klaase, J. van der Palen, Medisch Spectrum Twente, Dept. of Surgery, Enschede, The Netherlands

Introduction: Symptomatic anastomotic leakage after colorectal surgery results in a high incidence of morbidity and mortality. For many years research had been done on identifying potential risk factors for this. In this study we analyzed in literature described risk factors and our own formulated risk factors. Methods: In this prospective cohort study, previous in literature described risk factors and our own formulated risk factors have been analyzed with the use of an unselected patient group. Thirty-eight peri-operative potential risk factors were scored and statistically analyzed. Results: Between January 2007 and August 2008, 333 primary colorectal anastomoses were created amongst 329 patients. The anastomotic leakage percentage was 9.3%. The leakage related mortality was 20%. Multivariate analysis showed two significant risk factors: 1)pre-operative hypertension and 2)the duration of the peri-operative hypotensive period. The definition of the peri-operative hypotension is formulated as the absolute period of a systolic tension less than 100 mm/Hg during the operation. The median time of the peri-operative hypotensive period in the group that developed an anastomotic leakage was 30 minutes in comparison to 15 minutes in the group that did not developed a leakage (OR: 1.02, 95% CI: 1.01-1.03, p = 0,007). Of the patients with pre-existing hypertension, whether or not corrected by the use of medication, 14.9% developed an anastomotic leakage compared to 6.4% of the patients without pre-existing hypertension (OR: 2.52, 95% CI: 1.13-5.63, p = 0.024). Hypotension may result in a reduced micro perfusion in the intestinal wall (ischemia), resulting in impaired healing and anastomotic leakage. Patients with pre-existing hypertension may be relatively hypotensive at an accepted peri-operative systolic tension of around 100 mm/Hg. This may increase their risk of anastomotic leakage.
Conclusion: These findings are clinical significant since peri-operative hypotension can be influenced by the anesthesiologist. Now we maintain a systolic blood pressure of at least 100mm/Hg during all colorectal procedures. Relative peri-operative hypotension may be an underestimated parameter.

The ileo neo rectal anastomosis (INRA): long-term follow up

J.T. Heikens[1], W.E. Hueting[2], H.J. Oostvogel[3], Th.J.M.V. van Vroonhoven[2], H.G. Gooszen[1], C.J.H.M. van Laarhoven[1], [1]Dept. of Surgery, Radboud University Nijmegen Medical Centre, Dept. of Surgery, [2]Meander Medical Centre Amersfoort, [3]Dept. of Surgery, St Elisabeth Hospital, Tilburg, The Netherlands

The ileo neo rectal anastomosis (INRA), an alternative restorative procedure to the ileal pouch anal anastomosis for patients suffering from ulcerative colitis (UC) or familial adenomatous polyposis (FAP), was developed to reduce complications related to pelvic dissection whilst preserving an acceptable functional result. Favorable midterm results were published previously in 2004. Long follow-up results of INRA are needed to see if early results can be substantiated.All INRA patients are included in the analysis. Data was registered prospectively using pre-specified case record forms scoring patient demographics, clinical and follow-up data: morbidity, dietary problems, defecation frequency and faecal continence, bladder and sexual (dys)function, and medication use. Ano-(neo)rectal physiology was assessed by manometry. Eighty-two patients were enrolled, in 58 cases (50 UC, 8 FAP) an INRA procedure was carried out. Twenty-four cases were converted to IPAA (n=23) or proctectomy. In 49 patients (84.5%) a functional reservoir was achieved. The mean follow-up was 6.8 years. Two patients never opted to restore oro-anal continuity on their own demand, seven patients experienced failures due to neorectum related pathology. Rates of pelvic sepsis, bladder or sexual dysfunction were 0%. Thirteen patients (22%) experienced one or more episodes of “pouchitis” like inflammation. Median bowel movements of six with a nocturnal defecation frequency of one were recorded. Forty-five patients (91.9%) reported normal faecal continence or experienced minor incontince. Ano-(neo)rectal manometry showed an increase in the maximum tolerated volume and a decrease in compliance. The primary aim of INRA to reduce complications related to pelvic dissection has been achieved. INRA patients with a viable neorectum have good functional results. This is supported by the ano-(neo)rectal manometry results.

Development of a composite endpoint for randomized controlled trials in liver surgery

MAJ van den Broek[1], R.M. van Dam[1], G.J.P. van Breukelen[2], L.I. Mpabanzi[1], M.H. Bemelmans[1], C.H.C. Dejong[1,3], N. Freemantle[4], S.W.M. Olde Damink[1,3,5], [1]Dept. of Surgery, Maastricht University Medical Centre, Maastricht, [2]Dept. of Methodology and Statistics and [3]NUTRIM School for Nutrition, Toxicology and Metabolism, Dept. of Surgery, Maastricht University, Maastricht, The Netherlands, [4]Dept. of Primary Care and General Practice, University of Birmingham, Birmingham, United Kingdom, [5]Dept. of Surgery, University College London Hospital, London, United Kingdom

The feasibility of adequately powered randomized controlled trials (RCTs) in liver surgery using surgery related morbidity or mortality as primary endpoint is low as the sample size would be extremely large. A liver surgery specific composite endpoint (CEP) could solve this problem. This study aimed to design and validate a liver surgery specific CEP to be used as primary endpoint in RCTs in liver surgery. Dichotomous variables mostly used as primary or secondary endpoint of RCTs in liver surgery published between 2004 and 2008 were identified by an electronic literature search. A web-based survey was developed based on these endpoints and sent to 54 leading HPB surgeons worldwide in order to reach consensus on definitions and components of a liver surgery specific CEP. Major complications (Dindo grade ≥ 3) with a preference rate among respondents ≥ 66% were considered as components. A prospective database consisting of 321 patients who have undergone a partial hepatic resection in a single institute was used to determine the incidence of the liver surgery specific CEP. Sample sizes were calculated with the assumption that α=0.05 and β=0.8. Forty-seven RCTs in liver surgery were identified. The 12 dichotomous endpoints mostly used in these RCTs formed the basis of the survey. Thirty-one responses were collected (57%); all respondents were interested to use a liver surgery specific CEP. Complications selected as components of the liver surgery specific CEP were post-resectional liver failure (PLF; preference rate among respondents 100%), bile leakage (100%), ascites (89%), intra-abdominal hemorrhage (82%), intra-abdominal abscess (71%) and operative mortality (86%), all with a Dindo grade ≥ 3. Internal validation showed an incidence of 4% for PLF, 12% for bile leakage, 3% for ascites, 2% for intra-abdominal hemorrhage, 12% for intra-abdominal abscess and 5% for mortality. The incidence of the liver surgery specific CEP was 20.9%. An RCT aiming to show a 50% relative reduction in any of the individual components would need to include between 726 and 5808 patients; when using the liver surgery specific CEP as primary endpoint, this RCT would need 380 patients.
Conclusions: A liver surgery specific CEP increases the event rate up to 20.9%. When used as primary endpoint, it increases the feasibility of RCTs in liver surgery.

Prospective evaluation of endoscopic and conservative treatment of persistent symptomatic sterile pancreatic necrosis

RP Voermans[1,3], O.J. Bakker[2], S. van Brunschot[1,7], H.C. van Santvoort[2], M.A. Boermeester[3], R. Timmer[4], V.B. Nieuwenhuijs[5], M.J. Bruno[6], H. Gooszen[7] and P. Fockens[1] for the Dutch Pancreatitis Study Group, [1]Dept. of Gastroenterology and Hepatology & [3]Dept of Surgery, Academic Medical Centre, Amsterdam; [2]Dept of Surgery, UMCU, Utrecht; [4]Dept. of Gastroenterology and Hepatology, St. Antonius hospital, Nieuwegein; [5]Dept of Surgery, University Medical Centre Groningen; [6]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam; [7]Dept of Surgery, University Medical Centre St. Radboud, Nijmegen, The Netherlands

Most patients with sterile pancreatic necrosis can be treated conservatively. Intervention is indicated in patients with persisting symptoms despite conservative treatment. However, prospective studies with a standardized treatment algorithm regarding indication for, and timing and type of intervention, are lacking. Aim was to prospectively evaluate outcome of a standardized treatment algorithm for patients with symptomatic sterile pancreatic necrosis. Patients with sterile symptomatic pancreatic necrosis admitted at or transferred to 1 of 4 hospitals of the Dutch Pancreatitis Study Group were prospectively included from 01/2008 onwards. Initial treatment in all patients was conservative. Criteria for endoscopic intervention were severe abdominal pain insufficiently relieved by non-narcotic analgesic or requiring opiates, gastric outlet obstruction or obstructive jaundice persisting at least 6 weeks after onset of acute pancreatitis. Endoscopic intervention encompassed EUS-guided drainage of the necrotic collection with additional flushing via a nasocystic catheter plus endoscopic transluminal necrosectomy (ETN). Primary endpoint was clinical success defined as resolution of symptoms 12 months after onset. Secondary endpoints included resolution of the collection, adverse events, hospital stay and additional interventions. Until November 2009, 28 patients were included. Conservative treatment alone was successful in 9 patients (32%). Nineteen patients (68%) met predefined criteria for intervention at presentation (13 of 19 patients) or during follow up (6 of 19 patients) and were treated endoscopically at a median of 143 days (range 42-424) after onset of pancreatitis. A median of 3 ETN procedures (range 1-8) were performed. In 2 patients ETN was complicated by bleeding which was treated radiologically. There were no deaths. Transluminal stents were removed after a median of 23 weeks. At 12 months follow up, 93% of patients were asymptomatic (17 of 18 endoscopic and 8 of 9 conservative treated patients). After 1 year follow up abdominal imaging showed no recurrence in the endoscopically treated patients. In 56% of conservative treated patients there was a persistent asymptomatic fluid collection (median size 10 cm). In this first prospective study in patients with symptomatic sterile pancreatic necrosis, a standardized treatment algorithm resulted in clinical success in 93% within 1 year after onset of pancreatitis. ETN seems to be a safe and effective treatment option in patients with persisting symptoms of sterile pancreatic necrosis. Asymptomatic sterile necrosis does not warrant endoscopic intervention.

Route of gastroenteric anastomosis in pancreatoduodenectomy and delayed gastric emptying – a retrospective analysis

W.J. Eshuis, J.W. van Dalen, O.R.C. Busch, T.M. van Gulik, D.J. Gouma, Dept. of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Delayed gastric emptying (DGE) is a frequent and bothersome complication after pancreatoduodenectomy. Some authors suggest that an antecolic route of the gastroenteric anastomosis (duodenojejunostomy, DJ or gastrojejunostomy, GJ) lowers the incidence of DGE, compared to a retrocolic route. In our institution, a retrocolic route has been routinely used until 2005, after which an antecolic route became more frequent.Aim of the present study was therefore to investigate the relation between the route of gastroenteric anastomosis and the incidence of DGE after pancreas-toduodenectomy.In a consecutive series of 203 patients from our prospective pan-creatoduodenectomy database, the route of gastroenteric anastomosis was established by reviewing operation reports. Hospital course and follow-up were prospectively recorded. Patients with antecolic DJ or GJ were compared to patients with retrocolic DJ or GJ. Main outcome measure was the incidence of DGE according to the International Study Group of Pancreatic Surgery criteria. Secondary outcome measures were other complications and hospital stay. In 47 patients the route of gastroenteric anastomosis could not be determined. Two patients were excluded because they had Roux-en-Y reconstruction. Of the remaining 154 patients, 77 had a retrocolic anastomosis and 77 had an antecolic anastomosis. In the retrocolic group, DGE occurred in 58% of patients (25% grade A, 17% grade B and 17% grade C). In the antecolic group, 52% had DGE (21% grade A, 16% grade B and 16% grade C). This difference was not significant. 'Primary' DGE of any grade (not due to other intra-abdominal complications) occurred in 36% of the retrocolic group and 20% of the antecolic group (p 0.02). 'Primary' clinically relevant DGE (grade B or C) occurred in 18% and 10%, respectively (p 0.17). There was no difference in need for (par)enteral nutritional support, other complications, hospital mortality or length of hospital stay.
Conclusions: The route of DJ or GJ had no influence on the overall postoperative incidence of DGE. Clinically relevant DGE (overall and 'primary') was not different between the retrocolic and antecolic group. 'Primary' DGE (any grade) was more frequent in the retrocolic group, mainly due to a higher incidence of DGE grade A. The preferred route for gastroenteric anastomosis in pancreatoduodenectomy remains to be confirmed in well-powered randomized controlled trial.

Long-term outcomes of transanal hemorrhoidal dearterilisation (THD) for grade 2-4 hemorrhoids

S.M.J ter Veldhuis[1], R. Koop[1], J.M. Klaase[1], M.F. Lutke Holzik[1], [1]Dept. of Surgery, Medical Spectrum Twente, Enschede, The Netherlands

Transanal hemorrhoidal dearterilisation (THD) is a new, minimal invasive treatment for hemorrhoids, where hemorrhoidal arteries are first detected with Doppler sound and then selectively ligated. We investigated the long-term results of THD in our hospital in patients with grade two to four hemorrhoids. From January 2005 until September 2009, 245 consecutive patients (143 men, medium age 50 years) with grade two to four hemorrhoids were treated in our hospital with THD under spinal anesthesia in day care. All patients had previously been treated with rubber band ligation. We studied 245 patients, 126/245 (51%) patients had grade three hemorrhoids, 64/245 (26%) grade two and 54/245 (22%) grade four hemorrhoids. The main complaints were blood loss 113/245 (46%), pain 64/245 (26%), prolapse 9 (4%) and swelling 30/245 (12%), soiling 6/245 (2%), itching 8/245 (3%) and other (1%).After a median follow up of 23 months 166/245 (68 %) of patients were symptom free, 47/245 (19%) of patients had at least a 50% reduction of complaints and in 41/245 (16 %) of patients treatment had no effect. Remission percentages for grade two, three and four hemorrhoids were respectively 72%, 76% and 68.5%. 40 (16%) patients underwent a second THD procedure and one patient underwent a third THD procedure. 13 (5%) patients eventually underwent open hemorrhoidectomy because of persistent complaints. Post- operative complications occurred in 23/245 (8%) of patients, including bleeding in 7 (3%) patients, severe anal pain in 8 (3%) patients, urinary retention in one (0.4%) patient and other (2%). Re-hospitalization was necessary in three patients (two bleeding, one urinary retention).
Conclusion: THD is a safe and effective treatment for grade two to four hemorrhoids, also in view of longer term outcomes.

Percutaneous drainage for acute calculous cholecystitis.

K. Kortram[1], T.S. de Vries Reilingh[1], D. Boerma[2], M.J. Wiezer[1], B. v. Ramshorst[1], [1]Dept. of Surgery, St. Antonius Hospital, Nieuwegein, [2]Dept. of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Acute calculous cholecystitis is a frequently encountered problem in the surgical practice; laparoscopic cholecystectomy (LC) is still the standard treatment. LC for acute cholecystitis can be a more difficult procedure than elective LC for cholelithiasis and is associated with increased operating time, higher conversion rate and more postoperative complications. In the elderly patient with serious comorbidity surgery can result in serious complications and even mortality. Percutaneous drainage (PC) may be a preferable method. There is hardly any evidence in current literature regarding the safety, success rate and procedure specific technique of this procedure, and the question remains whether there is a place for PC in the treatment of acute calculous cholecystitis. Aim of this prospective cohort study was to evaluate the safety and efficacy of PC in the treatment of acute calculous cholecystitis.Data of 23 consecutive patients undergoing percutaneous drainage in acute calculous cholecystitis between December 1st 2008 and December 1st 2009 were collected in a prospective database. Comorbidity and ASA classification were determined, indication for drainage instead of cholecystectomy was recorded and procedure related data were collected. Duration of drainage, use of antibiotics and complications were documented. Primary outcomes were time to recovery, mortality and recurrent biliary disease.The cohort included 13 male and 10 female patients with a median age of 81 years (range 69-90). Most patients were ASA 3(n=14) or ASA 2(n=8), one patient was ASA 4. Indication for drainage was age and/or comorbidity in 20 cases and duration of symptoms in three cases. Drainage was performed using ultrasound in 21 cases and CT in two cases. Bile cultures were performed in 18 patients. Antibiotic treatment was given in all but two patients. Mean time to full recovery was nine days, the drain was in situ for a median period of 19 days (range 5-57). Relief of symptoms occurred in 22 patients; drain luxation occurred in eight patients. There was no procedure-related mortality; three patients died as a result of their comorbidity. Two patients underwent interval cholecystectomy, both two months after drainage. Percutaneous drainage in acute calculous cholecystitis seems to be a safe and successful treatment option in patients less eligible for surgery. In order to establish the exact value of PC, the CHOCOLATE (Acute calculous CHOlecystitis: laparosCOpic choLecystecomy in the Acute setting versus percuTanEous drainage) trial has been initiated, and inclusion will start in 2010.

Is sexual dysfunction in women after restorative proctocolectomy with ileal pouch anal anastomosis caused by autonomic pelvic nerve damage? - A prospective clinical trial

J Wind[1], M.S.Vlug[1], E.T. Laan[2], R.H.W. van Lunsen[2], P.J. van Koperen[1], S.W.Polle[1], W.A. Bemelman[1], [1]Dept. of Surgery, Academic Medical Centre, University of Amsterdam, [2]Dept. of Sexology and Psychosomatic Gynecology, Academic Medical Centre, University of Amsterdam, The Netherlands

Sexual dysfunction after restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) is common. The most systematic physical reaction to sexual stimulation is an increase in vaginal vasocongestion. Genital response can be assessed by vaginal pulse amplitude (VPA) using vaginal photoplethysmography. The objective of the present study was to assess whether restorative proctocolectomy with ileo pouch anal anastomosis is associated with autonomic pelvic nerve damage and changes in subjective indices of sexual function in women. Female patients undergoing IPAA between April 2004 and January 2006 were included. During sexual stimulation (visual and vibrotactile) changes in vaginal vasocongestion were measured by vaginal photoplethysmography. Concurrently, quality of life (SF-36) and sexual functioning (FSFI, FSDS) were assessed using validated questionnaires. Endpoints were difference in VPA, feelings of sexual arousal and estimated lubrication pre- and postoperatively and difference in psychological - and sexual functioning pre – and postoperatively. Eleven patients were included. For 8 patients (median age 37 [22-49 yrs]) pre- and post-operative data were collected. VPA analysis showed a significant reduction in vaginal vasocongestion during sexual stimulation post-operatively, P=0.012. Subjective sexual arousal and estimated lubrication during the experiment, reported psychological and sexual functioning pre- and postoperative were not different.
Conclusions: Vaginal vasocongestion after IPAA was significantly reduced; indicating that IPAA in women may be associated with autonomic pelvic nerve damage or partial devascularisation of the vagina. Subjectively reported sexual arousal, estimated lubrication, psychological and sexual functioning were not diminished. Future research should focus on the possible advantage of a full close rectal dissection in these patients.

Dyspeptic symptoms after laparoscopic large hiatal hernia repair and primary antireflux surgery for gastro-oesophageal reflux disease; a comparative study

E.J.B. Furnée[1], W.A. Draaisma[2], E.J. Hazebroek[1], N. van Lelyveld[3], A.J.P.M. Smout[4], I.A.M.J. Broeders[2], [1]Dept. of Surgery, University Medical Centre Utrecht, [2]Dept. of Surgery, Meander Medical Centre, Amersfoort, [3]Dept. of Gastroenterology, Meander Medical Centre, Amersfoort, [4]Dept. of Gastroenterology, University Medical Centre Utrecht, The Netherlands

Several patients with gastro-oesophageal reflux disease (GORD) suffer from functional dyspepsia, and these symptoms persist in a substantial part of patients after laparoscopic Nissen fundoplication. We hypothesised that dyspeptic symptoms are more frequent after laparoscopic large hiatal hernia (type II-IV) repair when compared to primary antireflux surgery due to a higher chance of vagal nerve impairment during extensive hernia sac resection and oesophageal mobilisation.From January 2003, 61 consecutive patients who underwent an antireflux fundoplication primarily for GORD and 27 consecutive patients who had large hiatal hernia repair with fundoplication for concomitant GORD were included. Patients scored eight dyspeptic symptoms (ie, postprandial fullness, early satiation, epigastric pain and burning, bloating, nausea, vomiting, and excessively belching), according to a system combining frequency and severity. Furthermore, preoperative presenting symptoms were scored as resolved, improved, unchanged, or worsened according to the Visick grading system. General quality of life was obtained using the Short Form 36.Preoperative symptoms resolved or improved in 43 of the 50 available patients (86.0%) who primarily underwent antireflux surgery, and in all 24 available patients who had hiatal hernia repair (100%). Mean symptom scores of all eight dyspeptic symptoms after surgery were comparable between both cohorts. General quality of life was equal in both cohorts, but was below the previously defined score in the general Dutch population.
Conclusion: dyspeptic symptoms are present after laparoscopic large hiatal hernia repair in similar figures as after primary antireflux surgery.

A pilot trial of endoscopic radiofrequency ablation for the eradication of esophageal squamous intraepithelial neoplasia and early squamous cell carcinoma limited to the mucosa

F.G.J. van Vilsteren[1], L. Alvarez Herrero[2,1], R.E. Pouw[1], C.M.T. Sondermeijer[1], F.J. ten Kate[3], M.I. van Berge Henegouwen[4], B.L. Weusten[2,1], J.J. Bergman[1], [1]Gastroenterology, Academic Medical Centre, Amsterdam, [2]Gastroenterology, St Antonius hospital, Nieuwegein, [3]Pathology, Academic Medical Centre, Amsterdam, [4]Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Background: Esophagectomy is indicated for esophageal squamous cell cancer (ESCC) involving the muscularis mucosae (T1m3) or deeper, due the elevated risk for lymphatic invasion associated with this and later stages. For the earlier lesions of high-grade intraepithelial neoplasia (HGIN) and ESCC (T1m2), however, endoscopic therapy may be a preferred approach due to a lower morbidity and mortality risk compared to surgery. Endoscopic resection (ER) and radiofrequency ablation (RFA) are safe and highly effective for dysplasia and early cancer in Barrett's esophagus, but less is known about their utility in squamous HGIN and early ESCC. Aims: Evaluate the feasibility of ER and RFA for esophageal squamous HGIN and early ESCC (T1m2). Methods: Patients were enrolled in this prospective, ethics committee approved trial and all signed informed consent. High-resolution chromoendoscopy (Lugol's) of the esophagus demonstrated ≥1 unstained lesion (USL) with HGIN or ESCC (T1m2) on biopsy or ER. Tattoos were placed 1 cm proximal and distal to the USL-bearing portion of the esophagus, defined as the treatment area (TA). Focal ER was used to remove visible lesions (type 0-IIa or 0-IIc) for staging and to render the mucosa flat prior to RFA. EUS/CT ruled out metastatic disease. Primary circumferential RFA was applied if TA ≥4 cm, while focal RFA was applied if TA <4 cm. Chromoendoscopy was repeated every 3 months with biopsy and focal RFA of residual USLs until all biopsies were negative for squamous neoplasia (CR-Neo). After CR-Neo, chromoendoscopy was repeated at 2 and 6 months and then annually with biopsy of TA (2 specimens/2 cm). Results: Twelve patients (6 male, median age 67 (IQR 58-73), 9 HGIN/3 ESCC) were enrolled. Nine patients had prior ER. Median length of TA was 5 cm (IQR 4-6), median extent of USLs was 50% of circumference (IQR 25-75%). All 12 patients achieved CR-Neo after median 1 RFA (IQR 1-2). During RFA, there were 2 mucosal lacerations (1 at ER scar) and 1 intramural hematoma, none requiring therapy. One patient developed stenosis after ER/RFA, dilation of which resulted in perforation managed with a covered stent. Median follow-up is now 19 months (IQR 13-24) and all patients remain CR-Neo.
Conclusions: In this single Centre, pilot trial of ER and RFA for esophageal squamous HGIN and ESCC (T1m2), we achieved a CR-Neo in all patients after 1 or 2 ablations. No recurrences have occurred 19 months after achieving CR-Neo. While these results are encouraging, larger studies in homogeneous patient populations are needed to address the role of endoscopic therapy for HGIN and early ESCC.

Lymphatic micrometastases in patients with early esophageal adenocarcinoma

B.A. Grotenhuis[1], M. van Heijl[2], B.P.L. Wijnhoven[1], M.I. van Berge Henegouwen[2], K. Biermann[3], F.J.W. ten Kate[4,5], O.R.C. Busch[2], W.N.M. Dinjens[3], H.W. Tilanus[1], J.J.B. van Lanschot[1], [1]Erasmus Medical Centre, Rotterdam, Dept. of Surgery; [2]Academic Medical Centre, Amsterdam, Dept. of Surgery; [3]Erasmus Medical Centre, Rotterdam, Dept. of Pathology; [4]Academic Medical Centre, Amsterdam, Dept. of Pathology; [5]University Medical Centre, Dept. of Pathology, Utrecht, The Netherlands

The management of early esophageal adenocarcinomas with invasion into the deepest mucosal layer (m3) or the most superficial layer of the submucosa (sm1) is under debate. Both endoscopic and surgical treatments are propagated, depending on patients' lymph nodal status. Lymphatic dissemination is related to the tumor infiltration depth, but varying incidences have been reported in m3 and sm1 adenocarcinomas. The aim of this study was to investigate whether the presence of occult tumor cells in lymph nodes could explain this variation. Sixty-three node-negative (N0) patients with early esophageal adenocarcinoma (m2, m3 and sm1 tumors) were included. Multilevel sectioning of lymph nodes was performed, and sections were stained by means of immunohistochemistry (IHC) with the cytokeratin marker CAM5.2. Two experienced GI pathologists searched for micrometastases (CAM5.2 positive lesions 0.2-2.0 mm in dimension) and isolated tumor cells (ITCs, <0.2mm). None of the 18 m2 tumors showed positive CAM5.2 staining in the lymph nodes. In two out of 25 m3 tumors (8.0%) an ITC was found, but no micrometastases. Tumor cells were identified in four out of 20 sm1 tumors (20.0%): three micrometastases (15.0%) and one ITC (5.0%). Median follow-up was 121 months. Two out of 63 (3.2%) patients, both were diagnosed with a m3 tumor, died due to locoregional tumor recurrence, including one patient in whom an ITC was detected.
Conclusions: In the present study, lymphatic migration of tumor cells has been found in node-negative m3 and sm1 esophageal adenocarcinomas (8.0% and 20.0%, respectively). However, the clinical relevance of these occult tumor cells should become apparent from large series of endoscopically treated patients with sufficiently long follow-up. Based on the presently available data, it seems unlikely that the morbidity and mortality of a surgical resection is counterbalanced by a substantial gain in long-term survival for patients with m3 lesions; a surgical resection seems the treatment of choice for patients with sm1 tumors.

The stromal part of adenocarcinomas of the oesophagus: does it conceal targets for therapy?

E.F.W. Courrech Staal[1], M.W.J.M. Wouters[1,2], J.W. van Sandick[1], V.T.H.B.M. Smit[3], T. Karsten[4], H.H. Hartgrink[2], W.E. Mesker[2], R.A.E.M. Tollenaar[2], [1]Dept. of Surgical Oncology, Cancer Institute / Antoni van Leeuwenhoek Hospital, [2]Dept. of Surgical Oncology, Leiden University Medical Centre, [3]Dept. of Pathology, Leiden University Medical Centre, [4]Dept. of Surgery, Reinier de Graaf Hospital, The Netherlands

In the literature, a refinement of oesophageal cancer staging has been proposed. Only recently, tumour-stroma ratio (TSR) has been identified as a histological characteristic that proved to be a strong predictor for survival in colorectal cancer. The objective of this study was to evaluate the prognostic value of TSR in oesophageal adeno-carcinoma. From a regional database, we identified 93 consecutive patients who underwent resection for oesophageal adenocarcinoma without neoadjuvant treatment between 1990 and 2004. Using a predefined histopathological protocol, TSR was determined on the original tissue sections of oesophagectomy specimens by 2 independent pathologists. Using a cut-off value of 50% tumour/stroma, patients were classified as TSR high (n=60) and TSR low (n=33). There were no significant differences in patient, tumour and treatment characteristics between the two groups, except for M status (M1a) and radicality of resection. Median follow-up for all patients was 23 months. Median overall survival for patients with a low TSR was 16 (95% confidence interval [C.I.] 13-19) months compared to 42 (95% C.I. 17-68) months for patients with a high TSR. Survival analysis showed that this difference was highly significant ($p<0.001$) with a Hazard Ratio of 2.4 for TSR low. For disease-free survival, similar results were found. In multivariate analysis, TSR was identified as a highly significant prognostic factor for overall survival (HR 2.0; $p=0.010$), independent of depth of tumour invasion, nodal status, lymph node ratio, extracapsular lymph node involvement, TNM stage, histological grade and radicality of resection.

Conclusion: TSR is a novel prognostic tumour characteristic for oesophageal adeno-carcinoma that can be determined on H&E sections during routine clinical practice. It has additional value in identifying patients who do not benefit from oesophageal resection alone. The present observation emphasizes that also the stromal part of the tumour should be acknowledged in understanding tumour growth and in the search for new cancer therapies.

Gastric acidity after pancreatoduodenectomy: influence of surgical technique and peri-operative medical treatment

MJM Morak[1], T.C.K. Tran[1], M.J. Bruno[2], W.C.J. Hop[3], G. Kazemier[1], J. de Jonge[1] and C.H.J. van Eijck[1], [1]Dept. of Surgery, Erasmus Medical Centre, Rotterdam, [2]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, [3]Dept. of Biostatistics Erasmus MC, Rotterdam, The Netherlands

Background: Gastric acid at the anastomotic site after pancreaticoduodenectomy might cause peptic ulcers. This study was performed to compare gastric acidity after pylorus-preserving pancreatoduodenectomy (PPPD) and classical Whipple's resection, in addition we assessed the effect of proton pump inhibitors (PPIs) and somatostatin analogues. Method: In a prospective cohort study, 50 (69%) patients underwent a PPPD and 22 a classical Whipple's resection. Patient received intramuscular Sandostatin long acting release (LAR) (n=48; 67%) or subcutaneous octreotide (n=23; 32%). Esomeprazole was started following operation if not used pre-operatively. Gastrin levels were measured before and on day 2 after surgery together with gastric acidity. Results: Multivariate analysis showed that the type of somatostatin analogue and pre-operative PPI were independent determinants of gastric acidity two days postoperatively. The type of resection or post-operatively started PPIs had no effect on gastric acidity. There was a positive relation between serum gastrin levels and gastric pH. The type of resection, type of somatostatin analogue or PPIs had no influence on serum gastrin.
Conclusion: There is no difference between PPPD or classical Whipple's resection on post-operative gastric acidity. Pre-operative use of PPIs and the administration of subcutaneous octreotide resulted in diminished gastric acidity on day 2 postoperatively, which may prevent anastomotic ulcers. Sandostatin LAR resulted in significantly higher gastric acidity.

Factors predicting stent patency in patients with malignant biliary strictures: a multiCentre study

P.G.A. van Boeckel[1], F.P Vleggaar[1], E.W. Steyerberg[2], M.J.M. Groenen[3], B.J.M. Witteman[4], B. Weusten[5], H. Geldof[6], A. Tan[7], M. Grubben[8], J. Nicolai [9], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, [2]Dept of Public Health, Erasmus MC - University Medical Centre Rotterdam, Rotterdam, [3]Dept. of Gastroenterology, Ziekenhuis Rijnstate, Arnhem, [4]Dept. of Gastroenterology, Ziekenhuis Gelderse Vallei , Ede, [5]Dept. of Gastroenterology, St. Antonius Ziekenhuis, Nieuwegein, [6]Dept. of Gastroenterology, Canisius Wilhelmina Ziekenhuis, Nijmegen, [7]Dept. of Gastroenterology, IJsselland Ziekenhuis, Capelle a/d IJssel, [8]Dept. of Gastroenterology, Elizabeth Ziekenhuis, Tilburg, [9]Dept. of Gastroenterology, Hagaziekenhuis, Den Haag, The Netherlands

Background: Stent placement is an effective and widely accepted treatment modality for the palliation of malignant biliary strictures. One of the main drawbacks is the limited stent patency resulting in recurrent symptoms of jaundice and cholangitis. Self-expanding metal stents (SEMS) are associated with a significantly higher patency rate than plastic stents.
Aim: The aim of this study was to establish non-stent factors that affect stent patency.
Methods: A retrospective multiCentre study was conducted in 8 Dutch (1 university and 7 general) hospitals. Data were collected from hospital and endoscopy records, and information provided by patients' general practitioners (patient characteristics, underlying disorders, and stent- and procedure-related features). The cumulative incidence of stent occlusion was analyzed with Kaplan-Meier curves and log rank testing, and prognostic factors were assessed by Cox regression analysis.Results: A total of 766 stents (588 plastic stents and 178 SEMS) were endoscopically inserted in 477 patients. Underlying malignancies included pancreatic cancer (55%), cholangiocarcinoma (20%), liver metastases (13%) and other causes (12%). A total of 295 plastic stents and 56 SEMS occluded over time. The occlusion rate at 8 weeks was 42% (n=140) for plastic stents and 29% (n=16) for SEMS. Median stent patency was almost twice as long for SEMS (18.3±2.8 weeks) compared to plastic stents (9.7±1.0 weeks) (log rank test: p=<0.001). Median survival after last stent placement was 9.4 ±0.7weeks (95% CI: 8.0-10.8) (plastic stents: 8.1 ±0.7weeks, SEMS: 11.6±1.5weeks). Univariate analysis showed that being male, younger age, stricture dilation, no adjuvant radiotherapy, and higher bilirubin levels at stent placement were significant predictors of stent occlusion, whereas a previous ERCP, underlying malignancy, previous biliary surgery, (pre-cut) papillotomy, hospital, co-morbidity, etiology of the stricture and stricture location were not. Multivariable Cox analysis confirmed that high initial bilirubin (HR 1.12, 95% CI 1.03-1.21) was a predictor of stent occlusion, whereas older age (HR 0.90, 95% CI 0.82-0.99) was associated with a lower risk of stent occlusion.
Conclusion: Older patients have a lower risk of stent occlusion, while patients with higher initial bilirubin levels have a slightly higher risk of stent occlusion. The latter suggests that when stent placement is indicated, reluctance in doing so increases the need for repeat procedures.

Clinical outcome of a progressive stenting protocol in patients with anastomotic strictures after orthotopic liver transplantation

M.N. Lekkerkerker[1], J.W. Poley[1], H.J. Metselaar[1], J. Haringsma[1], G. Kazemier[2], C.H.J. van Eijck[2], E.J. Kuipers[1], M.J. Bruno[1], [1]Gastroenterology & Hepatology, Erasmus Medical Centre, Rotterdam, [2]Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

Anastomotic strictures are an important cause of morbidity after orthotopic liver transplantation (OLT). Endoscopic dilation has emerged as a primary treatment modality for benign biliary strictures. In benign anastomotic strictures due to orthotopic liver transplanttation the outcome and complications of a progressive stenting protocol, inserting a cumulative number of plastic endoprosthesis with each successive intervention, is largely unknown. We performed a longitudinal cohort study. Treatment was considered successful if there was stricture resolution at cholangiography, a balloon could be passed without resistance and liver enzymes returned to normal values. Between May 2000 and June 2009, 375 orthotopic liver transplantations were performed in which a duct-to-duct anastomosis was created in 304 cases (81,1%). In 63 patients (20.7%) an anastomotic stricture developed. Of these patients, a progressive stenting protocol was started in 35. During treatment 1 patient died of a non-treatment-related cause (intra-abdominal bleeding). Two patients underwent a second OLT while still being stented, one because of ischemic biliary complications and 1 because of liver failure due to a hepatitis C re-infection. One patient was still being stented at the time of follow-up. After excluding these patients, 31 patients were available for the present analysis (male: female 21: 10, median age 61 years, range: 28 – 75). A progressive stenting protocol in these patients required a median number of 5 ERCP procedures (range: 2 – 11). A median of maximal 3 plastic stents (range: 2 – 8) were inserted during treatment. Twenty-one patients (67.7%) required hospital admission because of treatment-related complications. In 33 out of a total of 155 ERCPs (21.3%) a complication occurred: 12 events of cholangitis, 11 events of cholestasis, 7 events of (mild) post-ERCP pancreatitis and 3 events of treatment-related pain. The median follow-up time after stent removal was 26 months (range: 2 – 92). Treatment was successful in 25 patients (80.6%). Alternative treatment for the 6 patients in whom progressive stenting was not successful was the creation of a Roux-Y choledocho-jejunostomy (n=5) or placement of an expandable metal stent (n=1).
Conclusions: Progressive stenting for anastomic strictures after orthotopic liver transplantation is demanding and strenuous, necessitating a median of 5 ERCP procedures with complications occurring in 1 out of 5 ERCPs. Its success rate however is high (80%), avoiding surgery in the large majority of patients.

Low inter-observer agreement on nodular regenerative hyperplasia of the liver: an european inter-observer analysis

B Jharap[1], D.P. van Asseldonk[1], K.H.N. de Boer[1], J.F. Colombel[3], J. Diebold[5], A.M. Jonker[6], E. Leteurtre[4], W. Reinisch[7], G. Vernier-Massouille[3], D. Wendum[9], F. Wrba[8], P.E. Zondervan[10], C.J.J. Mulder[1], A.A. van Bodegraven[1], E. Bloemena[2], Dept. of Gastroenterology & Hepatology, VU Medical Centre, Amsterdam[1], Dept. of Pathology, VU Medical Centre, Amsterdam, The Netherlands[2], Dept. of Gastroenterology & Hepatology, Academic Medical Centre Lille, France[3], Dept. of Pathology, Academic Medical Centre Lille, France[4], Dept. of Pathology, Cantonaal Hospital, Luzern, Switserland[5], Dept. of Pathology, Delfzicht Hospital, Delfzijl, The Nederlands[6], Dept. of Gastroenterology & Hepatology, Academic Medical Centre Vienna, Austeria[7], Dept. of Pathology, Academic Medical Centre Vienna, Austria[8], Dept. of Pathology, Saint-Antonie Hospital, Paris, France[9], Dept. of Pathology, Erasmus Medical Centre, Rotterdam, The Nederlands[10]

Background: In recent years the use of thiopurines has been associated with the induction of nodular regenerative hyperplasia (NRH). However, the incidence of NRH is expected to be underestimated as NRH is pathohistologically difficult to diagnose. Therefore, we performed an inter-observer agreement analysis on the pathohistological diagnosis and features of NRH. Methods: Seven experienced liver pathologists participated in an international, multicentre study. Liver specimens from 72 patients with inflammatory bowel disease treated with thiopurines with a prior diagnosis of NRH were collected from 6 European third- referral hospitals. NRH had previously been established in the liver specimens at the local pathohistological departments. Following staining with haematoxylin-eosin (H&E), reticulin and Sirius red/trichrome, these liver slides were scored for the presence of NRH by all pathologists without knowledge of the original diagnosis. After histological examination, 5 out of 7 pathologists additionally assessed the specific histological features of NRH, including the presence of hepatocellular nodules, hyperplasia of liver cells in the nodules, areas of atrophic liver cells surrounding the nodules, compression zones at periphery of the nodules and (absence of) septal fibrosis. The inter-observer agreement was evaluated by using the kappa index, called κ, ranging from <0.4 = poor; 0.4-0.75 = fair to good; >0.75 = excellent. Results: NRH was highly variable diagnosed; the range of positive diagnoses varied between 8% and 39% (29% median) by the 7 pathologists. Inconclusive NRH-related findings and no NRH were found in 18% (median, range 8-38%) and 56% (median, range 32-83%), respectively. The mean inter-observer agreement for specific histological features of NRH was 0.36 ± 0.14 for hepatocellular nodules, 0.11 ± 0.08 for hyperplasia, 0.25 ± 0.17 for atrophy, 0.20 ± 0.16 for compression zones and 0.52 ± 0.12 for absence of septal fibrosis. The mean inter-observer agreement for NRH, scored by all 7 pathologists was poor (κ = 0.27 ± 0.05).
Conclusion: The (international) inter-observer agreement of NRH in properly stained liver biopsies is very poor, even when assessed by well-known liver pathologists. Reports on the incidence and prevalence of NRH in thiopurine users must be interpreted with caution. Additional analysis on the observed large inter-observer variability on NRH is warranted.

PET/CT using ^{18}F-fluoromethylcho to differentiate focal nodular hyperplasia from hepatocellular adenoma; preliminary results

J.W. van den Esschert[1], M. Bieze[1], R. Bennink[2], T.M. van Gulik[1], Dept. of Surgery[1] and Nuclear Medicine[2], Academic Medical Centre Amsterdam, The Netherlands

It is important to differentiate Focal Nodular Hyperplasia (FNH) from Hepatocellular Adenoma (HCA) because of the therapeutic consequences. Unlike FNH, HCA>5cm should be resected because of the potential risk of bleeding and malignant transformation. Diagnosis based on radiological studies remains difficult and when the diagnosis is unclear, a tumor biopsy is ultimately performed. Therefore, there is a need for accurate non-invasive diagnostic imaging techniques. A recent report suggests PET/CT using the tracer ^{18}F-fluoromethylcho (FCh) to be able to differentiate between FNH and HCA. Aim of the study was to evaluate the accuracy of PET/CT using the FCh tracer in differentiating FNH from HCA. This study is part of a large clinical trial and supported by the local ethics committee. Informed consent was obtained of all patients. Twelve patients with a lesion in the liver suspected of FNH or HCA underwent a FCh PET/CT. Fifteen minutes after intravenous injection of the FCh, a PET and a low dose CT scan were performed. The FCh PET/CT was found positive if the ratio between the maximum standardized uptake value (SUV) of the tumor and the mean SUV of the normal surrounding liver parenchyma was above 1.15. Imaging results were compared with histological outcome obtained by either liver biopsy or resection specimen. Twelve women were included with histologically proven FNH (n=6) and HCA (n=6). All FNH lesions showed increased uptake of FCh (mean SUV ratio 1.78±0.09 SD). In contrast, none of the HCAs showed increased uptake (mean SUV ratio 0.92±0.06 SD).
Conclusion. FCh PET/CT is a promising diagnostic tool to differentiate FNH from HCA. In contrast to HCA, FNH shows increased uptake of FCh.

Minimally invasive step-up approach versus open necrosectomy in necrotizing pancreatitis: a randomized controlled multiCentre trial

HC van Santvoort[1], M.G. Besselink[1], O.J. Bakker[1], H.S. Hofker[2], M.A. Boermeester[3], C.H. Dejong[4], H. van Goor[5], A.F. Schaapherder[6], C.H. van Eijck[7], T.L. Bollen[8], B. van Ramshorst[9], V.B. Nieuwenhuijs[2], R. Timmer[10], J.S. Laméris[11], F.M. Kruyt[12], E.R. Manusama[13], E. van der Harst[14], G.P. van der Schelling[15], T. Karsten[16], E.J. Hesselink[17], C.J. van Laarhoven[18], C. Rosman[19], K. Bosscha[20], R.J. de Wit[21], A.P. Houdijk[22], M.S. van Leeuwen[23], E. Buskens[24] and H.G. Gooszen[1] for the Dutch Pancreatitis Study Group [1]Dept. of Surgery, University Medical Centre, Utrecht, [2]Dept. of Surgery, University Medical Centre, Groningen, [3]Dept. of Surgery, Academic Medical Centre, Amsterdam, [4]Dept. of Surgery and NUTRIM, Maastricht University Medical Centre, Maastricht, [5]Dept. of Surgery, Radboud University Nijmegen Medical Centre, Nijmegen, [6]Dept. of Surgery, Leiden University Medical Centre, Leiden, [7]Dept. of Surgery, Erasmus Medical Centre, Rotterdam, Depts. of [8]Radiology, [9]Surgery, and [10]Gastroenterology, St. Antonius Hospital, Nieuwegein, [11]Dept. of Radiology, Academic Medical Centre, Amsterdam, [12]Dept. of Surgery, Gelderse Vallei Hospital, Ede, [13]Dept. of Surgery, Leeuwarden Medical Centre, [14]Dept. of Surgery, Maasstad Hospital, Rotterdam, [15]Dept. of Surgery, Amphia Medical Centre, Breda, [16]Dept. of Surgery, Reinier de Graaf Hospital, Delft, [17]Dept. of Surgery, Gelre Hospital, Apeldoorn, [18]Dept. of Surgery, St. Elisabeth Hospital, Tilburg (currently: Dept. of Surgery, Radboud University Nijmegen Medical Centre, Nijmegen), [19]Dept. of Surgery, Canisius Wilhelmina Hospital, Nijmegen, [20]Dept. of Surgery, Jeroen Bosch Hospital, Den Bosch, [21]Dept. of Surgery, Medisch Spectrum Twente, Enschede, [22]Dept. of Surgery, Medical Centre, Alkmaar, [23]Dept. of Radiology, University Medical Centre Utrecht, Utrecht, [24]Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht (currently: Dept of Epidemiology, University Medical Centre, Groningen), The Netherlands

Infected necrotizing pancreatitis is associated with high morbidity and mortality. Current standard treatment is open necrosectomy. Outcome may be improved by a minimally invasive step-up approach. In the PANTER trial, we randomly assigned 88 patients with (suspected) infected necrotizing pancreatitis to primary open necrosectomy or a step-up approach in 19 participating hospitals. The step-up approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The primary endpoint was a composite of major morbidity (new onset multiple organ failure, perforation of a visceral organ or enterocutaneous fistula, bleeding) and mortality during admission and 3 months follow-up. Secondary endpoints included other morbidity and total costs at 6 months follow-up. Infected necrosis was present in 81 patients (92%). The primary endpoint occurred in 31 of 45 patients (69%) assigned to open necrosectomy and in 17 of 43 patients (40%) assigned to the step-up approach (risk ratio 0.57; 95% confidence interval 0.38 to 0.87; P=0.006). In the step-up approach group, 35% of patients were successfully treated with percutaneous drainage only and did not require necrosectomy. New onset multiple organ failure occurred less often in the step-up approach group (12% versus 40%; P=0.002). At 6 months follow-up, patients in the step-up approach group had a lower rate of incisional hernias (7% versus 24%; P=0.03), use of pancreatic enzymes (7% versus 33%; P=0.002) and new onset diabetes (16% versus 38%; P=0.02). Mean total costs per patient were €10,839 (12%) lower in the step-up approach group.

Conclusions A minimally invasive step-up approach, as compared to open necrosectomy, reduced the rate of the composite endpoint of major morbidity and mortality as well as long-term morbidity and costs in patients with (suspected) infected necrotizing pancreatitis. In these patients, percutaneous drainage should be considered the first step of treatment.

Interobserver agreement between experienced, semi-experienced and non-experienced endosonographers for features and specific diagnosis of pancreatic cysts

K de Jong[1], T. Verlaan[1], M. Dijkgraaf[2], J.W. Poley[3], H. van Dullemen[4], M.J. Bruno[3], P. Fockens[1], [1] Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam[2] Dept. of Biostatistics and Epidemiology, Academic Medical Centre, Amsterdam[3] Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam[4] Dept. of Gastroenterology and Hepatology, University Medical Centre Groningen, The Netherlands

Pancreas cysts (PCs) are diagnosed with increasing frequency while preoperative differential diagnosis of cystic lesions remains difficult. Endoscopic ultrasonography (EUS) is regarded a promising technique. Aim of this study was to assess the degree of interobserver agreement of EUS in the diagnostic work up of PCs.Videotapes of 40 EUS procedures of PCs including IPMN, mucinous cyst adenoma, serous cyst adenoma, neuroendocrine tumor and pseudocyst were prepared. Three different groups were formed with four observers in each group. Group 1 consisted of experts with extensive experience in EUS (> 2500), group 2 of intermediates with experience in EUS in less than 200 examinations and group 3 of non-expert residents without any experience in EUS. Before reviewing the videotapes all were exposed to a training set demonstrating specific features of PCs. Observers were blinded to clinical and histological results. Features scored included: septations, nodules, solid components and pancreatic duct communication. Observers were asked whether they would advise surgery or follow-up at regular intervals. Furthermore, an etiologic diagnosis had to be specified. Intraclass correlation coefficient (icc) was used to measure agreement within the groupsInter-observer agreement for septations was moderate in all groups(icc=0.444(1), icc=0.518(2), icc=0.435(3)). For the presence of nodules agreement was good in group 1 (icc=0.645) and fair in the other groups (icc=0.317(2) and icc=0.365(3)). Agreement for solid component was moderate in group 1 (icc=0.518) and poor in the other two groups (icc=0.09(2), icc=0.032(3)). The agreement for communication with the pancreatic duct was moderate in group 1(icc=0.435) and fair in the other groups (icc=0.204(2), icc=0.223(3)). Agreement for an etiologic diagnosis was fair in group 1(icc=0.436), poor in group 2 (icc=0.093) and fair in group 3 (icc=0.301). Agreement for suspicion of malignancy was poor in group 1 and 3 (icc=0.092(1) and icc=0.183(3)) and moderate in group 2 (icc=0.435). Agreement for surgery was poor in all groups (icc=0.160(1), icc=0.101(2), icc=-0.028(3)). Interobserver agreement was equal or higher in the group of experts than in the intermediate and non-experts groups for all items, except for the suspicion of malignancy. This is remarkable as individual items internationally recognized as indicators for surgery, such as the presence of nodules or solid components, were not interpreted and valued as such in this series.

Neoadjuvant radiochemotherapy in esophageal carcinoma: a high incidence of complete pathological response

R.L.G.M. Blom[1], W. Schreurs[2], G. Lammering[3], R.F.A. Vliegen[4], L.E. Oostenbrug[5], M. Nap[6], M.N. Sosef[1], [1]Dept. of Surgery, Atrium Medical Centre, Heerlen, [2]Dept. of Nuclear Medicine, Atrium Medical Centre, Heerlen, [3]Dept. of Radiation Oncology (MAASTRO), University Medical Centre Maastricht, Maastricht, [4]Dept. of Radiology, Atrium Medical Centre, Heerlen, [5]Dept. of Internal Medicine and Gastroenterology, Atrium Medical Centre, Heerlen, [6]Dept. of Pathology, Atrium Medical Centre, Heerlen, The Netherlands

Neoadjuvant therapy (NT) for esophageal cancer (EC) can result in tumor downstaging and even complete tumor regression in a subset of patients, which is known to correlate with a better prognosis. The purpose of our study was to retrospectively analyze the tumor response rate in our own series of EC patients preoperatively treated with NT and restaged with PET-CT before surgical resection. Preoperative staging was correlated with the tumor regression grade (TRG) as scored on the resected specimen. 43 patients who underwent an esophagectomy after NT (radiochemotherapy and chemotherapy only respectively; 88.4% and 11.6%) between January 2008 and July 2009 were included in this analysis. Pretreatment staging included endoscopic ultrasonography and PET-CT in all patients. Neoadjuvant radiochemotherapy consisted of 50.4 Gy in 1.8 Gy fractions 3-D conformal radiotherapy combined with two cycles of cisplatin (100mg/m2) and 5-FU (4 days of continuous infusion of 1000mg/m2) in week 1 and 5. A repeat PET-CT was performed after NT shortly before surgery in order to evaluate treatment response and to confirm the absence of metastases in a total of 20 patients. TRG was re-scored on all resected specimens by an experienced GI-pathologist. The analyzed EC group consisted of 74% adenocarcinoma (AC) and 23% squamous cell carcinoma (SCC). For AC, 12,17 and 3 patients were staged as having stage II, III and IVa disease respecttively; 5, 4 and 1 patients for SCC. Decreased SUV values were observed in 80% of cases (25% SCC, 75% AC). The median interval between NT and resection was 8.5 weeks (chemo-radiotherapy) or 5 weeks (chemo only). Twenty-seven patients (63%) were classified as pathological responders (19 TRG 1, 8 TRG 2, 80% of patients with SCC, 56% with AC) and 16 patients (37%) were classified as pathological non-responders (7 TRG 3, 5 TRG 4 and 4 TRG 5). Response on PET-CT and TRG corresponded in 75% of patients. We found a high percentage of complete or nearly complete tumor responses after NT, which was more frequently present in SCC patients (80% vs. 56%).
In conclusion, we feel that our regional regimen of NT for EC with a relatively long interval is an effective treatment, which might even lead to a better prognosis in a certain percentage of our patients. However, since not all patients benefit from this preoperative treatment, parameters to better select patients for this NT are urgently needed.

Lysophosphatidic acid is a potential mediator of cholestatic pruritus

A.E. Kremer[1], J.J. Martens[1], W. Kulik[2], C. Williamson[3], W.H. Moolenaar[4], J. Kondrackiene[5], U. Beuers[1], R.P.J. Oude Elferink[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, University of Amsterdam, [2]Laboratory Genetic Metabolic Diseases, Academic Medical Centre, University of Amsterdam, The Netherlands; [3]Maternal and Fetal Disease Group, Institute of Reproductive and Developmental Biology, Imperial College London, London, United Kingdom; [4]Division of Cellular Biochemistry, Centre for Biochemical Genetics, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [5]Dept. of Gastroenterology, Kaunas University of Medicine, Kaunas, Lithuania

Introduction: Although pruritus is a common and disabling symptom in patients with cholestatic liver disorders, the causing factors are unknown. Bile salts and opioids have, among others, been implicated in the aetiology of pruritus, but a relation with itch intensity has never been established. We hypothesized that potential pruritogens accumulate in the circulation of cholestatic patients and activate sensory neurons. Methods: Cytosolic free calcium $(Ca^{++})_i$ was measured in neuronal cell lines by ratio-metric fluorimetry upon exposure to diluted serum samples of women with intrahepatic cholestasis of pregnancy (ICP; n=33), patients with other causes of cholestasis (mainly PBC; n=72), pregnant controls (PC; n=29) and healthy subjects (HC; n=202). The $(Ca^{++})_i$ inducing factor in pruritic serum was identified by analytical techniques including quantification by HPLC-MS/MS. Autotaxin activity, bile salts and histamine were quantified by enzymatic assays, m-opioid activity by receptor binding assay. Intensity of pruritus was quantified on a visual analogue scale (VAS, 0-10). In mice, scratch activity after intradermal pruritogen injection was quantified using a magnetic device. Results: Transients in $(Ca^{++})_i$ in human SH-SY5Y neuroblastoma cells, induced by PBC and ICP sera were higher than those of corresponding controls. On the basis of physicochemical properties, lysophosphatidic acid (LPA) could be identified as major $(Ca^{++})_i$ agonist in pruritic sera. Serum LPA concentrations were increased only in those cholestatic patients that suffered from pruritus. LPA injected intradermally into mice, induced scratch responses. Serum autotaxin (ATX) is the enzyme that converts lysophosphatidylcho into LPA. ATX was markedly increased in sera of ICP patients vs. PC ($p<0.0001$) and in sera from cholestatic patients with vs. without pruritus ($p<0.0001$). ATX activity correlated highly with intensity of pruritus ($p<0.0001$). In PBC patients who underwent nasobiliary drainage both, itch intensity and autotaxin activity, significantly decreased during drainage and returned to increased levels when pruritus had returned. Neither bile salts nor histamine or μ-opioids correlated with itch intensity.
Conclusion: Our data suggest that autotaxin and its product, LPA, play a key role in cholestatic pruritus. We speculate that ATX inhibitors and LPA-receptor blockers may be useful as anti-pruritic agents in treatment of cholestatic pruritus.

Is visceroperception influenced by meal ingestion in irritable bowel syndrome (IBS)?

S. Ludidi, J.M. Conchillo, C.J. Koning, S. Vanhoutvin, D. Jonkers, A.A. Masclee, Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

In patients with irritable bowel syndrome (IBS) symptoms are often provoked by meal ingestion. Higher symptom severity after ingestion of a meal has been attributed to a postprandial increase in visceroperception. Aim of this study was to evaluate the influence of meal intake on visceral perception (threshold and intensity) and rectal compliance in response to rectal distension in both IBS patients and healthy controls (HC). Ninety-two IBS patients (30 male, mean age 39 years) according to the Rome III criteria and 20 HC (6 male, mean age 34 years) were included in the study. In 71 IBS patients and 20 HC, visceral perception was assessed on a single occasion with 2 experiments: in the fasting state and after ingestion of a mixed liquid meal (370 kcal, 19.3 g fat) using a random staircase barostat protocol. Twenty-one of the 91 IBS patients served as non-intervention control patients to determine the effect of repeated sequence on barostat parameters. During each distension step urge, discomfort and pain were assessed using a visual analogue scale (VAS). Threshold level for perception was defined as the pressure step at which the pain VAS-score >10 mm occurred for the first time. Cut-off value for hypersensitivity was calculated as mean pain threshold minus 2SD in HC. Rectal dynamic compliance was assessed by max volume increase between two consecutive pressure steps, divided by pressure difference of the two steps. Urge, discomfort and pain thresholds were significantly lower in IBS patients than in HC, both before and after the meal ($p<0.05$ for all comparisons). Ingestion of a liquid meal significantly reduced pain thresholds in IBS patients (17.1±1.8 mmHg vs. 19.8±1.9 mmHg, $p<0.05$), but not in HC (36.5±3.3 mmHg vs. 39.5±2.9 mmHg, $p=0.15$). No significant order effect was observed between first and second barostat measurement. The cut-off for hypersensitivity was 17 mmHg. Hypersensitivity percentage in IBS patients increased from 53 to 69% in the IBS meal group ($p=0.01$) but also from 5 to 15% in controls ($p=0.50$). Rectal compliance increased after the meal in IBS patients (from 17.4±0.8 to 19.2±0.8 mL/mmHg, $p<0.001$), as well as in HC (from 20.8±1.1 to 23.6±1.3 mL/mmHg, $p<0.01$).

Conclusion: Ingestion of a liquid meal improves differentiation between IBS patients and controls as groups based on visceral perception and compliance. Barostat measurements in the postprandial state identify individual IBS patients with hypersensitivity with higher sensitivity, but lower specificity. For identification of IBS patients with hypersensitivity, barostat recording in the fasting state already allows adequate differenttiation.

Ano-reservoir function after ileal neorectal anastomosis for ulcerative colitis; a comparison with the ileal pouch anal anastomosis

J.T. Heikens[1], W. Hopmans[2], D.J. de Jong[2], C.J.H.M. van Laarhoven[1], [1]Dept. of Surgery, Radboud University Nijmegen Medical Centre, [2]Dept. of Gastroenterology, Radboud University Nijmegen Medical Centre, The Netherlands

Introduction: Impaired gastrointestinal (GI) transit or postoperative ileus (POI) largely determines clinical recovery and duration of hospitalization after abdominal surgery. As colonic motility is the main determinant of clinical recovery, first defecation and flatus are often used as primary outcome parameters in clinical trials. However, whether they actually correlate with GI transit remains unclear. Especially as new potential treatments for POI are emerging, there is a definite need for accurate and reliable outcome variables to objectively evaluate new treatments. Aim: To study the relationship between GI transit and clinical symptoms after GI surgery and to evaluate which symptoms/signs are reliable markers of GI recovery. Methods: Between Oct 2005 and Aug 2009, 85 patients (26-81 y) undergoing segmental colectomy for malignant colorectal disease were included. Clinical symptoms of upper- and lower GI motility were evaluated daily using self-designed questionnaires. 24 h after surgery, patients underwent a solid gastric emptying test (^{99m}Tc labelled pancake, 115 Kcal) and ingested 60 ml of indium-111 labelled water to assess colonic transit on postoperative day 2 and 3. The latter was measured by calculating the geometrical center (GC) of activity (segment 0=small intestine; 1=proximal-; 2=distal colon; 3=toilet). A composite score of upper- and lower GI recovery was calculated as time until tolerance of solid food in combination with defecation. Statistical analysis was done using Spearman's rank correlation. Results: On postoperative day 1, only nausea correlated with gastric retention ($r=0.30$, $p=0.010$). Similarly, first flatus ($r=-0.27$, $p=0.022$) and first day of tolerance of solid food ($r=-0.33$, $p=0.004$) showed a weak correlation with colonic transit on day 3. On the other hand, colonic transit correlated significantly with time until discharge ($r= -0.55$, $p<0.001$), time to first defecation ($r=-0.46$, $p<0.001$), and the composite score ($r=-0.45$, $p<0.001$). 7 patients developed a major complication (i.e. anastomosis leakage and hernia) with paralytic ileus requiring a nasogastric tube on day 3. In these patients indium-111 had not reached the colon at day 3 corresponding to a colonic GC of 0.
Conclusions: Paralytic ileus is a distinct type of POI characterized by total inhibition of GI motility. Time until first defecation and time to tolerance of solid food in combination with defecation correlate significantly with colonic GC at day 3 and are the most reliable parameters to indirectly evaluate GI transit. In contrast, time to first flatus is an inaccurate surrogate marker of colonic transit and should not be included in clinical trials.

Which clinical symptoms reflect postoperative recoveryof gastrointestinal motility?

S.H.W. van Bree[1], L.E. Nijhuis[1], M.S. Vlug[2], W.A. Bemelman[2], W.J. de Jonge[1], S.A. Snoek[1], E.P. van der Zanden[1], F.O. The[1], M.W. Hollmann[3], R.J. Bennink[4], G.E. Boeckxstaens[1,5], Dept. of [1]Gastroenterology, [2]Surgery, [3]Anesthesiology, [4]Nuclear Medicine, Academic Medical Centre, Amsterdam, The Netherlands, [5]Dept. of Gastro-enterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium

Introduction: Impaired gastrointestinal (GI) transit or postoperative ileus (POI) largely determines clinical recovery and duration of hospitalization after abdominal surgery. As colonic motility is the main determinant of clinical recovery, first defecation and flatus are often used as primary outcome parameters in clinical trials. However, whether they actually correlate with GI transit remains unclear. Especially as new potential treatments for POI are emerging, there is a definite need for accurate and reliable outcome variables to objectively evaluate new treatments. Aim: To study the relationship between GI transit and clinical symptoms after GI surgery and to evaluate which symptoms/signs are reliable markers of GI recovery. Methods: Between Oct 2005 and Aug 2009, 85 patients (26-81y) undergoing segmental colectomy for malignant colorectal disease were included. Clinical symptoms of upper- and lower GI motility were evaluated daily using self-designed questionnaires. 24 h after surgery, patients underwent a solid gastric emptying test (99mTc labelled pancake, 115 Kcal) and ingested 60 ml of indium-111 labelled water to assess colonic transit on postoperative day 2 and 3. The latter was measured by calculating the geometrical Centre (GC) of activity (segment 0=small intestine; 1=proximal-; 2=distal colon; 3=toilet). A composite score of upper- and lower GI recovery was calculated as time until tolerance of solid food in combination with defecation. Statistical analysis was done using Spearman's rank correlation. Results: On postoperative day 1, only nausea correlated with gastric retention ($r=0.30$, $p=0.010$). Similarly, first flatus ($r=-0.27$, $p=0.022$) and first day of toleranceof solid food ($r=-0.33$, $p=0.004$) showed a weak correlation with colonic transit on day 3. On the other hand, colonic transit correlated significantly with time until discharge ($r= -0.55$, $p<0.001$), time to first defecation ($r=-0.46$, $p<0.001$), and the composite score ($r=-0.45$, $p<0.001$). 7 patients developed a major complication (i.e.anastomosis leakage and hernia) with paralytic ileus requiring a nasogastric tube on day 3. In these patients indium-111 had not reached the colon at day 3 corresponding to a colonic GC of 0.
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The effect of laparoscopy and/or fast track multimodal management on post-operative gastrointestinal motility after colonic surgery

S.H.W. van Bree[1], M.S. Vlug[2], W.A. Bemelman[2], M.W. Hollmann[3], W.J. de Jonge[1], S.A. Snoek[1], E.P. van der Zanden[1], F.O. The[1], R.J. Bennink[4], G.E. Boeckxstaens[1,5], Depts. of [1]Gastroenterology, [2]Surgery,[3]Anesthesiology, [4]Nuclear Medicine, Academic Medical Centre, Amsterdam, The Netherlands, [5]Dept. of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium

Postoperative ileus is a major determinant of recovery after colorectal surgery characterized by delayed gastrointestinal (GI) transit. Both laparoscopic surgery (Lap) and fast track multimodal perioperative care (FT) have been reported to improve recovery. However, randomized trials comparing the effect on postoperative GI motility are lacking. The aim of this trial is to determine whether FT and Lap lead to faster recovery of GI transit after colonic surgery, and to evaluate the relationship between GI transit and clinical recovery.
Patients requiring segmental colectomy for malignant colorectal disease were invited to participate in this randomized controlled trial. Patients were randomized to FT- or Standard care, and to Lap- or Open colectomy. Primary endpoint was GI transit. Secondary endpoints were clinical signs/symptoms of GI motility, recorded daily until discharge. 24 h after surgery, patients underwent a solid gastric emptying test (^{99m}-Tc labelled pancake, 115 Kcal) and ingested 60 ml of indium-111 labelled water to assess colonic transit on postoperative day 2 and 3. The latter is represented as geometrical center (GC) of activity (segment 0=small intestine, 1=proximal colon, 2=distal colon, 3=toilet).
In total 93 patients were randomized to one of the 4 treatment groups. 22 patients had to be excluded because of protocol violations or major surgical complications. Patients undergoing Lap FT had a significantly higher colonic GC (0-3) on postoperative day 3 (median 2.6; IQR (2.0-2.9)) compared to Lap Standard (2.2; (1.6-2.5), p=0.044), Open FT (2.0; (1.6-2.4), p=0.010) and Open Standard (1.3; (1.0-1.5), p<0.001). Similarly, the Lap FT group recovered significantly better and had a shorter time to first defecation compared to the other 3 treatment groups. However, gastric retention 24 h after surgery did not differ between groups (p=0.613). Clinical recovery correlated significantly with colonic GC at day 3 (r= -0.42, p<0.001;Spearman's rank correlation).
Conclusions: Colonic transit, but not gastric emptying, recovers significantly faster after Lap FT compared to the other 3 treatment groups, leading to a more rapid clinical recovery. These data provide objective information that Lap FT is the surgical procedure of choice with the fastest recovery of GI function after colorectal surgery.

Functional Nonretentive Fecal Incontinence, do enemas help?

R.E. Burgers, C.J.C. Hoppenbrouwers, M.E.J. Bongers, F. de Lorijn, W.P. Voskuijl, M.M. van den Berg, N. Bekkali, O. Liem. B. Peeters, C.M. Loots, M.P. van Wijk, M.A. Benninga
Emma Kinderziekenhuis AMC, Amsterdam, The Netherlands

Fecal incontinence (FI) represents an upsetting and psychologically distressing problem in childhood. Treatment of Functional Nonretentive Fecal Incontinence (FNRFI) consists of education, toilet training, and positive motivation. Oral laxative treatment increases the number of incontinence episodes. Only 30% of these patients are cured after two years of intensive treatment. To investigate whether rectal enemas are effective in the treatment of children with FNRFI. Children were randomized to either conventional treatment (CT); education, toilet training, bowel diary and a reward system or treatment consisting of daily enemas during two weeks in addition to CT. Subsequently, the enema frequency was reduced stepwise by 1-2 per week every week. Bowel diaries of all patients were evaluated weekly during treatment and after 12 months. Success was defined as < 1 episode of FI every two weeks. Analyses were performed according intention-to-treat. A total of 64 children (47 boys, median age 9,3 (range 4-14) years) with FNRFI were included. At intake the median FI frequency was 6 per week (range 2-42), whereas the median defecation frequency was 7 per week (range 3-21). 41 children had abdominal pain, 23 children had enuresis. At the end of the intervention period, the number of FI episodes was significantly decreased in both groups: from 7 (2-42) to 0.8 (0-13) in the intervention group and from 6 (2-21) to 2 (0-8.5) in the control group. At 4 weeks treatment with enemas was superior, with a significantly greater reduction in FI episodes compared CT ($P<.05$). However, the success rates at 4 weeks were not statistically significant between the two groups (19.4% versus 9.1%). A year after the start of treatment, treatment success was achieved in only 12.9% in the intervention group as compared with 24.2 % of the patients in the conventional group, without a significant difference between the groups. None of the children were still using enemas. Conventional therapy - with and without temporarily use of additional rectal enemas, results in a significant decrease in the number of episodes of FI. The number of FI episodes 4 weeks after start of therapy was significant lower with the use of daily rectal enemas in addition to conventional therapy. However, the low success rates in both treatment groups stresses that treatment of FNRFI remains a challenge.

IgE immunoglobulins and mast cells in colonic mucosa of patients with Irritable Bowel Syndrome

B. Braak[1], S.A. van Diest[2], T.K. Klooker[1], O. Welting[2], C.M. van der Loos[3], R.M. van den Wijngaard[2], G.E.E. Boeckxstaens[1,4], [1]Gastroenterology and Hepatology, AMC, Amsterdam, [2]Tytgat Institute of Liver and Intestinal Research, AMC, Amsterdam, [3]Pathology, AMC, Amsterdam, The Netherlands; [4]Gastroenterology, University Hospital Leuven, Catholic University Leuven, Leuven, Belgium

Mast cell activation has been introduced as an important pathophysiological mechanism underlying the Irritable Bowel Syndrome (IBS). The exact triggers leading to mast cell activation remain however unclear. Recently, increased levels of antibodies to flagelin have been demonstrated in IBS patients, raising the possibility that the adaptive immune system, including mast cell activation by cross linking of immunoglobulins, may be involved. In the present study, we tested this hypothesis by immunohistochemical double staining for mast cells and IgE antibodies of biopsies obtained from patients with IBS. Paraffin embedded biopsies of the descending colonic mucosa of 64 IBS patients (73% F, 39±2 yr) and 18 healthy volunteers (HV; 67% F, 30 ±3 yr) were collected for immunohistochemical staining for mast cells (CD117, DAKO, 1:4000) and IgE (DAKO, 1:3000). Furthermore 5 patients with eosinophilic esophagitis (EE) were used as positive control. Sections were analysed for double staining using Spectral Imaging, which enables unmixing multicolor stainings into individual colours (markers) based on their spectral characteristics. In a different series of sections, the number of mast cells was assessed.The number of mast cells in the descending colon was decreased in IBS compared to HV (186±10 /mm^2 vs 370±39/mm^2, p=0.001). Double staining for CD117 and IgE antibodies could not be demonstrated in HV. In IBS patients, only 1 out of 64 patients showed double staining. In this patient, 45% of mast cells were positive for IgE. This IBS patient was normosensitive to rectal distention and had no medical history of food associated symptoms or other types of allergy. Two out of 5 patients with EE showed double staining for CD117 and IgE (12% and 10% of mast cells were positive for IgE).
Conclusions: In the present study, only 1 of the 64 IBS patients showed double staining for c-kit and IgE antibodies, arguing against IgE mediated mast cell activation as an important pathophysiological mechanism in IBS. Immunohistochemical stainings evaluating a possible role for IgG-mediated activation of mast cells are currently ongoing.

Free immunoglobulin light chains may be involved in stress-induced visceral hypersensitivity in maternal separated rats

S.A. van Diest[1], O.I. Stanisor[1], O. Welting[1], W.J. de Jonge[1], A.D. Kraneveld[2], F.A. Redegeld[2], G.E. Boeckxstaens[1,3], R.M. van den Wijngaard[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, [2]Division of Pharmacology & Pathophysiology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands, [3]Department of Gastroenterology, Catholic University of Leuven, Belgium

Introduction: Although aberrant immune responses are thought to play a role in IBS, the functional involvement of immune cells other than mast cell has not been shown yet. Earlier we used a rat model of maternal separation (MS) to show that stress-induced mast cell degranulation induces visceral hypersensitivity. In this model we now investigate the possible role of B-cells that, next to complete immunoglobulins, release free Immunoglobulin Light Chains (IgLCs). We have previously shown that IgLCs bind to the mast cell surface and, upon antigen-mediated cross-linking, induce their degranulation as well as synthesis of inflammatory mediators in in vitro and in vivo model systems (Redegeld et al. Nature Med 2002). Aim: To establish whether peri-stress application of F991, an IgLC antagonist, is sufficient to prevent stress-induced visceral hypersensitivity in MS-rats. Methods: Adult MS and NH rats (n=7 in all groups) were subjected to acute stress (1 hr water avoidance, WA). The visceromotor response (VMR) to colorectal distension (1, 1½, 2ml) was established pre- and 24 hours post-WA and expressed as area-under-curve (AUC, volume-vs-response, significant difference when $P<0.05$: Wilcoxon). Rats were treated with F991 or vehicle (i.p.) 30 minutes pre-WA, 6 hours post-WA (both 280µg/kg) and 23 hours post-WA (160µg/kg). Results: WA induced an increased VMR to distension in MS vehicle-treated rats (pre-WA vs post-WA AUC; 65.3±5.1 vs 93.7±8.7, P=0,038), but not in NH rats. F991 prevented the development of visceral hypersensitivity in MS rats (pre-WA vs post-WA; 65.3±3.0 vs 69.0±6.6), but did not alter post-stress sensitivity in NH rats (pre-WA vs post-WA; 64.2±5.2 vs 63.6±6.2).
Conclusion: Our present data indicate that B-cell derived IgLC's may contribute to stress-induced mast cell activation and subsequent visceral hypersensitivity in MS-rats. Thus, humoral antigen-specific mechanisms may be involved in the post-stress hypersensitive phenotype of MS rats.

The peripheral Histamine 1-receptor antagonist fexofenadine effectively reverses stress-induced visceral hypersensitivity in a rat model of maternal separation

O.I. Stanisor[1], S.A. van Diest [1], O. Welting [1], C. Cailotto [1], J. van der Vliet [1], W.J. de Jonge [1], G.E. Boeckxstaens [2], R.M. van den Wijngaard [1], [1]Tytgat Institute for Liver and Intestinal Research, (former AMC Livercentre), Academic Medical Centre, The Netherlands, [2]Gastroenterology, Katholieke Universiteit , Leuven, Belgium

Background: We previously showed that the mast cell stabilizer ketotifen reduces IBS symptoms and increases the threshold of discomfort in hypersensitive IBS-patients. However, as ketotifen also has Histamine 1-receptor antagonistic properties and is known to penetrate the blood-brain barrier, its beneficial effect observed in this trial could also result from H1 receptor blockade, either at the peripheral or central level. Aim: To establish whether fexofenadine, a peripherally restricted 2nd generation Histamine 1-receptor antagonist, can mimic the effect of ketotifen and A) reverse stress-induced, mast cell dependent visceral hypersensitivity in a rat model of maternal separation (MS), and B) modulate gastrointestinal transit in MS and non-handled (NH) rats. Methods: Adult MS and NH rats (n=9 in all groups) were subjected to acute stress (1 hr water avoidance, WA). The visceromotor response (VMR) to colorectal distension (1, 1½, 2ml) was established pre- and 24 hours post-WA and expressed as area-under-curve (AUC, volume-vs-response, significant difference when $P<0.05$: Wilcoxon). Rats were then treated with fexofenadine (1,8 mg/kg or 18 mg/kg) or vehicle and re-evaluated 48 hrs post-WA. Pre-WA transit was measured in NH (n=4) and MS (n=5) rats treated with fexofenadine or vehicle by evaluating the transit (geometric centre or GC) of orally administered fluorescein-labeled dextran (MW=70.000) (1 is stomach, 2 most proximal small bowel, 11 most distal, 12 cecum, 13-15 colon). Results: WA induced an increased VMR to distension in MS rats (pre-WA vs post-WA, 64±4 vs 98±6 (mean±SEM), P=0.012) which was reversed by 1.8 mg/kg fexofenadine (post-WA vs post-fexofenadine, 98±6 vs 69±5, P=0.012). High concentration fexofenadine (18 mg/kg) showed similar results (pre-WA vs post-WA, 72±4 vs 97±6, P=0.012 and post-WA vs post fexofenadine 97±6 vs 60±6, P=0.008). NH rats remained normo-sensitive under all conditions. Base pre-WA transit times of NH and MS were equal (10±0.2 vs 9.6±0.4). Administration of high-dose fexofenadine decreased transit time in NH (vehicle vs fexofenadine, 10±0.2 vs 6.4±1.1, P=0.028) and MS-rats (9.6±0.4 vs 6.9±0.2, P=0.008).
Conclusion: The peripheral H1 receptor antagonist fexofenadine effectively reverses stress-induced visceral hypersensitivity and decreases intestinal transit. As low dose fexofenadine does not cross the blood brain barrier, these data justify future IBS patient trials with 2nd generation H1-receptor antagonists.

ApoA-IV and CCK signalling is enhanced in the duodenum of GERD patients

O.S. van Boxel, J.J.M. ter Linde, J. Oors, A.J.P.M. Smout, P.D. Siersema, Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, The Netherlands

Introduction: Duodenal lipid intensifies perception of esophageal acid perfusion. Recently, we showed that upon duodenal lipid load mRNA expression levels of several genes implicated in lipid absorption are upregulated in GERD patients compared to healthy volunteers (HV). These genes play roles in triglyceride resynthesis and intracellular vesicular transport, both rate-limiting processes for chylomicron production and secretion, or may be involved in chylomicron clearance. This indicates that in GERD patients, chylomicron production and secretion may be enhanced and consequently release of apolipoprotein A-IV (apoA-IV), a chylomicron derived signalling component. It has been hypothesized that apoA-IV stimulates adjacent endocrine cells to release cholecystokinin (CCK), an activator of extrinsic primary afferents. Aim: Increase insight into the role of the duodenum in symptom generation in GERD by comparing Apo-AIV and CCK concentrations in plasma and duodenal mucosa between GERD patients and HV upon duodenal lipid load.
Methods: Ten symptomatic GERD patients off PPI and 10 age- and sex-matched HV underwent duodenal perfusions with Intralipid 20%, 1 ml/min, for 60 min. Blood samples were collected every 15 min and 15 min after discontinuation of the lipid infusion, mucosal duodenal biopsies were taken by upper GI endoscopy. Plasma and mucosal apoA-IV concentrations were determined using an established enzyme-linked immuno-sorbent assay. Plasma and mucosal CCK concentrations were determined by a sensitive and specific radioimmunoassay. Results: The mean mucosal apoA-IV concentration was significantly lower in GERD patients compared to HV; 1.8 ±0.8 and 4.2 ±3.9 µg/mg protein respectively (P=0.023). There was a trend toward elevated apoA-IV plasma concentrations in patients when compared to HV (P=0.067), ApoA-IV plasma concentrations were significantly higher in patients at 15 and 30 min of lipid infusion (P=0.019 and 0.026 respectively). The mean mucosal CCK concentration in GERD patients was 4.1 ±1.0 and in HV 5.3 ±0.8 pmol/mg protein, which differed significantly (P=0.009). No significant differences in CCK plasma concentrations between the two groups were found.
Conclusion: The lower duodenal apoA-IV concentration and elevated plasma concentrations suggest a higher release of apoA-IV in GERD patients during lipid absorption. Accordingly, release of CCK is enhanced in GERD patients as can be deduced from the lower duodenal CCK concentration. The resulting heightened activation of duodenal extrinsic primary afferents may induce central sensitization and thereby intensify the perception of reflux.

High Resolution Esophageal Topography is superior to conventional sleeve manometry for the detection of TLESRs associated with reflux

W.O.A. Rohof[1], G.E.E. Boeckxstaens[1,2], D.P. Hirsch[1], [1] Dept of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands[2] Dept of Gastroenterology, University Hospital, Leuven, Belgium

Aim: Transient lower esophageal sphincter relaxations (TLESRs) are the main mechanism underlying gastro-esophageal reflux and are detected during manometric studies using well defined criteria. Until recently, water perfused sleeve manometry was considered the gold standard to detect TLESRs. Recently, high-resolution esophageal pressure topography (HREPT) has been introduced and is now considered the new standard to study esophageal and lower esophageal sphincter (LES) function. To what extent this technique using the isocontour or Clouse plot mode is superior to depict TLESRs remains to be studied. In the present study we performed a head-to-head comparison between HREPT and conventional manometry for the detection of TLESRs. Methods: A setup with two parallel synchronized MMS-solar systems was used. A solid state HREPT catheter, a water perfused sleeve catheter and a multi intraluminal impedance pH (MII-pH) catheter were positioned in ten healthy volunteers (M6F4, age 19-56). Subjects were studied 0.5hr before and 3hrs after ingestion of a standardized meal. Tracings were blinded and analyzed by the three authors according to the modified TLESR criteria presented at the DDW2008. Sleeve manometry criteria were applied to HREPT, with an exception for the relaxation rate, which cannot be determined in HREPT. A TLESR was scored when there was agreement between at least two out of the three investigators. Results: In the HREPT mode 157 TLESRs were scored, versus 143 with the sleeve manometry (P=0.08). 123 TLESRs were scored by both techniques. Of all TLESRs (177), 131 were associated with reflux (74%). HREPT detected significantly more TLESRs with reflux (126 vs 113, P=0,011, McNemar test) resulting in a sensitivity of 96% compared to 86% respectively. Analysis of the discordant TLESRs with reflux showed that TLESRs were missed by sleeve manometry due to low basal LES pressure (N=4), unstable pharyngeal signal (N=4) and residual sleeve pressure > 2mmHg (N=10). This high residual sleeve pressure is explained by the axial movement of the gastric sleeve after esophageal shortening, when the LES is fully relaxed (N=10). Inter-observer variability for HREPT is comparable to sleeve manometry (K=0,59 (P=0,066) vs K=0,69 (P=0,053)).
Conclusion: HREPT is superior to conventional sleeve manometry for the detection of TLESRs associated with reflux.

Prevalence of gastrointestinal symptoms in diabetics is related to psychological factors

S. de Kort[1], J. Kruimel[1], I. Arts[3], J. Sels[2], N. Schaper[2], A. Masclee[1], Division of Gastroenterology[1] and Endocrinology[2], Dept. of Internal Medicine and Dept. of Epidemiology[3], Maastricht University Medical Centre, The Netherlands

Background: Previous studies have pointed to a higher prevalence of gastrointestinal symptoms in patients with diabetes type 1 and 2 versus controls. These gastrointestinal symptoms may have a negative impact on regulation of diabetes, diabetic complications, quality of life and survival. It is well known that several gastrointestinal disorders are influenced by psychological factors such as anxiety and depression. Previous studies in diabetics have not taken into account the influence of psychological factors on gastrointestinal symptoms. Our aim was to assess the prevalence of gastrointestinal symptoms in diabetics versus a control population taking into account the association between these symptoms and anxiety or depression.Methods:280 diabetic patients (32% type 1, 68% type 2; mean age 58 years, 61% males) from our Centre and 324 non-diabetic, age and sex matched controls (same region) were studied. They filled out validated questionnaires including 1) PAGI-SYM and the GSRS to quantify common gastrointestinal symptoms and 2) the HADS questionnaire to assess the degree of anxiety and depression. GSRS scores and PAGI-SYM scores ranging from “little trouble” up to “very severe” complaints were considered positive for that symptom and clinically relevant. Data were compared using logistic regression analysis and adjusted for age, sex, and anxiety and depression scores. Results: After adjustment for age and sex, diabetic patients scored significantly ($p<0.05$) higher on the following symptom complexes: GSRS diarrhoea (OR 1.66, 95% CI 1.04-2.64), PAGI-SYM early satiety (OR 2.30, 95% CI 1.26-4.19) and PAGI-SYM bloating (OR 1.56, 95% CI 1.00-2.43). GSRS abdominal pain, GSRS constipation and PAGI-SYM nausea were not significant different from controls. The median (25%-75%) HADS scores for diabetics and controls on the anxiety score were respectively 5 (2-8) and 4 (3-7), $p = 0.64$, and on the depression score respectively 3 (1-7) and 2 (1-5), $p = 0.01$. After adjusting for anxiety and depression only the “PAGI-SYM early satiety” score remained significantly more prevalent in diabetics (OR 2.17, 95% CI 1.14-4.12). For other complex and total scores, anxiety was a covariable significantly affecting all scores. Neither BMI, nor autonomic neuropathy influenced gastrointestinal symptoms.
Conclusion: The gastrointestinal symptoms diarrhoea, early satiety and bloating are signifycantly more prevalent in diabetic patients compared to a control population. However, after adjusting for anxiety, only early satiety remained associated with diabetes. Anxiety is a factor contributing to GI symptoms in diabetics and may have therapeutic relevance in this respect.

Impedance recording and high resolution manometry help to better define rumination episodes

B.F. Kessing, F. Govaert, A.A. Masclee, J.M. Conchillo, Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

Rumination syndrome is a functional gastroduodenal disorder of unknown aetiology characterized by persistent or recurrent regurgitation of recently ingested food into the mouth not preceded by retching. Manometry combined with pH metry is used for diagnosis of rumination but the technique has its limitations. Newer techniques such as combined manometry/impedance recording offer the advantage of better differentiation between belching and regurgitation and also detect non-acidic regurgitation. High resolution manometry combined with impedance recording (HRMIM) even allows additional and detailed measurement of the whole esophageal body and upper esophageal sphincter (UES) with one single catheter. We aimed in this study to improve the diagnosis rumination syndrome by classification of each separate rumination symptom and event using 1) an ambulant manometry/impedance (AMIM) measurement and 2) a single HRMIM catheter. Three patients (2 women, age 21-56 years) with rumination syndrome according to the Rome III criteria participated and generated a total 71 symptomatic episodes during 24 hr AMIM measurement. Thereafter, a 2 hr postprandial measurement with HRMIM and a conventional impedance catheter was performed after a mixed liquid meal (480kcal). A rumination event was defined as gastric strain followed by common cavity (manometry) and retrograde fluid flow (impedance). Symptom index (SI) was calculated as percentage of symptoms associated with a rumination event. Impedance results obtained by HRMIM were compared with conventional impedance outcomes. AMIM measurement identified rumination events in 68 out of 71 reported symptoms (SI 96%). Of these events, 58% were non-acidic and would have been missed by pH metry. Onset of gastric strain before the retrograde esophageal fluid flow occurred in 49% of the events and simultaneously in 46% of the events. Typically, all 68 rumination events occurred in upright position and 90% in the postprandial setting. Notably, in 18 out of 60 events (30%) rumination events were preceded by a non-perceived reflux event. During HRMIM the symptom index for rumination was 82%. In addition, UES relaxation was observed during all rumination events identified by HRMIM. Conventional impedance measurement confirmed the retrograde fluid flow during all rumination events identified by HRMIM.
Conclusions: New techniques as impedance recording and high resolution manometry contribute to a more exact description and recognition of rumination events. The rumination events thus recorded are characterised by gastric strain, common cavity phenolmenon, retrograde esophageal fluid flow and UES relaxation.

High cumulative and relative cancer risk and increased mortality in patients with Peutz-Jeghers syndrome

M.G.F. van Lier[1], A.M. Westerman[2], A. Wagner[3], C.W.N. Looman[4], J.H.P. Wilson[2], F.W.M. de Rooij[2], V. Lemmens[5], E.J. Kuipers[1,2], E.M.H. Mathus-Vliegen[6], M.E. van Leerdam[1], Dept. of Gastroenterology and Hepatology[1], Internal Medicine[2], Clinical Genetics[3] and Public Health[4], Erasmus MC, University Medical Centre, Rotterdam, Dept. of Research[5], Comprehensive Cancer Centre South, Eindhoven, Dept. of Gastroenterology and Hepatology[6], Academic Medical Centre, Amsterdam, The Netherlands

Peutz-Jeghers syndrome (PJS) is a hereditary disorder caused by STK11-gene mutations and is associated with an increased risk for gastrointestinal (GI) and extra-GI cancers. Therefore surveillance is recommended, but the development of optimal strategies is hampered by wide ranges in cancer risk estimates. In addition, data on the mortality in PJS patients are lacking. Hence, we aimed to assess cancer and mortality risks in a large cohort of PJS patients. Patients diagnosed with PJS based on diagnostic criteria (WHO) or proven STK11-mutation, were included in this prospective cohort study (1995-July 2009). Deceased family members with PJS were included retrospectively. Data were obtained by interview and chart review. Cumulative cancer risks were calculated by Kaplan-Meier analysis. The overall cancer incidence and mortality in PJS patients were compared to the general population (adjusted for age and period) by Poisson regression analysis. We included 133 PJS patients (48% males) from 54 families. In July 2009, 42 patients had deceased at a median age of 45 (3-76) yrs and 89 patients were alive at a median age of 34 (4-75) yrs (2 patients were lost to follow-up). An STK11-mutation was detected in 72/78 patients tested (92%). Forty-nine cancers were diagnosed in 42 patients (32%), including 24 GI cancers, 6 gynecological cancers, 6 breast cancers and 5 adenocarcinomas of unknown origin. The median age at first cancer diagnosis was 45 (15-76) yrs, and for GI cancers 43 (15-76) yrs. Univariate analysis showed no difference in cancer incidence according to sex (p=0.41) or mutation-status (p=1.00). The Kaplan-Meier estimate for the cumulative cancer risk was 19% ±4% at age 40 (GI cancer 11% ±3%), 34% ±6% at age 50 (GI cancer 19% ±5%), 55% ±7% at age 60 (GI cancer 32% ±7%), and 71% ±7% at age 70 (GI cancer 46% ±9%). Poisson regression analysis showed that the overall cancer risk (1960-2009) was higher in PJS patients than in the general population (hazard ratio (HR) 8.7; 95%CI 6.3-12.1). Cancer risks were higher in females (HR 18.1; 95%CI 11.9-27.6) than in males with PJS (HR 4.9; 95%CI 2.9-8.2) (p<0.001). The mortality excess was 77% in PJS patients compared to the general population (HR 1.77; 95%CI 1.28-2.45), without a significant difference between males and females (p=0.30).
Conclusions: PJS patients are at high risk for cancers at a young age, mainly in the GI tract. The mortality is increased compared to the general population. These results justify surveillance to detect premalignant lesions and cancer in an early phase in order to improve outcome. The effects of surveillance on outcome remain to be established.

High intussusception risk at young age in patients with Peutz-Jeghers syndrome: time to update surveillance guidelines?

M.G.F. van Lier[1], E.M.H. Mathus-Vliegen[2], A. Wagner[3], M.E. van Leerdam[1], E.J. Kuipers[1,4], Depts. of Gastroenterology and Hepatology [1], Clinical Genetics[3] and Internal Medicine[4], Erasmus MC, University Medical Centre, Rotterdam, Dept. of Gastro-enterology and Hepatology[2], Academic Medical Centre, Amsterdam, The Netherlands

Peutz-Jeghers Syndrome (PJS) is caused by STK11-gene mutations and characterized by gastrointestinal hamartomas and mucocutaneous pigmentations. The hamartomas are located in the small bowel in 90% of patients and may cause intussusceptions. As surveillance recommendations may include enteroscopic polypectomy to prevent such intussusceptions, we aimed to assess characteristics, risk and onset of intussusception in a large cohort of PJS patients. Patients diagnosed with PJS based on diagnostic criteria, were included in this prospective cohort study (1995-July 2009). Deceased family members with PJS were included retrospectively. We obtained data by interview and chart-review, including sex, date of birth and death, diagnosis of PJS, STK11 mutation status, family history, and diagnosis and characteristics of intussusceptions. Cumulative intussusception risks were calculated by Kaplan-Meier analysis. After excluding 23 patients with incomplete data, we included 110 PJS patients (46% males) from 50 families. In July 2009, 24 patients had deceased at a median age of 44 (3-74) years, and 86 patients were alive at a median age of 35 (4-75) years. An STK11 mutation was detected in 67 of 76 patients (88%) tested. Seventy-six patients (69%) experienced at least 1 intussusception (range 1-6). The median age at the first intussusception was 16 (3-50) years. There was no significant difference in intussusception incidence according to sex (p=0.47) or mutation-status (p=0.33). Kaplan-Meier analysis showed that an intussusception had occurred in 50% of the cohort at a median age of 20 years (95%CI 17-23), increasing to 75% at the age of 36 years (95%CI 26-46).A total of 129 intussusceptions occurred in 76 patients, presenting as an acute abdomen in 70% of events. Nearly all events (96%) occurred in the small bowel (53% in the jejunum and 47% in the ileum), and 4% occurred in the colon. Therapy was surgical in 93%, enteroscopic in 5% and by barium enema in 2% of events. Based on 37 available histology reports, intussusceptions were caused by polyps with a median size of 35 mm (15-60 mm, 3/37 polyps < 20 mm).

Conclusions: PJS patients carry a high cumulative risk of intussusception already at a young age. Intussusceptions are predominantly caused by polyps > 20 mm and treatment is mostly surgical. These results support the approach of enteroscopic surveillance with timely removal of small bowel hamartomas > 15 mm, in order to prevent intussusceptions and surgical emergencies. The effect of this approach on the incidence of intussusceptions remains to be established.

The European Achalasia trial: a randomized multi-centre trial comparing endoscopic pneumodilation and laparoscopic Heller myotomy as primary treatment of idiopathic achalasia

G.E.E. Boeckxstaens[1,2], V. Annese[3], S. Bruley des Varannes[4], S. Chaussade[5], M. Costantini[6], I. Elizalde[7], U. Fumagalli[8], M. Gaudric[5], E.H. Metman[9], J. Pérez de la Serna[10], W.O. Rohof[1], A.J. Smout[11], J. Tack[2], G. Zaninotto[6], O.R. Busch[12], [1]Dept. of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, University Hospital, cathololic University, Leuven, Belgium, [3]Ospedale Casa Sollievo della Sofferenza, S. Giovanni Rotondo, Italy, [4]Gastroenterology, Centre Hospitalier Universitaire, Nantes, France, [4]Cochin University Hospital, Paris, France, [6]Surgery, S Giovanni e Paolo Hospital, Venice, Italy, [7]Gastroenterology, University of Barcelona, Barcelona, Spain, [8]Surgery, Istituto Clinico Humanitas, Milan, Italy, [9]Gastroenterology, Hôpital Trousseau, Tours, France, [10]Gastroenterology , Hospital Universitario San Carlos, Madrid, Spain, [11]Gastro-enterology, University Medical Centre, Utrecht, The Netherlands, [12]Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Achalasia is currently treated by pneumatic dilation (PD) or laparoscopic Heller myotomy (LHM) with success rates varying between 70 and 90%. Randomised clinical studies with adequate power comparing the clinical efficacy of PD and LHM are currently lacking. Therefore, a large multi-centre randomised clinical trial to compare the treatment success of these two different therapies was designed.From Feb. 2003 to Feb. 2008, 204 newly diagnosed achalasia patients (117M, 83F; age 19-74 mean 46) from 5 European countries agreed to participate. Subjects underwent physical examination, esophageal manometry, endoscopy and radiographic assessment of esophageal emptying, and filled out several questionnaires (SF-36, GERD-HRQOL, OES24). Symptoms (weight loss, dysphagia, retrosternal pain and regurgitation) were assessed using the Eckardt score (each symptom scored from 0-3). Patients were subsequently randomised to either PD (n=94) (Rigiflex balloon, 30 and 35 mm) or LHM (+ Dor anti-reflux procedure) (n=106). Patients were re-evaluated at 1, 3, 6, 12 months after treatment followed by a yearly visit. Treatment was considered unsuccessful if Eckardt score > 3. Retreatment for recurrent symptoms was allowed once during the first two years of follow up in the PD group.Of the 204 randomised patients, 4 patients had pseudo-achalasia and were excluded. 4 perforations occurred after PD compared to 11 peroperatively recognized perforations (1 converted to open) during LHM. Median follow-up (FU) was 38 months (range 0 - 82 months). 13 PD patients required redilation during the first 2 years. The success rate of PD is comparable to LHM, 92% vs 87% respectively. Clinical outcome and sphincter function after 1 and 2 years of FU are similar in both groups, except that lower esophageal sphincter pressure is higher after 1 year FU in the PD group (10,2±0,7 vs 14,1±1,1 mmHg (P<0,01)). SF-36, GERD-HRQOL and OES24 scores were similar in both groups. No effect of age or sex could be demonstrated on the success rate. Esophageal acid exposure and the occurrence of esophagitis were similar in both groups. Dropout rates were similar in both groups (8% vs 17%, LHM vs PD after 2y FU).
Conclusion: After 2 years of FU, PD and LHM have a comparable success rate of 92-87%. Lower esophageal sphincter pressure is higher in PD after 1 year FU. Based on these data, we conclude that either treatment can be proposed as initial treatment, although further FU is required to evaluate long-term outcome.

Laparoscopic Nissen (posterior total) versus Toupet (posterior partial) Fundoplication for Gastro-oesophageal Reflux Disease A meta-analysis of randomised trials

J.A.J.L. Broeders[1], F.A. Mauritz[1], U. Ahmed Ali[1], W.A. Draaisma[1], J.P. Ruurda[1], H.G. Gooszen[1], A.J. Smout[2], I.A. Broeders[3], E.J. Hazebroek[1], [1]Dept. of Surgery, Gastrointestinal Research Centre of the University Medical Centre Utrecht, Utrecht, [2]Dept. of Gastroenterology, Gastrointestinal Research Centre of the University Medical Centre Utrecht, Utrecht, [3]Dept. of Surgery, Meander Medical Centre, Amersfoort, The Netherlands

Laparoscopic Nissen (LNF) is currently considered the surgical therapy of choice for GORD, with excellent long-term reflux control. However, a substantial proportion of patients develops troublesome dysphagia and gas-related symptoms. These post-fundoplication symptoms have been alleged to occur less frequently after laparoscopic Toupet fundoplication (LTF). Therefore the current study aimed to compare LNF versus LTF for gastro-oesophageal reflux disease (GORD) through a systematic review and meta-analysis of randomised controlled trials (RCTs). Four electronic databases (MEDLINE, EMBASE, Cochrane Library and ISI Web of Knowledge CPCI-S) were searched for RCTs comparing primary LNF versus LTF for GORD. The methodological quality of all included trials was evaluated to assess bias risk. Primary outcomes were postoperative dysphagia, dilatation for dysphagia, objective reflux recurrence (recurrent pathological acid exposure or oesophagitis) and reoperation rate. Results were pooled in meta-analysis as risk ratios (RRs) and weighted mean differences (WMDs). Out of 2363 potential relevant publications, six eligible RCTs comparing LNF (n=354) versus LTF (n=338) fundoplication were identified. LNF had a significantly higher prevalence of postoperative dysphagia (14.8 vs 9.9 %; RR 1.55; 95% CI [1.02-2.37]; P=0.04; figure 1) and postoperative dilatation for dysphagia compared to LTF (6.9 vs 2.7 %; RR 2.45; 95% CI [1.06-5.68]; P=0.04). In addition, the number of surgical reinterventions was higher after LNF (6.7 vs 2.6%; RR 2.50; 95% CI [1.12-5.61]; P=0.03). No differences could be found regarding the percentage of patients with objective (14.6 vs 12.7%; RR 1.17; 95% CI [0.74-1.86]; P=0.49) or subjective reflux recurrence (11.5 vs 10.4%; RR 1.13; 95% CI [0.73-1.74]; P = 0.58), patient satisfaction (90.5 vs 89.5 %; RR 1.01; 95% CI [0.95-1.07]; P = 0.77), operating time (WMD -8.1 min; 95% CI [-17.2, 1.1]; P = 0.08) and in-hospital complications (2.5 vs 4.4%; RR 0.62; 95% CI [0.29-1.32]; P = 0.22). A higher prevalence of disability to belch (15.7 vs 7.8 %; RR 2.04; 95% CI [1.19-3.49]; P=0.009) and gas bloating (35.9 vs 22.5%; RR 1.58; 95% CI [1.21-2.05]; P<0.001) was found after LNF. Mean LOS pressure was slightly higher after LNF (WMD 1.0 mmHg; 95% CI [0.2-1.9]; P = 0.02).

Conclusions: LTF is associated with less postoperative dysphagia and reduces dilatation for dysphagia compared to LNF. Reoperation rate and prevalence of gas-related symptoms were lower after LTF as well, with similar subjective and objective reflux control at one year. These results lend level 1a support for the use of LTF as the surgical treatment of choice for patients with GORD.

Concomitant use of a proton pump inhibitor does not increase the risk of recurrent myocardial infarction among clopidogrel users

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

Background: Both clopidogrel and proton pump inhibitor (PPI) drug metabolisms involve cytochrome P450 (CYP) enzymes, which could lead to drug competition on the CYP2C19 level. It has been hypothesized that concurrent use of PPIs may diminish clopidogrel efficacy. The US Food and Drug Administration therefore recommends to discourage the concurrent use of CYP2C19 inhibiting drugs. However, evidence on the association between cardiovascular events and co-administration of PPIs with clopidogrel remains inconclusive. Aim: To assess the association between concomitant use of PPIs and recurrent myocardial infarction (MI) in patients using clopidogrel.Methods: We conducted a nested case-control study within the PHARMO Record Linkage System (1999-2008), which includes data on hospitalisations and drug utilisation (both in- and outpatient) from >2 million residents from the Netherlands. The cohort consisted of patients hospitalized for acute MI, followed by a clopidogrel prescription within 90 days. Cases with a readmission for acute MI while using clopidogrel were matched to controls on age, gender, and calendar time (index date). Exposure to PPI was categorized as current (within 30 days prior to the index-date), past (31-180 days prior to the index-date), remote (>181 days prior to the index-date) or never use. Use of histamine-2-receptor antagonists (H_2RAs) was also assessed. Multivariate conditional logistic regression analysis was used to calculate adjusted odds ratios (OR) with 95%-confidence intervals (95%CI).Results: Among 9,077 patients prescribed clopidogrel following acute MI, we identified 151 cases readmitted for MI while still using clopidogrel and 9351 clopidogrel-using matched controls. Cases were more likely to have co-morbidities and to have had used aspirin. Controls were more likely to have undergone a percutaneous coronary intervention after first MI. Sixty (39.7%) of the cases and 3,107 (33.2%) of the controls used PPIs and 3 (2.0%) of the cases and 207 (2.2%) of the controls used H_2RAs prior to recurrent MI. Both current use of PPIs and current use of H_2RAs were not associated with a significantly increased risk of recurrent MI (OR: 1.30, 95%CI: 0.91-1.85 and OR: 1.00, 95%CI: 0.31-3.25, respectively) compared to never users. Of all PPIs, pantoprazole was used most frequently (49.5%), followed by omeprazole (28.1%). In a stratified analysis, none of the PPIs was significantly associated with an increased risk of recurrent MI.
Conclusions: In this population-based observational study, concomitant use of PPIs with clopidogrel did not increase the risk of recurrent MI. This is in with results from recent randomized clinical trials.

Proton pump inhibitor use is associated with an increased risk for microscopic colitis: a case-control study

D. Keszthelyi[1], S. Jansen[1], B. Scholtes[2], L.G. Engels[2], A.A.M. Masclee[1], [1]Division of Gastroenterology-Hepatology, Dept. of Internal Medicine, Maastricht University Medical Centre+, Maastricht, [2]Division of Gastroenterology, Dept. of Internal Medicine, Orbis Medical Concern, Sittard, The Netherlands

Microscopic colitis (collagenous and lymphocytic colitis) is a well known cause of chronic diarrhea. The pathogenesis of microscopic colitis is still poorly understood. Use of medication (such as NSAIDs), and changes in gut integrity or permeability have been proposed as possible etiological factors. Recently, the use of proton pump inhibitors (PPI) such as lansoprazole, and omeprazole/esomeprazole has been associated with microscopic colitis in several case reports. Aim of this study was to determine whether an association exists between microscopic colitis (MC) and proton pump inhibitor use in patients with documented MC versus age and sex-matched controls. Cases of microscopic colitis from our hospital pathology database diagnosed in the last 5 years were reviewed. Diagnosis was based on clinical symptoms, data from histology and endoscopy. Controls from the population were matched to cases by gender and by age (within 1 year). Information on prescribed medication from patients and controls was obtained from the pharmacy database. Cases were considered PPI-related in case of PPI (esomeprazole, omeprazole, lanzoprazole, pantoprazole or rabeprazole) exposure up to the time of diagnosis. Similarly, exposure to NSAIDs was assessed. Statistical analysis was performed using χ^2 test and generalized linear model for binomial regression to calculate ORs and 95% CIs. During the investigated period, 70 cases of microscopic colitis were retrieved for analysis after confirmation of the diagnosis by an expert pathologist. Mean age of MC patients was 58±1 yrs, 68% were women. Cases did not differ significantly in BMI vs controls (25±5 vs 26±4 kg/m^2). Exposure to both proton pump inhibitors and NSAIDs at the time of the histological diagnosis was significantly higher in patients than in controls (PPI 35,7% vs 12,8%, p= 0,002 and NSAIDs 17,9 vs 5,7%, p=0,03 vs control, resp.). Both PPI and NSAID exposure proved to be associated with microscopic colitis when analyzed separately (unadjusted OR 3,9; [95% CI 1,6-8,9] for PPI and 3,8 [95% CI 1,1-13,0] for NSAIDs resp.). After adjustment for concomitant exposure to NSAIDs as covariate, an adjusted OR of 3,6 [95% CI 1,5-8,8] was found for PPI exposure, whereas no significant association with increased risk for microscopic colitis was found for NSAID exposure (adjusted OR 3,3; [95% CI 0,9-11,6]). This observation confirms the presumed association between microscopic colitis and PPI use and supports the possible etiological role of PPI exposure in the development of microscopic colitis.

New clopidogrel users on PPIs are at an increased risk of cardiovascular and gastrointestinal complications - results of a large Dutch cohort study

O.S. van Boxel[1], M.G.H. van Oijen[2], M.P. Hagenaars[3], A.J.P.M. Smout[1], P.D. Siersema[1]
[1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, [2]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, [3]Achmea Health Insurance, Leiden, The Netherlands

Introduction: Recent studies have raised concerns on the clinical effectiveness of clopidogrel when taken in combination with proton pump inhibitors (PPIs), showing an increase in the occurrence of cardiovascular events. Until now, studies investigating this association have not been undertaken in Europe and the incidence of GI events and related hospitalization rates in clopidogrel users with or without PPI use are still unknown.Aim: To investigate the association between the co-administration of clopidogrel and PPIs and the occurrence of cardiovascular and gastrointestinal events in a large population cohort in the Netherlands. Methods: A retrospective study was conducted using data from 4 million individuals provided by two Dutch health insurance companies. New clopidogrel users between January 2006 and December 2007 were selected and followed over time. Primary cardiovascular outcome was defined as the composite of myocardial infarction, unstable angina pectoris, stroke and/ or all-cause mortality. Peptic ulcer disease was also used as primary gastrointestinal outcome. The presence of risk factors for cardiovascular and gastrointestinal complications was identified for each subject during a 1-year history period prior to index date. These included all diagnoses, procedures and treatments reimbursed by the health insurance. Cox proportional hazard regression analysis was used to calculate the risk of cardiovascular and gastrointestinal outcomes in clopidogrel patients with or without PPI use.Results: A total of 18,139 new clopidogrel users were identified, of whom 5,734 (32%) used PPIs concurrently. Patients on PPIs were significantly older, used more co-medications and suffered from more co-morbidities. Use of clopidogrel and PPIs was associated with an increased risk of myocardial infarction (HR 1.93, 95% CI 1.40-2.65), unstable angina pectoris (HR 1.79, 95% CI 1.60-2.03) and the composite cardiovascular endpoint (HR 1.75, 95% CI 1.58-1.94) compared to clopidogrel users without PPIs. PPI users also had an increased risk of gastrointestinal events compared those not using PPIs (HR 4.76, 95% CI 1.18-19.17). No significant differences were found between different types of PPIs and associated risks of adverse outcomes.
Conclusion: New clopidogrel users on PPIs are at an increased risk of cardiovascular and gastrointestinal complications compared to those not using PPIs. Although a metabolic effect of PPIs on clopidogrel cannot be excluded, we suggest that the inferior cardiovascular profile of clopidogrel users on PPIs and the occurrence of channelling bias are important factors underlying this observation.

Proton pump inhibitor use and health-related quality of life in patients with gastroesophageal reflux disease and functional dyspepsia

O.S. van Boxel[1], B.L.A.M. Weusten[2], P.D. Siersema[1], A.J.P.M. Smout[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Utrecht, [2]Dept. of Gastroenterology, Saint Antonius Hospital, Nieuwegein, The Netherlands

Introduction: The introduction of proton pump inhibitors (PPIs) has largely improved the management of gastroesophageal reflux disease (GERD). Furthermore, PPI treatment also gives symptom relief in a proportion of dyspepsia patients; however, this effect has not been reported consistently in all studies. Until now, the frequency of PPI use, the subjective efficacy of PPIS in GERD and FD patients and the possible relationship with health related quality of life (HRQOL) in these patients have not been investigated. Aim: To investigate a possible relationship between PPI use and HRQOL in a cohort of GERD and FD patients in secondary and tertiary care. Methods: One hundred consecutive GERD patients and 100 FD patients were selected from a secondary and tertiary care Centre in the Netherlands. Patients were asked to fill out the SF-36 questionnaire assessing scores on eight dimensions of health. The raw score of each of the eight SF-36 dimensions was derived by summing the item scores, and converted to a value for a dimension from 0 (worst possible health state) to 100 (best possible health state). In addition, a Visual Analogue Scale (VAS) was used to asses the subjective efficacy of medication(s), including PPIs, used by GERD and FD patients for gastrointestinal symptoms. Results: Seventy-three GERD patients and 62 FD patients returned the questionnaires. PPI use in GERD patients was common, with 90% using PPIs at the time of filling out the questionnaire. More than 55% of FD patients also used PPIs and of these more than 50% used more than the daily defined dose of PPIs, which was in fact also true for GERD patients on PPIs. FD patients scored significantly lower on the SF-36 mental component summary than GERD patients (p=0.013). Mean VAS for efficacy of medication was 53.2 (SD 27.1) for GERD patients and 37.1 (SD 25.4) for FD patients (p=0.004). FD patients using PPIs scored slightly higher on the VAS for efficacy of medication than those not using PPIs, 38.8 (SD 24.3) and 33.9 (SD 27.7), respectively (p=0.35). No differences were found in HRQOL between FD patients using PPIs and those not using PPIS.
Conclusion: HRQOL is significantly impaired in FD patients when compared to GERD patients. Since FD patients on PPIs do not score better with regard to symptom relief and HRQOL than those not on PPIs, physicians, particularly in secondary and tertiary care, should be reluctant in prescribing PPIs to these patients and discontinue its use when a clear effect is not demonstrated.

The interval between the diagnosis of long segment Barrett's esophagus and symptomatic esophageal adenocarcinoma as found in an observational cohort followed up for 35 years

CM den Hoed ,C.M. den Hoed[1], M. van Blankenstein[1], J. Dees[1], E.J. Kuipers[1,2], Depts. of Gastroenterology and Hepatology[1], and Internal Medicine[2], Erasmus Medical Centre, Rotterdam, The Netherlands

Barrett's esophagus(BE) constitutes a premalignant condition preceding esophageal adenocarcinoma(EAC). An incidence of EAC in BE of 0.41/100 persyrs was reported in a meta-analysis of the literature, with a large interval between BE onset and EAC occurrence. In the majority of patients the onset of BE is too late in life to develop EAC. The unknown onset of BE precludes determining the length of the incubation period by direct observation.To calculate the range of intervals between BE diagnosis and EAC within possibly the longest observational BE follow-up study, the Rotterdam Barrett's cohort, comprising 166 patients with BE >2cm, diagnosed 1973-1984. Excluding 2 incident cases of high grade dysplasia(HGD) at BE diagnosis, 19 dying within 2 yrs, 1 case of esophagectomy without HGD/ EAC and 11 lost to follow up, 133 patients (M/F 73/60) were taken into account. We distinguished 3 endpoints: symptomatic HGD/EAC (sHGD/EAC), death without sHGD/EAC and survival without sHGD/EAC. Univariate analysis, Kaplan-Meier and Log rank tests were used. The cohort had a mean age at diagnosis of 62.4 yrs(14.4-92.3), mean interval of 14.8 yrs (2.1-32.0), mean age at endpoint of 76.6 (37.2-92.9) and mean length BE at diagnosis of 6.0 cm (3-15). 13 cases of sHGD/ EAC (6/7), were observed over 1967.2 persyrs of follow-up; 0.66% p.a. Patients who developed sHGD/EAC were at base characterized by a higher prevalence of low grade dysplasia (LGD) (54% vs 17%, p=0.005) and a larger BE segment (mean length: 8.3 cm vs 6.3, p=0.03). The mean age at BE diagnosis was 61.0 yrs (37.2-77.8) and the mean interval between BE diagnosis and sHGD/EAC was 11.0 yrs (1.6-20.4). 96 patients died without sHGD/EAC. They died at a mean age of 77.0 yrs (63.2-97.0) after a mean interval of 12.6 yrs (2.1-26.8). Survivors without sHGD/ EAC had a lower age at BE diagnosis (mean 42.8 yrs, log rank p<0.001). Their mean BE length at diagnosis was 6.0 cm (3-10) and the mean interval period was 25.5 yrs (20.8-32.0) This group comprises the best candidates for establishing the maximum incubation period to sHGD/EAC. Our data indicate that the incidence of sHGD/EAC is in accordance with previous data despite the fact that we did not apply surveillance and the long observational period. LGD and a longer BE length at diagnosis were more prevalent in patients that developed sHGD/EAC. Our data show a mean survival of 25.5 years without sHGD/EAC in patients diagnosed with BE at an early age (mean 42.8 yrs).

Prevalence of esophagitis and Barrett's esophagus patients undergoing routine colonoscopy; a cohort study

C.M. den Hoed[1], B.C. van Eijck[1], P.D. Siersema[1], E.J. Kuipers[1,2], Dept. of Gastroenterology and Hepatology[1], and Internal Medicine[2], Erasmus Medical Centre, Rotterdam, The Netherlands

A dramatic increase in the incidence of esophageal carcinoma (EC) has occurred over the last 3 decades. Its precursor, Barrett's esophagus (BE), seems to show the same trend. The prevalence of BE and its trend over time are the main predictor for the changes in incidence of EC in the coming two decades. Unfortunately however, the majority of data on the prevalence of BE come from endoscopy series which only included symptomatic cases. These data are unlikely to reflect the prevalence in the general population. To identify the prevalence of esophagitis and BE in asymptomatic subjects and identify possible risk factors. Patients visiting our out-patient clinic for routine, non-urgent colonoscopy were included in this study. With IRB and informed patient consent, all patients completed the Gastrointestinal Symptom Rating Scale (GSRS) and subsequently underwent upper GI endoscopy prior to colonoscopy). Biopsies were taken from the esophagus and scored for the presence of inflammation, specialized intestinal metaplasia and dysplasia. All biopsies were reviewed by an expert GI pathologist. 383 patients (F/M: 192 /191; mean age 53.1; range 17-86) were included. Macroscopic evidence of esophagitis was demonstrated in 14.4% (grade A-D: 64.4/23.5/5.1/7%). Diaphragmatic herniation (HD) was present in 17% (n=65), and correlated with the presence of esophagitis. PPI's were used by 20% of patients, 37% of patients scored positive for dyspepsia with the GSRS.BE was diagnosed histologically in 13.6% of patients of which a fifth (20%) showed low grade dysplasia. The proportions were similar in GSRS-positive and –negative patients (p=0.4). BE was correlated with a BMI>25 (r^2 0.159, p=0.003) and higher age (p=0.001) with an increase from 1 subject with BE (1%) in those below the age of 30 yrs to 20% (21 subjects) above 60 yrs.
No associations were demonstrated with GSRS scores, PPI use, alcohol and smoking. Esophagitis was only associated with the presence of HD (X^2 p 0.018). Microscopic esophagitis was demonstrated in 50.8% of patients, it was correlated with macroscopic esophagitis (p=0.01). Asymptomatic subjects have a considerable prevalence of esophagitis and BE. BE is more common in elderly and overweight subjects, but is not associated with GSRS scores. Esophagitis was only associated with the presence of HD, but not with GSRS scores and overweight subjects in our study.

Covered self-expandable stents for the treatment of benign esophageal perforations and anastomotic leaks

P.G.A. van Boeckel[1], K.S. Dua[2], R.J.H. Schmits[1], N. Surapaneni[2], F.P. Vleggaar[1], P.D. Siersema[1], [1]Dept. of Gastroenterology & Hepatology, University Medical Centre, Utrecht, The Netherlands[2], Dept. of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, USA

Background: Esophageal perforations are potentially life-threatening injuries, and may occur spontaneously (Boerhaave's syndrome) or have an iatrogenic cause (instrumentation, anastomotic leak). Placement of covered stents has emerged as a minimally invasive treatment option for benign esophageal perforations and anastomotic leaks.Aim: To determine the clinical effectiveness of covered stent placement for the treatment of esophageal perforations and leaks. Methods: Consecutive patients who underwent placement of a fully covered self-expandable metal stent (FSEMS), a partially covered SEMS (PSEMS) or a self-expanding plastic stent (SEPS) for a benign esophageal perforation or anastomotic leak after upper gastrointestinal surgery between January 2006 and July 2009 were included. Data on demographics, type of lesion, stent placement and removal, clinical success and complications were collected.Results: A total of 42 patients (27 males; mean age 60 (range 22-83) years) received 81 esophageal stents (52 PSEMS, 19 FSEMS, 10 SEPS) for anastomotic leak (n=23), iatrogenic perforation (n=11), spontaneous perforation eci (n=3), post radiation perforation (n=3) or Boerhaave's syndrome (n=2). Stent placement was technically successful in all but one patient. Stents were endoscopically removed after a median period of 30 (range 1-197) days (PSEMS 28 (6-197) days, FSEMS 12 (1-120) days, SEPS 42 (14-90) days). Endoscopic stent removal was successful in all but five patients having a PSEMS due to tissue ingrowth. Clinical success was achieved in 23/27 (85%) patients (86% PSEMS, 86% FSEMS, 83% SEPS) after a median of 2 (range 1-5) stent placements and a mean stenting time of 46 (range 7-97) days. Of the other patients, 8 died before stent removal and 7 patients still have a stent in situ. Best clinical success was achieved after a total stenting time of 6-8 weeks. In total, 26 complications in 21 patients (45%) occurred (tissue in- or overgrowth (n=8), stent migration (n=8), ruptured stent cover (n=3), food obstruction (n=3), pneumonia (n=2), hemorrhage (n=1), persisting leakage through an uncovered stent part (n=1)). Stent migration occurred most frequently with SEPS (20%) compared to FSEMS (16%) and PSEMS (6%), while tissue in- or overgrowth was only seen with PSEMS (16%).Two (4%) stent-related deaths (both severe hemorrhage, including one after surgical stent removal) occurred.
Conclusions: Covered stents, placed for a period of 6-8 weeks, are effective and safe in sealing benign esophageal ruptures or leaks. As efficacy between PSEMS, FSEMS and SEPS is not different, but removal of PSEMS may be complicated, it is suggested to initially use FSEMS in these patients.

Endoscopic extraction of self-expandable metal stents from the esophagus: outcome and complications in 107 procedures

N.C.M. van Heel, J. Haringsma, E.J. Kuipers, Dept. of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, The Netherlands

Self-expandable metal stents (SEMS) are increasingly used as a temporary treatment for patients with benign esophageal lesions, and also to bridge therapy for malignant disease. Although some of these stents are labeled removable, removal was long thought to be difficult and complications during stent extraction may occur. The feasibility of endoscopic stent extraction has largely been underreported. The aim of the present study was to evaluate the outcome of SEMS extraction in a large cohort of patients after temporary stent insertion. This prospective observational cohort study was conducted in a single tertiary referral Centre. Between 2001 and 2009, all consecutive patients referred for endoscopic SEMS extraction were included. Patients with migrated stents were excluded. Endoscopic stent removal technique depended on stent design. A total of 107 stent extractions were undertaken in 90 patients (58% male; median age 61 years (range: 14-90 years)) with benign (n=58; 64%) and malignant (n=32; 36%) esophageal disease. Seventeen patients needed re-stenting with subsequent extraction. In total, 30 SEMS (28%) were fully covered, and 77 SEMS (72%) were partially covered. Endoscopic stent extraction was immediately successful (primary removal rate) in 91% (97/107), extractions were performed in multiple endoscopic sessions (range 2-7) in 4.7% (5/107), and SEMS were surgically removed in 3.7% (4/107). One (0.9%) SEMS failed to be removed because of severe tumour tissue ingrowth. Major complications occurred during or after 7 stent removals (6.5%): 5 stent fractures, 1 esophageal sleeve mucosectomy with subsequent stenosis after healing, 1 thoracic empyema, 1 osteodiscitis, and 2 self-limiting bleedings. No significant differences in primary removal rate and complication rate were found between fully covered vs partially covered stents (97% vs 88%, p=0.28 and 0% vs 9%, p=0.19) and between benign vs malignant disease (90% vs 91%, p=1.00 and 8% vs 3%, p=0.42). Patients with a complicated stent extraction had had the stent significantly longer in place as compared to patients with an uncomplicated stent extraction; 126 days (range: 14-587) vs 28 days (range: 1-393) (p=0.01).
In conclusion, primary endoscopic removal of a self-expandable stent is feasible in the majority of patients with benign and malignant esophageal disease. However severe complications during stent extraction do occur, irrespective of the type of stent or indication. A prolonged stenting period is associated with an increased complication rate.

Intestinal bile salt nuclear receptor FXR protects from inflammatory bowel disease: potential therapeutic implications

R.M. Gadaleta[1,2,3], K.J. van Erpecum[1], B. Oldenburg [1], E.C.L. Willemsen[2], S. Murzilli[3], L.W.J.Klomp[2], P.D. Siersema[1], A. Moschetta[3] , S.W.C. van Mil[2], [1]Dept. of Gastro-enterology and Hepatology, [2]Laboratory of Metabolic and Endocrine Diseases and Netherlands Metabolomics Centre, UMC Utrecht, The Netherlands; [3]Laboratory of Lipid Metabolism and Cancer, Consorzio Mario Negri Sud, S.ta Maria Imbaro (Ch), Italy

Bile salt nuclear receptor Farnesoid X Receptor (FXR) was recently implicated in intestinal antibacterial defense and barrier function. We aimed to study its role in pathogenesis of inflammatory bowel disease. Colitis was induced in Wild Type (WT) and FXR knockout (ko) mice (n=8 to 10) by Dextran Sodium Sulphate (DSS: 2.5% in drinking water, 10 days) with or without synthetic FXR ligand 6-Ethyl Chenodeoxycholic Acid (6ECDCA: 5 mg/kg/day, 13 days, starting 3 days before DSS). Colitis symptoms were checked daily and intestinal permeability (FITC-dextran assay), bile salt composition (HPLC), histology and colonic inflammatory gene expression (Q-PCR) determined. mRNA expression of FXR and target genes was determined in patient biopsies. Underlying mechanisms were explored in complementary in vitro experiments. 6ECDCA-treated WT but not FXR ko mice were protected from DSS-induced colitis, as shown by highly significant reduction of body weight loss, rectal bleeding, colonic shortening, normalization of intestinal permeability, 49% reduction in blinded histological score and 55% reduction in goblet cell loss. Only in 6ECDCA-treated WT mice, mRNA levels of pro-inflammatory genes (IL-1β, IL-6, IL-10 and MCP-1) were strongly down-regulated while antibacterial defense gene iNOS was upregulated. 6ECDCA was enriched in both WT and FXR ko mice (10% and 5% of total bile salts, respectively). However intestinal expression of FXR target genes FGF15 and SHP was increased 4.5- and 19-fold with 6ECDCA treatment only in WT mice. In patients with quiescent Crohn colitis (n=17), mRNA expression of FXR and SHP was significantly altered compared to patients with ulcerative colitis (n=16) or healthy controls (n=17). In differentiated CaCo2 cells grown on trans-well plates, FXR activation by GW4064 prevented DSS-dependent loss of integrity of the monolayer. In differentiated HT29 cells, TNFα-induced 20-fold increase of IL-1β expression was abolished by GW4064-dependent FXR activation. In reporter assays, GW4064 prevented TNFα-induced NF-κB activity in HEK293 cells transfected with WT FXR, but no effect was achieved with FXR mutant W469A (defective in Ligand Binding Domain), indicating FXR-mediated inhibition of NF-κB signalling.
In conclusion, FXR activation protects against experimental murine colitis, supposedly by preserving the intestinal barrier and inhibiting NF-κB activity. Currently available FXR agonists may offer new therapeutic strategies for inflammatory bowel disease.

Development of colitis in Muc2-deficient mice: diet matters!

N. Burger-van Paassen[1], P.J. Puiman[1], P. Lu[1], N. Le Polles[1], J. Bouma[1], A.M. Korteland-van Male[1], G. Boehm[1,2], J.B. van Goudoever[1], I.B. Renes[1], [1]Erasmus MC-Sophia, Lab.[1]Pediatrics, Neonatology,, Rotterdam, The Netherlands, [2]Danone Research, Friedrichsdorf, Germany

Background: Muc2-knock out mice (Muc2KO) do not have a protective mucus layer and spontaneously develop colitis. In ulcerative colitis (UC) and necrotizing enterocolitis, MUC2 synthesis is decreased and the mucus layer is thinner. Nutrition plays an important role in the management of UC. Objective: To study the effects of a purified diet and probiotics on growth and disease severity in Muc2KO mice. Methods: Muc2KO and wildtype (WT) mice were fed a non-purified (NP, i.e., standard chow) diet, a NP-diet supplemented with probiotics (NP+PRO; supplementation consisted of daily administration of *Bifidobacterium breve* and *Bifidobacterium animalis subsp. Lactis*), or a purified (AIN93G) diet during 5 weeks, starting directly after weaning. Purified diet contains 60% less fibers and milk-casein proteins in stead of plant proteins. Clinical symptoms and colonic morphological changes were monitored. Inflammation status was analyzed by immunohistochemistry. Results: Type of diet did not induce significant differences in body weight, crypt length, or influx of immune cells in WT mice. However, in Muc2KO mice the AIN93G diet significantly increased bodyweight compared to the NP and NP+PRO diet. Remarkably, bodyweights of Muc2KO mice fed AIN93G diet were similar to WT mice. Crypt length was increased in Muc2KO mice compared to WT mice regardless the type of diet. Moreover, in Muc2KO mice the AIN93G diet limited the increase in crypt length compared to NP or NP+PRO diet. Interestingly, in Muc2KO mice the NP+PRO diet reduced the crypt lengthening compared to NP diet. Finally, Muc2KO mice that were fed the AIN93G diet showed a limited influx of CD3-positive T cells, S100a8 and S100a9-positive cells compared to Muc2KO mice fed NP or NP+PRO diet. Conclusions: Type of diet and substitution with probiotics affects the severity of colitis in Muc2KO mice. Specifically, the AIN93G diet limits disease severity, suggesting that type of protein and amount of insoluble fibers modulate disease activity in mice prone to develop colitis. Moreover, probiotics might have beneficial effects in Muc2KO mice as NP+PRO diet reduced crypt lengthening compared to NP diet. Therefore, feeding strategy in subjects that are susceptible to develop colitis might have considerable implications for disease severity.

Lipid-rich nutrition inhibits mast cell activation via the vagal anti-inflammatory pathway

J.J. de Haan[1], M. Hadfoune[1], T. Lubbers[1], W.A. Buurman[1], J.W.M. Greve[2,1], [1] Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht; [2] Surgery, Atrium Medisch Centre, Heerlen, The Netherlands

Mast cell degranulation is considered a crucial event in the development of postoperative ileus and other intestinal complications following surgery. Previously, we demonstrated that lipid-rich enteral nutrition attenuates systemic inflammation and preserves intestinal integrity via a cholecystokinin (CCK)-receptor dependent vagal pathway. Here, we investigate 1) the effects of lipid-rich nutrition on intestinal mast cell degranulation and 2) the involvement of the vagal pathway. Two rodent models of shock were used. Male Sprague Dawley rats were subjected to non-lethal hemorrhagic shock and in male C57Bl6 mice shock was induced by intraperitoneal endotoxin administration. Before shock, rats and mice were fasted or fed nutrition enriched with phospholipids or low-lipid control feeding. Animals were sacrificed at 30 minutes after shock. Mast cell degranulation was assessed by measuring plasma MMCP and RMCP; mouse- resp. rat-specific proteases abundantly expressed by intestinal mucosal mast cells. CCK-receptor antagonists were administered 20 minutes before shock in rats. To confirm vagal inhibition of mast cell activation, the MC9 mast cell was used. Effects of the principal vagal neurotransmitter acetylcho on endotoxin-induced mast cell degranulation was assessed by a hexosaminidase assay. A Mann-Whitney U-test was used for between group comparisons; $p<0.05$ was considered significant. Following administration of endotoxin, lipid-rich nutrition reduced plasma MMCP in comparison with low-lipid (0.3±0.1 ng/mL vs 0.6±0.1 ng/mL, $p<0.01$) and fasted controls (1.5±0.3 ng/mL, $p<0.05$). Also following hemorrhage, lipid-rich nutrition reduced RMCP levels compared with fasting (1.8±0.3 ng/mL vs 4.9±0.6 ng/mL, $p<0.01$). Protective effects of lipid-rich nutrition were abrogated by CCK-receptor antagonists (2.1±0.2 vs 4.5±0.8 ng/mL RMCP [vehicle], $p<0.01$), indicating a crucial role for the vagal pathway. Further evidence was provided in vitro: acetylcho dose-dependently reduced mast cell activation (maximal reduction: 86%).

In conclusion, this study demonstrates that lipid-rich nutrition strongly reduces intestinal mast cell degranulation following inflammatory hits such as endotoxin exposure or hemorrhagic shock. These protective effects were mediated by CCK-receptors, indicating a crucial role for the vagal pathway. In line, acetylcho was shown to inhibit mast cell activation in vitro. Taken together, this study identifies nutritional activation of the vagal pathway with lipid-rich feeding as a potential therapy to prevent mast cell-related complications such as postoperative ileus.

Functional splanchnic hypoperfusion precedes intestinal epithelial cell damage during strenuous exercise

K. van Wijck[1,2,3], K. Lenaerts[1,2,3], L.J.C. van Loon[1,2,4], J.M. Senden[1,2,4], C.H.C. Dejong[1,2,3], W.A. Buurman[1,2,3], [1]Top Institute Food and Nutrition, Wageningen, [2]NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht, [3]Dept. of Surgery, Maastricht University Medical Centre+, Maastricht, [4]Dept. of Human Movement Sciences, Maastricht University Medical Centre+, Maastricht, The Netherlands

Background Intestinal hypoperfusion is a common phenomenon in various pathophysiological conditions, and occurs in response to acute vascular diseases, major surgery or trauma, and shock. Challenging situations such as exhaustive physical exercise can reduce blood flow to the splanchnic bed by as much as 80%, to allow adequate flow to the contracting muscle. Previous studies suggest that gastric ischemia develops during high-intensity exercise in healthy humans. Therefore, this study aims (1) to evaluate the development of exercise-induced splanchnic hypoperfusion and (2) to analyze the impact on gut mucosal integrity in healthy males. Methods Sixteen healthy, recreationally active males performed a 60 min exercise bout on a cycle ergometer, aiming at an exercise intensity corresponding with 70% of maximal workload capacity, followed by 60 min of recovery. Blood samples were collected at baseline, and every 10 min during exercise and recovery. Plasma samples were analysed for intestinal fatty acid binding protein (I-FABP), a small (15 kDa) protein reflecting intestinal epithelial cell damage. To assess functional gastrointestinal (GI) hypoperfusion, gastric air tonometry was performed in a subset of 9 subjects. Results were analyzed using repeated measures analysis of variance with Tukey's post hoc test for multiple comparisons. Data are presented as means (SEM). Results: Plasma I-FABP levels gradually increased from 328 (52) pg/ml at base to a maximum of 629 (119) pg/ml ($P<0.001$) at completion of the exercise bout. I-FABP levels returned to base within 1 h of post-exercise recovery. Gap pCO_2 (ΔpCO_2) steadily increased from -0.85 (0.15) kPa at base to 0.85 (0.42) kPa ($P=0.0009$) at completion of the exercise bout, indicating splanchnic hypoperfusion. ΔpCO_2 approximated basal level within 1 h of post-exercise recovery ($P>0.05$). Interestingly, the increase in ΔpCO_2 occurred 10 min before I-FABP levels were elevated.

Conclusions: Exhaustive physical exercise rapidly induces GI hypoperfusion in healthy subjects, reflected by a gradual increase in ΔpCO_2. The observed functional splanchnic hypoperfusion is accompanied by intestinal epithelial cell damage, demonstrated by an increase in plasma I-FABP concentrations. This is the first study to demonstrate that exercise-induced intestinal hypoperfusion precedes epithelial damage in healthy individuals.

Increasing intestinal threonine metabolism improves gut barrier function and resistance to necrotizing enterocolitis in preterm pigs fed colostrums

P. Puiman[1], M.L. Jensen[2], B. Stoll[3], K. Dorst[1], I. Renes[1], P. Sangild[2], J.B. van Goudoever[1], [1]Pediatrics, Neonatology, Erasmus MC-Sophia, Rotterdam, The Netherlands, [2]Dept. of Human Nutrition, University of Copenhagen, Denmark, [3]Pediatrics, Children's Nutrition Research Centre, Houston, Texas, U.S.

Threonine is an essential amino acid necessary for synthesis of gut mucins that form the protective intestinal mucous layer. In premature infants, this function might be compromised leading to necrotizing enterocolitis (NEC). We hypothesized that enteral feeding with colostrum, relative to infant formula, would stimulate intestinal threonine utilization, and thereby protect against necrotizing enterocolitis (NEC) in preterm neonates. Preterm piglets were delivered at 90% of gestation and received 2 days of total parenteral nutrition, followed by 3 days of formula (n=7; threonine intake 4 mg/ml) or bovine colostrum (n=7; threonine intake 3.8 mg/ml). Prior to euthanasia, piglets were infused with U-^{13}C threonine intravenously and 1-^{15}N threonine intragastrically to measure intestinal threonine and protein metabolism. Plasma and tissues were collected for histology and mass spectrometry. In the formula group, 57% (4/7) developed NEC compared to 14% (1/7) in the colostrum group, while body weight and intestinal weight were not affected. Histological analysis showed a higher density of goblet cells in the colon of colostrum piglets ($p<0.05$). Protein contents of the small intestine and colon were similar between groups, although protein synthesis in the distal small intestine was increased with colostrum feeding ($p<0.05$). Plasma concentrations of threonine were lower in colostrum pigs ($p<0.01$), while intestinal uptake of threonine in first pass was increased (27 mg/kg/d vs. 21 mg/kg/d; $p<0.05$).
In conclusion, colostrum feeding stimulated the fractional intestinal threonine utilization, intestinal protein synthesis, increased goblet cell density, and improved NEC resistance in preterm pigs. This suggests that impaired barrier function plays an important role in NEC development in preterm neonates and that colostrum feeding might prevent NEC via enhanced intestinal threonine metabolism.

Vagus nerve released acetylcho can inhibit intestinal inflammation via cross talk with vasoactive intestinal peptide

E.P. van der Zanden[1], C. Cailotto[1], L.E.J. Nijhuis[1], G. Boeckxstaens[1,2], W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, Catholic University of Leuven, Leuven, Belgium

Vagus nerve activity attenuates NF-κB activation and production of pro-inflammatory cytokines by macrophages. In vitro studies have shown that this is mediated by the vagal neurotransmitter acetylcho (ACh) via nAChR activation. However, it is unclear whether ACh is the sole mediator of the vagal anti-inflammatory potential. In the present study, we questioned whether vagus nerve activity may amplify its anti-inflammatory effect via co-release of the neuropeptide vasoactive intestinal peptide (VIP) that has been shown to have significant immuno-modulatory properties. Immunohistochemical staining or detection for VIP protein was performed on transversal sections of intestinal tissue. Electrical vagal nerve stimulation (VNS) was performed using bipolar electrodes, after which intestinal tissue was analyzed for expression of the VIP receptors VPAC1-2 using QPCR and normalized to B2M levels. In vitro, peritoneal mouse macrophages were pretreated with ACh and/or VIP for 30 min. ACh (10µM) was applied 30 minutes before VIP (10µM) incubation, followed by 3hrs LPS challenge (10ng/mL), and cytokine levels were determined using ELISA. VIP-positive fibers were found throughout the plexus and lamina propria. VNS decreased the expression of VPAC2 transcript at the myenteric plexus (down to 4±1.2% of sham stimulation) but increased mucosal VPAC2 transcript (VPAC/B2M(%):0.6± 0.17 (SHAM) vs. 12.48 ± 2.6 (VNS)). Next, we assessed the potential of VIP and ACh to modulate macrophage activation in vitro. VIP inhibited LPS-induced TNF production in a dose dependent fashion in RAW macrophages, down to 52.4+/-4.2% of control release. ACh pretreatment (30 min) attenuated LPS-induced TNF production down to 59±4.5% confirming previous studies. However, when ACh and VIP (at 10 uM) were co-administered, LPS induced TNF production was decreased almost down to unstimulated levels (25±4.2% of LPS vehicle).
Conclusion: The vagal transmitters ACh and VIP inhibit LPS induced pro-inflammatory cytokine release in macrophages in a cumulative manner. Vagus nerve activity enhances VPAC receptor expression in the mucosa. Hence, VIP co-released after vagus nerve activity may amplify the vagal anti-inflammatory pathway in intestinal inflammation.

Intestinal integrity is preserved and inflammation is reduced by lipid-rich enteral nutrition in a rat hemolysis model

J.J. de Haan[1], B. Hanssen[1], I. Vermeulen Windsant[1], T. Lubbers[1], M. Hadfoune[1], W.A. Buurman[1], J.W.M. Greve[2,1], [1]Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht; [2]Surgery, Atrium Medical Centre, Heerlen, The Netherlands

Acute hemolysis is a frequent event in surgical settings. Hemolysis-induced free circulating hemoglobin impairs microcirculation via scavenging of intravascular nitric oxide (NO), a phenomenon that is associated with the development of organ damage and systemic inflammation. Previously, we demonstrated that lipid-rich enteral feeding prevents organ damage and reduces inflammation via stimulation of the vagus nerve. Acetylcholine, the principal neurotransmitter of the vagus, is a known vasodilator acting largely independent of NO. Here, we investigate the effects of nutritional activation of the vagus nerve on intestinal integrity and systemic inflammation in a rodent model of acute hemolysis. Hemolysis in Sprague-Dawley rats was simulated by administration of free hemoglobin (fHb). Following a bolus, fHb was infused continuously for 60 minutes to reach clinically relevant plasma concentrations (37 ± 2 μM). Prior to fHb administration, rats were fasted or fed nutrition enriched with phospholipids per gavage. Chlorisondamine, an antagonist to peripheral acetylcho receptors, was administered at 30 minutes before fHb infusion. Microcirculatory changes in jejunum and ileum were evaluated using fluorescent microspheres. Blood and tissue samples were harvested at 120 minutes to assess intestinal barrier function and systemic inflamemation. Comparisons between groups (all n=6) were performed with a Mann Whitney U test and $p<0.05$ was considered significant.Lipid-rich nutrition reduced bacterial translocation compared with fasting (108 ± 8 CFU/g tissue vs 154 ± 8 CFU/g tissue; $p<0.05$). Furthermore, intestinal permeability to horseradish peroxidase was decreased in fed rats (2.9 ± 0.2 μg/mL vs 4.0 ± 0.2 μg/mL [fasting]; $p<0.01$), which was accompanied by improved splanchnic perfusion compared with fasted animals ($p<0.01$). Also circulatory IL-6 levels were significantly reduced in lipid-rich treated animals (32.8 ± 6.4 pg/mL) compared with fasted controls (64.2 ± 8.6 pg/mL; $p<0.01$). Chlorisondamine abrogated the protective effects of lipid-rich nutrition compared with vehicle (all parameters; $p<0.05$), indicating a crucial role for the vagal pathway.

In conclusion, this study demonstrates that enteral nutrition enriched with phospholipids preserves intestinal integrity and reduces systemic inflammation following administration of fHb in an acetylcho receptor-dependent manner. These findings implicate nutritional intervention of the vagus nerve as a novel therapeutic approach in patients with severe hemolysis.

Hepatitis B virus impairs the interaction between natural killer cells and plasmacytoid dendritic cells

C.C. Shi[1,2], E.T.T.L. Tjwa[1], P.J. Biesta[1], Q. Xie[2], H.L.A. Janssen[1], A.M. Woltman[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands, [2]Dept. of Infectious Disease, Rujin Hospital, Shanghai, China

Hepatitis B virus (HBV) infection does not effectively activate innate immunity and may therefore induce chronic infection. The mechanism underlying this defective innate immune response is not known. Natural killer (NK) cells and plasmacytoid dendritic cells (pDC) are both important innate immune cells. pDC are antigen presenting cells and the major producers of anti-viral and immune stimulating type I interferons upon viral recognition. Activated NK cells contribute to virus elimination via direct killing of infected cells and the production of IFN-γ. Functional bidirectional cross-talk between pDC and NK cells supports the development of an adequate virus-specific T cell response required for viral clearance. Therefore, the effect of HBV on the functional interaction between pDC and NK cells was investigated. Healthy human peripheral blood pDC and NK cells were isolated by magnetic selection and FacSorting, then cocultured for 48 h at a pDC/NK ratio of 1:5 in the presence of IL-3 with or without CpG-A ODN2216, CpG-B ODN2006, HepG2.215 cell-derived HBV (3.24×10^8 particles/ml), Herpes simplex virus (HSV) (7.3×10^8 particles/ml). In contrast to other DNA viruses, such as HSV, addition of HBV to pDC/NK cultures did not enhance pDC/NK crosstalk. HBV neither increased the expression of pDC (CD83, CD86) and NK cell (CD69, CD25, HLA-DR) activation markers as assessed by flow cytometry nor induced IFN-γ production as examined by ELISA. Moreover, HBV significantly inhibited pDC-induced IFN-γ production by NK cells, independent of the stimulus used, whereas cytokine-induced IFN-γ production by NK cells cultured alone was not inhibited by HBV. In the presence of HBV, pDC-induced NK cell cytotoxicity towards K562 target cells was not significantly altered. Although HBV did not change IFN-α production by pDC, IL-6 production was decreased in cocultures with HBV, suggesting defective NK cell-induced pDC function. Since the presence of IL-10 inhibited IFN-γ production by NK cells without affecting their cytotoxic capacity, the role of IL-10 was investigated. IL-10 receptor neutralization partly restored the impaired IFN-γ production in pDC/NK cell cocultures with HBV, which suggests that IL-10 could be one of the factors induced by HBV to disturb pDC/NK interaction. These data show that HBV is not only a weak inducer of innate immunity, but also actively interferes with the functional interaction between pDC and NK cells leading to diminished cytokine production by pDC and NK cells without affecting NK cell cytoxicity. The lack of activation as well as the active interference with innate immunity may both contribute to HBV persistence.

Novel semi-synthetic flavonoid monoHER prevents monocrota induced sinusoidal obstruction syndrome in rats

M.A.J. van den Broek[1], D.K. Dhar[2], T.M. Ezzat[2], N.A. Davies[3], A. Bast[4], M. Malagó[2], S.W.M. Olde Damink[1,2], [1]Dept. of Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands, [2]HPB Research Group, Dept. of Surgery, University College London, London, United Kingdom, [3]Liver Failure Group, Institute of Hepatology, University College London, London, United Kingdom, [4]Dept. of Toxicology and Pharmacology, Maastricht University Medical Centre, Maastricht, The Netherlands

The sinusoidal obstruction syndrome (SOS) is a frequent complication of oxaliplatin-based neoadjuvant chemotherapy for colorectal liver metastases. Approximately 60-70% of patients treated with oxaliplatin-based neoadjuvant chemotherapy show signs of sinusoidal injury. This sinusoidal injury is associated with an increased risk of morbidity after partial liver resection. Depletion of glutathione in sinusoidal endothelial cells is central in the pathophysiology of SOS. This study aimed to assess the protective effect of the antioxidant monoHER on the development of monocrota (MCT) induced SOS in rats. Male Sprague Dawley rats (n= 7 animals per group) received a single gavage of MCT (160mg/kg b.w.) to induce hepatic SOS. The intervention groups were treated with monoHER (500mg/kg b.w. i.p.) and the control groups with monoHER vehicle (NaOH i.p. in equivalent amount), starting 24 hr before MCT gavage and continuing once daily for 24 or 72 hrs. Seven animals in the intervention group and seven animals in the control group were sacrificed after 24 and 72 hrs. The primary endpoints were liver injury assessed by alanine aminotransferase (ALT) and portal pressure. The effect of monoHER combined with either oxaliplatin or MCT on proliferation and viability of 2 different human colorectal cancer cell lines (LoVo & LS174T) was studied by the colori-metric MTS assay. Data are given as mean ± SD. $P<0.05$ was considered statistically significant. ALT levels were significantly lower in monoHER treated rats when compared with controls (24h: 47 ± 15 vs. 73 ± 7, $p = 0.004$; and 72h: 103 ± 96 vs. 327 ± 171, $p= 0.029$). Also, there was a significant difference in portal pressure between intervention and control rats (24h: 7.43mmHg ± 0.94mmHg vs. 9.17mmHg ± 0.71mmHg, $p= 0.003$; and 72h: 8.57mmHg ± 1.26mmHg vs. 11.73 mmHg ± 2.78mmHg, $p = 0.018$). Oxaliplatin had a dose dependent growth inhibitory effect on colorectal cancer cells, whereas MCT had no effect. MonoHER had no effect on cell proliferation when used either alone or in combination with oxaliplatin or MCT (MTS-assay ≤ 10% difference between groups).
Conclusions: The flavonoid monoHER significantly prevented MCT induced sinusoidal injury and portal hypertension in rats. Furthermore, monoHER could be used safely along with oxaliplatin without interfering with its cytotoxic effect. MonoHER may serve as a novel preventive strategy for oxaliplatin induced SOS in man. Further studies are ongoing to elucidate the mechanism(s) of action of monoHER.

Myeloperoxidase promotes progression of non-alcoholic steatohepatitis in mice

S.S. Rensen[1], V. Bieghs[2], E. Arfianti[1,#], J.A. Bakker[3], R. Shiri-Sverdlov[2], J.W. Greve[1,4], W.A. Buurman[1], [1]Dept. of Surgery, [2]Dept. of Genetics and Cell Biology, [3]Dept. of Clinical Genetics, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, [4]Dept. of Surgery, Atrium Medical Centre Parkstad, Heerlen, The Netherlands, [#]Currently at the Dept. of Medical Biology, Riau University, Indonesia

Chronic inflammation and oxidative stress play fundamental roles in the pathogenesis of non-alcoholic steatohepatitis (NASH). Previously, we found that myeloperoxidase (MPO), an important neutrophil enzyme that generates aggressive oxidants, is associated with NASH severity in man. We now generated low-density lipoprotein receptor-deficient mice with an MPO-deficient hematopoietic system ($LDLR^{-/-}/MPO^{-/-}$ mice) to investigate the hypothesis that MPO plays an active role in the development of NASH. High-fat feeding caused a ~4-fold induction of liver MPO in $LDLR^{-/-}/MPO^{+/+}$ mice and was associated with hepatic sequestration of MPO-positive cells and high levels of nitrotyrosine, a marker of MPO activity. Importantly, $LDLR^{-/-}/MPO^{-/-}$ mice showed substantially reduced hepatic neutrophil and T-lymphocyte infiltration, and strong downregulation of pro-inflammatory genes such as TNF-α and IL-6. Visceral adipose tissue inflammation was markedly reduced as well, with a complete lack of macrophage crown-like structures in $LDLR^{-/-}/MPO^{-/-}$ mice. Next to the generalized reduction of inflammation, liver cholesterol accumulation was significantly diminished in $LDLR^{-/-}/MPO^{-/-}$ mice. Moreover, MPO deficiency attenuated the development of hepatic fibrosis as evident from reduced hydroxypro levels. Collectively, these results show that MPO is a driving factor in the development of NASH, and support an important role for neutrophils in the pathogenesis of metabolic liver disease.

Regulation of hCTR1-dependent cellular copper uptake by heteromerization with the homologous hCTR2 copper transporter

P.V.E. van den Berghe, L.W.J. Klomp, Dept. of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, The Netherlands

The transition metal copper is an essential trace element for all organisms that utilize oxygen. Its potential toxicity dictates a delicate balance between copper import and copper export to maintain copper homeostasis. Disturbances of cellular copper export result in severe disorders like the autosomal recessive hepatic copper overload disorder, Wilson's disease. Intestinal dietary copper uptake is critically dependent on the high-affinity human copper transporter 1 (hCTR1), whereas hepatic copper uptake is not solely dependent on hCTR1 expression. Biochemical and structural analyses indicated that hCTR1 forms oligomeric complexes. Similar results were obtained for the homologous low-affinity human copper transporter 2 (hCTR2). This study aimed to characterize the formation of hCTR1 and hCTR2 oligomers and to assess the functional role of homomerization and heteromerization in cellular copper uptake. Expression of hCTR1 resulted in strong activation of a cytoplasmic copper sensor, with maximal induction at 1 μM $CuCl_2$. In contrast, expression of hCTR2 resulted in copper-dependent reporter activation starting at a concentration of 20 μM $CuCl_2$. hCTR1- or hCTR2-dependent copper uptake was completely abolished by conversion of two highly conserved methionine residues in the second transmembrane region of hCTR1 or hCTR2 into isoleucines (hCTR1 M150I-M154I or hCTR2 M111I-M115I). hCTR1- dependent copper uptake was inhibited in a dominant-negative manner when wild type hCTR1 and hCTR1 M150I-M154I were co-expressed, suggesting that the functional unit of CTR1 is composed of oligomers. Indeed, hCTR1 M150I-M154I subunits interacted with wild type hCTR1. Interestingly, co-expression of hCTR1 and hCTR2 resulted in decreased hCTR1-dependent copper uptake at 1 μM $CuCl_2$, and hCTR1-dependent copper uptake was even further inhibited by co-expression with hCTR2 M111I-M115I. This suggests a functional interaction between hCTR1 and hCTR2. Importantly, co-immunoprecipitation after chemical cross-linking revealed that hCTR1 and hCTR2 form heteromeric complexes. Finally, the plasma membrane localization of hCTR1 was almost completely abolished by co-expression of hCTR2, resulting in co-localization of both proteins in a vesicular compartment.
In conclusion, these data provide biochemical and functional evidence that hCTR1 and hCTR2 form homomeric and heteromeric complexes with different copper-transport kinetics. This enables a novel regulation mechanism of hCTR1-dependent copper uptake by regulation of hCTR2 expression.

Changes in transmembrane lipid distribution in human erythrocytes as a possible cause for Ribavirin-induced anemia

K. Mast[1], M.C. Kleinegris[1], J.M. Balk[2], G.R.M.M. Haenen[2], A. Bast[2], G.H. Koek[1], E.M. Bevers[3], [1]Dept. Internal Medicine, Maastricht UniversityMedical Centre, [2]Dept. Pharmacology and Toxicology and [3]Dept.Biochemistry, Maastricht University, The Netherlands

Ribavirin (RBV), an antiviral nucleoside analogue, is one of the drugs of choice for the treatment of chronic hepatitis C. However, a clinically relevant adverse effect of this drug is severe anemia. We explored the possibility that RBV-induced anemia is caused by alterations in the normal asymmetric lipid distribution of the erythrocyte membrane. Phospholipids in the plasma membrane of eukaryotic cells are asymmetrically distributed over both leaflets of the bilayer. The outer leaflet is dominated by the choline-containing phospholipids, phosphatidylcholine and sphingomyelin, whereas the inner leaflet mainly consists of the aminophospholipids, phosphatidylserine (PS) and phosphatidylethanolamine. Several lipid transporters control this asymmetric distribution, of which aminophospholipid translocase is the most important, being responsible for an active inward directed transport of aminophospholipids. Several physiological conditions can give rise to a collapse of lipid asymmetry, mediated by a protein called scramblase. As a conesquence, PS becomes exposed in the outer leaflet of the plasma membrane. Surface exposed PS, which is a hallmark of cells that undergo apoptosis, forms a so-called 'eat me' signal for macrophages to engulf cells before releasing their inflammatory contents.
We hypothesize that RBV interferes with the mechanism(s) that control membrane lipid asymmetry, leading to increased surface exposed PS and subsequent removal of these cells by the reticulo-endothelial system. Erythrocytes from healthy donors were exposed to RBV and PS exposure was measured by flow cytometry, using fluorescent-labeled Annexin V, a protein which specifically binds PS. We found that up to 30-40% of the cells became annexin positive after 4-5 days incubation of washed erythrocytes with 1 mM RBV. PS exposure was not due to loss of membrane integrity (hemolysis less than 5%) and was found to be partially dependent on the presence of extracellular Ca^{2+} ions. Incubation with RBV was also accompanied by changes in cell volume and cell morphology. The effect of RBV on aminophospholipid translocase and scramblase activity is under current investigation.
In conclusion: RBV-induced anemia may be caused by a disturbance of the normal transbilayer lipid distribution in the erythrocyte membrane, leading to PS-mediated uptake by macrophages.

Multi-Band Mucosectomy in Barrett Esophagus: a prospective registration of 1060 resections in 243 procedures

L. Alvarez Herrero[1,2], R.E. Pouw[2], B.L. Weusten[1], J.J. Bergman[2], [1]Dept. of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

Multi-Band Mucosectomy (MBM) is a relative new technique for endoscopic resection (ER) in Barrett Esophagus (BE). This suck-and-cut technique uses a modified variceal band ligator which allows for up to 6 consecutive resections without prior submucosal lifting. The aim was to prospectively evaluate the safety of MBM and to evaluate its efficacy for complete endoscopic removal of predefined focal lesions in BE. Prospective registration of all MBM procedures in BE was performed between Nov'04-Oct'09. Prior to MBM, the target area was delineated with electrocoagulation markers followed by ERs until the delineated area, including all markers, was resected. Pts were discharged after 2-4 hrs observation and followed up by telephone at 24 hrs and 2 wks. Primary endpoints were the number of acute (during procedure) and early (<1 week) complications and the rate of complete endoscopic removal of the delineated focal lesion. 243 MBM procedures, with a total number of 1060 resections, were performed in 170 BE pts (median age 68 [IQR 61-75]; 150 male). MBM was performed for focal lesions in 113 procedures (32 en-block; 81 piecemeal (279 resections; median 3 [IQR 2-5])), for removal of BE as part of a (stepwise) radical ER protocol in 117 procedures (713 resections; median 5 [IQR 3-9]) and for escape treatment after radiofrequency ablation in 13 procedures (36 resections; median 2 [IQR 1-3]). Acute complications occurred in 7/243 procedures (2.9% [95% CI 1.4-5.8%]): all bleedings treated with standard endoscopic therapy during the procedure and graded as "mild". Pts were observed for 1-2 days and only 1 pt underwent elective endoscopic re-inspection. Despite the absence of submucosal lifting no perforations occurred in 1060 MBM resections (0% [95% CI 0-0.4%]). Early complications consisted of 5/243 delayed bleedings (2.1% [95% CI 0.9%-4.7%]), 4 occurring within 48 hrs and 1 after 6 days. All delayed bleedings were effectively managed endoscopically and graded as "moderate". Bleedings were significantly more frequent after MBM of focal lesions. Complete resection of targeted area was achieved in 103/113 (91% [95% CI 84%- 95%]). All failures were due to scarring of the tissue after prior ulceration prohibiting suctioning of tissue into the MBM-cap ($p<0.001$).

Conclusions: This is the largest prospective series of MBM in BE. Despite the absence of submucosal lifting, perforations did not occur. Post-MBM bleeding occurs in approximately 2% and can generally be managed endoscopically. MBM allows for effective removal of the delineated target area in the vast majority of cases unless the area is scarred due to prior ulceration or endoscopic therapy.

Safety outcomes of balloon-based circumferential radiofrequency ablation after focal endoscopic resection of early Barrett's neoplasia in 118 patients: results of an ongoing European multiCentre study

R.E. Pouw[1], R. Bisschops[2], O. Pech[3], K. Ragunath[4], B.L. Weusten[5], B. Schumacher[6], B. Rembacken[7], A. Meining[8], H. Messmann[9], E.J. Schoon[10], L. Gossner[11], J. Mannath[4], C.A. Seldenrijk[12], M. Visser[13], A. Leruth[14], J. Devière[15], T. Rösch[16], S. Seewald[16], F.J. ten Kate[13], C. Ell[3], H. Neuhaus[3], J.J. Bergman[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology and Endoscopy, University Hospitals Leuven, Leuven, Belgium, [3]Dept. of Internal Medicine II, Dr. Horst-Schmidt-Kliniken, Wiesbaden, Germany, [4]Division of Gastroenterology, Wolfson Digestive Diseases Centre, Nottingham, UK, [5]Dept. of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, The Netherlands, [6]Dept. of Gastroenterology, Evangelisches Krankenhaus Düsseldorf, Düsseldorf, Germany, [7]Dept. of Gastroenterology, The General Infirmary at Leeds, United Kingdom, [8]Second Medical Dept. Technical University of Munich, Munich, Germany, [9]Third Medical Clinic, Klinikum Augsburg, Augsburg, Germany, [10]Dept. of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands, [11]Dept. of Medicine I, Klinikum Karlsruhe, Karlsruhe, Germany, [12]Dept. of Pathology, St. Antonius Hospital, Nieuwegein, [13]Dept. of Pathology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands, [14]Dept. of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium, [15]Dept. of Gastroenterology and Hepatology, Erasme University, Brussels, Belgium, [16]Dept. for Interdisciplinary Endoscopy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

In patients with a Barrett's esophagus (BE) containing high-grade dysplasia (HGD) or early cancer (EC), endoscopic resection (ER) of visible lesions followed >6 weeks later by step-wise radiofrequency ablation (RFA) for residual BE is highly effective, however, limited data is available related to the adverse event profile of this approach. Aim was to evaluate the frequency and severity of adverse events related to balloon-based circumferential RFA of BE >6 weeks after ER. This prospective European trial is conducted at 13 tertiary referral Centres with expertise in BE neoplasia. Investigators were trained at the coordinating site and the first 4 RFA cases were supervised on-site by the principal investigator. The coordinating study team attended all treatment sessions and first follow-up at each site to maximize protocol compliance and to standardize technique. A single expert pathologist interpreted all ER specimens, post-ER/pre-RFA and post-RFA biopsies. Eligibility criteria: BE ≤12cm with HGD/EC; ER of visible lesions pre-RFA (ER <2cm length; <50% circumference); no invasion >T1sm1; no N+ on EUS; 2 endoscopies post-ER/pre-RFA with 4-quad/2cm biopsies to exclude residual EC. At least 6 weeks after ER, balloon-based circumferential RFA was performed, followed every 2-3 months by additional RFA until clearance of BE achieved. A total of 118 patients (96 male, mean age 65yrs, median BE length 6cm) underwent en-bloc (n=57) or piecemeal ER (n=61, median 3 (IQR 2-4) pieces/session). Worst ER histology: EC (n=75), HGD (n=35), LGD (n=5), no dysplasia (n=3). Worst histology post-ER/pre-RFA: HGD (n=30), LGD (n=50), no-dysplasia (n=38, all had HGD/EC in ER). Acute adverse events included superficial mucosal laceration evident after inflation of the RFA balloon: at the ER scar (n=10, 8.5%) or at a reflux stenosis (n=2, 1.7%), none required intervention. One delayed adverse event occurred: melena (n=1, 0.8%), no intervention was required. All adverse events were categorized on the protocol case report forms as "mild". By November 2009, 55 patients completed treatment: complete eradication of neoplasia (CR-N) and intestinal metaplasia (CR-IM) was achieved in 55/55 (100%) and 53/55 (96%) patients, respectively.

Conclusion: This is the largest prospective multiCentre study combining ER and RFA for treatment of HGD/EC in BE. Our safety outcomes suggest that when performed by trained, expert endoscopists in carefully selected patients after limited ER for staging purposes, adverse events related to balloon-based RFA are infrequent and mild. Interim efficacy outcomes from 55 patients (CR-N 100%, CR-IM 96%) are very favorable and comport with those from other studies.

Simultaneous (same session) radiofrequency ablation and endoscopic resection is feasible, safe and effective for selected cases of early neoplasia in Barrett's esophagus

F.G.I. van Vilsteren[1], R.E. Pouw[1], L. Alvarez Herrero[2,1], M. Visser[3], F.J. ten Kate[3], B.L. Weusten[2,1], J.J. Bergman[1], [1]Gastroenterology, Academic Medical Centre, Amsterdam, [2]Gastroenterology, St Antonius hospital, Nieuwegein, [3]Pathology, Academic Medical Centre, Amsterdam, The Netherlands

Background: Endoscopic resection (ER) of visible mucosal lesions followed by radiofrequency ablation (RFA) after 3 months is safe and effective for eradication of Barrett's esophagus (BE) with high-grade dysplasia (HGD) and early cancer (EC ≤T1sm1). Circumferential balloon-based RFA (c-RFA) is the preferred primary RFA modality after ER, allowing for uniform ablation of the entire remaining BE. However, ER-related scarring after more extensive ER creates challenges for c-RFA, such as non-uniform electrode contact, risk for mucosal laceration and severe stenosis. Therefore, we have limited the extent of ER prior to c-RFA (ER<2 cm, <50% circ) to avoid these issues. In selected patients, however, it may be necessary to resect more tissue to stage the lesion and render the mucosa flat prior to RFA. For these cases, we hypothesized that c-RFA immediately followed by ER in the same session would avoid the impact of scarring on delivery of c-RFA and reduce the risk for laceration and severe stenosis. Methods: Patients had a BE >3 cm and at least 1 visible lesion (HGD/EC) and all signed informed consent (ethics committee approved trial). During endoscopy, visible lesion(s) were marked with cautery. C-RFA (12 J/cm^2) was delivered using 2 applications and a cleaning step. Each marked lesion was then resected using multi-band mucosectomy. Outcome Measures: Procedure time; feasibility of ER after c-RFA; acute and delayed adverse events; quality of ER specimens; regression of BE surface area at 3 months. Results: Eleven patients (10 male, median age 67 yrs, median BE C6M8) underwent c-RFA and ER with median 4 (IQR 2-5) ER specimens per patient. ER after c-RFA was technically similar as in RFA-naïve mucosa. Median procedure time was 53 min (IQR 46-75). There were no lacerations or other acute adverse events. One patient developed mild dysphagia due to ER scarring, resolving after 1 dilation. ER-specimens allowed for assessment of neoplasia depth, differentiation, and lymphatic/vascular invasion. Worst grade of ER histology by patient was EC (n=8) and HGD (n=3). Median regression of BE surface area at 3 months was 90% (IQR 88-96).
Conclusions: Circumferential balloon-based RFA followed by ER in the same session appears to be feasible and safe. ER after c-RFA was technically similar as in RFA-naïve mucosa and all ER specimens allowed for staging of histology. C-RFA lacerations were avoided and a single case of stenosis after combined therapy was mild. This combined approach may be a safe, effective, and perhaps more efficient option for selected patients with HGD/EC who require more extensive ER at baseline.

A prospective, group sequential study evaluating a new type of fully covered self expandable metal stent with a proximal retrieval lasso for the treatment of benign biliary strictures

J.W. Poley[1], D. Cahen[1], G. Kazemier[2], H.J. Metselaar[1], J. Haringsma[1], C.H.J. van Eijck[2], E.J. Kuipers[1], M.J. Bruno[1], Dept. of Gastroenterology & Hepatology[1] and Surgery[2], Erasmus MC, University Medical Centre Rotterdam, The Netherlands

Background: the use of fully-covered self expandable metal stents (fcSEMS) has shown promise in the treatment of benign biliary strictures. Key to this novel treatment is safe removal. Pulling the stent at its distal end can be complicated since the entire surface area has to detach from the wall of the common bile duct at the same time.Aim: we investigated the feasibility and safety of stent removal of a fcSEMS (MITech, Korea) with a proximal retrieval lasso: a long wire thread integrated in the proximal ends of the wire mesh that hangs freely in the stent lumen. Pulling it enables gradual removal of the stent inside-out. Secondary aim was success of stricture resolution.Methods: non-randomized, prospective follow-up study with 3 sequential groups of 8 patients with benign biliary strictures. Patients eligible for inclusion had iatrogenic bile duct strictures (post-cholecystectomy (LCx) or liver transplantation (OLT)), strictures due to chronic pancreatitis (CP), or papillary fibrosis (PF). Strictures had to be located at least 2 cm below the liver hilum. The first cohort of patients underwent stent placement for 2 months, followed if necessary by 3 months. The second cohort started with 3 months, followed by 4 months and the last cohort underwent stent placement for 4 months twice if the stricture did not resolve after the first period. Treatment success was defined by cholangiography and the ability to pass an inflated extraction balloon through the former stricture.Results: 24 patients (11 female; 20–67 yrs) have been included. Strictures were caused by CP (13), OLT (6), LCx(3) and PF(2). At present 40 fcSEMS have been placed and 27 removed. Removals were easy and without complications. Stent placement led to transient pain in 14 of 24 (60%) patients that in all cases could be managed by analgesics. Other complications were cholecystitis (1, managed by percutaneous drainage), cholangitis due to stent migration (1, managed by stent replacement) or stent clogging (2, managed endoscopically) and worsening of CP (2). In these patients, the fcSEMS was removed and replaced after pancreatic sphincterotomy and stent placement. After the first case of cholecystitis, patients with gallbladder in situ, received prophylactic antibiotics. At present, 11 patients have finished the protocol; treatment was successful in 73%.
Conclusions: removal of a new type of fcSEMS with a proximal retrieval lasso proved easy and uncomplicated, even after 4 months. Attention must be given to the prevention of cholecystitis and outflow obstruction of the pancreatic duct. Follow-up data are awaited to evaluate treatment success and to determine the optimal treatment duration.

A multi-centre randomized cross-over trial comparing Endoscopic Trimodal Imaging (ETMI) with standard endoscopy (SE) for the detection of dysplasia in Barrett's esophagus (BE) in patients with a confirmed diagnosis of low-grade dysplasia (LGD) performed in a non-university setting

WL Curvers[1], F.G.I. van Vilsteren[1], L.C. Baak[2], C. Böhmer[3], R.C. Mallant-Hent[4], A.H. Naber[5], A. van Oijen[6], C.Y. Ponsioen[1], P. Scholten[7], E. Schoon[8], E. Schenk[9], G.A. Meijer[10], F.J. ten Kate[11], J.J.G.H.M. Bergman[1], [1]Dept. of Gastroenterology and Hepato-logy, Academic Medical Centre, Amsterdam, [2]Dept. of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, [3]Dept. of Gastroenterology and Hepatology, Spaarne Hospital, Hoofddorp, [4]Dept. of Internal Medicine, Flevohospital, Almere, [5]Dept. of Internal Medicine, Tergooi Hospitals, Hilversum, [6]Dept. of Gastroenterology and Hepatology, Medical Centre Alkmaar, Alkmaar, [7]Dept. of Gastroenterology and Hepato-logy, St Lucas Andreas Hospital, Amsterdam, [8]Dept. of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, [9]Dept. of Gastroenterology and Hepatology, Isala Clinics, Zwolle, [10]Dept of Pathology, Free University Medical Centre, Amsterdam, [11]Dept. of Pathology, Academic Medical Centre, Amsterdam, The Netherlands

Introduction: ETMI incorporates high-resolution endoscopy (HRE), autofluorescence imaging (AFI) and narrow band imaging (NBI) in a single system. Recent studies suggest that ETMI may improve the detection of dysplasia (DYS) (e.g. LGD, HGD and carcinoma) in BE up to 90%. These studies, however, were a) uncontrolled, b) performed in tertiary referral centres by BE-experts, and c) included patients with a high-risk profile for DYS. Aim: To compare ETMI with standard endoscopy (SE) for the detection of DYS in a) a randomized-cross over design, b) performed by general endoscopists, c) in pts with an intermediate risk profile for DYS. Methods: This is a multi-centre randomized cross-over study in 8 non-university centres. BE pts with a prior diagnosis of LGD, confirmed by a panel of expert GI-pathologists, were eligible. After randomization, either SE or ETMI was used for the first procedure followed by the other technique within an interval of 6-16 weeks. Both procedures were performed by two different general endoscopists with no specific expertise in BE imaging. The endoscopist assigned to the second procedure was blinded for the results of the first procedure. During SE targeted Bx were obtained from all visible lesions followed by 4q/2cm random Bx. During ETMI, BE was inspected with HRE followed by AFI. All visible lesions were then inspected with NBI and biopsied followed by 4q/2cm Bx. The combined histological outcome of both procedures was regarded as gold standard. Results: 92 pts have been included, 4 patients were excluded. 88 pts (70 male; 63 yrs SD 10) completed both procedures. DYS was detected in 61 pts (69%). Sensitivity for the overall detection of DYS with SE was 0.79 compared to 0.85 for ETMI ($p = 0.53$). Sensitivity for the targeted detection of DYS with SE was 0.34 compared to 0.54 for ETMI ($p < 0.01$). SE detected 73 suspicious lesions of which 26 contained DYS (FP-rate 64%). ETMI detected 139 lesions (HRE: 71; AFI: 68) of which 45 contained DYS (FP-rate 68%). 22 lesions containing DYS were detected with AFI only. After detailed inspection with NBI the FP-rate of ETMI was reduced to 43% but 5 lesions with DYS were misclassified as being “NBI-normal”. There was no difference in detection rate for HGD or carcinoma between ETMI and SE.
Conclusion: ETMI did not improve the overall detection of DYS in BE compared to SE. AFI detected 22 additional DYS lesions that were missed with HRE resulting in a significantly higher targeted detection rate for ETMI compared to SE. NBI marginally reduced the FP-rate of ETMI at the expense of misclassifying 5 lesions containing DYS as unsuspicious.

Endoscopic Tri-modal Imaging (ETMI) for the detection and classification of early colorectal neoplasia; a multi-centre randomized controlled trial

T. Kuiper[1], F.J.C. van den Broek[1], A.H. Naber[2], E.J. van Soest[3], P. Scholten[4], R.Ch. Mallant - Hent[5], J. van den Brande[2], J.M. Jansen[6], A.H.A.M. van Oijen[7], W.A. Marsman[3], J.J.G.H.M. Bergman[1], P. Fockens[1], E. Dekker[1] , [1]Academic Medical Centre, Dept of Gastroenterology, Amsterdam,[2]Tergooi hospitals, Hilversum [3]Kennemer Gasthuis, Haarlem [4]St Lucas Andreas Hospital, Amsterdam [5]Flevohospital, Almere [6]OLVG, Amsterdam [7]Medical Centre Alkmaar, Alkmaar, The Netherlands

Introduction Endoscopic Tri-modal Imaging (ETMI) is a novel technique which combines high-resolution endoscopy (HRE), autofluorescence imaging (AFI) and narrow band imaging (NBI) and may improve the detection and differentiation of colonic lesions. ETMI has only been subjected to research in expert settings. This randomized controlled multi-centre study compared ETMI with standard video endoscopy (SVE) for the detection and differentiation of early colorectal neoplasia in a non-expert setting. Methods: Patients undergoing colonoscopy in non-academic hospitals for screening or surveillance were randomized to undergo either ETMI or SVE. All segments were inspected twice. In the ETMI group, first inspection was done with HRE followed by inspection with AFI. In the SVE group, inspection was performed twice with SVE. All detected lesions were inspected by AFI for colour and by NBI for pit pattern analysis. The calculated sample size of this study was 234 patients (117 per group). Enrolment is anticipated to be complete in January 2010. Results: Up to date, 210 patients have been randomised (119 males, mean age 57 yrs), 102 to the ETMI group and 108 to the SVE group. In the ETMI group, 175 lesions (80 adenomas) were detected during first inspection with HRE. During second inspection with AFI, 68 additional lesions (35 adenomas) were found.In the SVE group, 181 lesions (75 adenomas) were detected during first inspection and 89 additional lesions (25 adenomas) during second inspection. There was no significant difference in adenoma detection rate between the two groups ($p= 0.386$), despite a longer withdrawal time in the ETMI group (12.10 vs. 14.40 minutes, $p<0.001$).The adenoma miss rates of HRE and SVE were 30.4% and 25.0 %, respectively ($p= 0.172$). The sensitivity, specificity and accuracy of NBI for differentiating adenomatous from non-adenomatous tissue were 88%, 66% and 76%. Corresponding figures for AFI were 91%, 36% and 62%. When combining AFI and NBI, the corresponding figures were 88%, 58% and 74%.
Conclusion Our preliminary results show that ETMI does not improve the adenoma detection rate compared to SVE in a non-expert setting. Furthermore, the additional value of AFI on top of HRE proved unsatisfactory. Both NBI and AFI had high sensitivities and low specificities in the differentiation of colonic lesions. Also, the accuracy of AFI and NBI together for differentiating lesions was not or only marginally higher than the accuracy of AFI or NBI alone.

Post-polypectomy surveillance practice of adenoma patients – considerable room for improvement

E M B van Heijningen[1], I. Lansdorp-Vogelaar[1], E.J. Kuipers[2], M. van Ballegooijen[1], [1]Dept. of Public Health, Erasmus MC, Rotterdam, [2]Dept. of Gastroenterology and Hepatology and Dept. of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

Surveillance colonoscopy (SC) is effective in reducing CRC mortality in adenoma patients. In the Netherlands, until 2001, it was recommended that newly diagnosed adenoma patients have SC 1 year after index colonoscopy (IC). Current surveillance guidelines, launched in January 2002, recommend all patients with ≥3 adenomas to have SC after 3 years and patients with <3 adenomas to come back for SC after 6 years. For (cost-) effectiveness of surveillance, guide adherence is mandatory. The aim of this study was to determine the adherence to SC guidelines. 10 hospitals throughout the Netherlands agreed to collaborate and had electronic files for endoscopies. We used the nationwide network and registry of histo- and cytopathology in the Netherlands to select newly diagnosed adenoma patients in these 10 hospitals from 1988 to 2002. Electronic medical records were reviewed until December 1, 2008 to obtain follow-up data for average risk adenoma patients (without hereditary cancer syndromes or inflammatory bowel disease). We divided patients into 2 groups, a group with IC before 2002 (A) and a group with IC in 2002 (B), according to the change in guideline. The follow up time after IC considered in the present analysis was the first 90 months. SC within a time interval of ±25% of the guideline-recommendation was considered adequate. 3066 patients (56.8% male, mean age 62.9 yrs, range 40 - 92) were analyzed. 2662 patients had their IC before 2002 (group A) and 404 in 2002 (group B) of which 1351 (51%) and 292 (72%) respectively had SC. A total of 1423 (46%) patients had no SC (86.4% for unknown reason, the remainder for reasons of death (4.5%), in adherence with physicians' decision (3.6%), old age (3.2%), co-morbidity (1.1%), refusal (0.8%), and removed colon (0.3%)). Median (inter quartile range, IQR) time to SC was 17 (12-36) and 26 (11-43) months for group A and B respectively (p=0.03). In group A, 35% had SC according to the guideline. In group B, 31 patients had ≥3 adenomas and 261 patients had <3 adenomas. In these subgroups, median (IQR) time to SC was 14 (11-34) and 27 (11-44) months, adequate surveillance was obtained in 19% and 15% respectively. According to national guidelines, the majority of adenomas patients received either no SC or too early SC in the Netherlands. Given the importance for effectiveness and efficiency, it is worthwhile investigating what the reasons are for non-compliance in post adenectomy surveillance.

Nurse endoscopists performing colonoscopy: a prospective study on quality and patient experiences

P.G. van Putten[1], F. ter Borg[2], R.P.R. Adang[3], M.E. van Leerdam[1], and E.J. Kuipers[1, 4], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, [2]Dept. of Gastroenterology and Hepatology, Deventer Hospital, Deventer, [3]Dept. of Gastroenterology and Hepatology, Viecuri Medical Centre, Venlo, [4]Dept. of Internal Medicine, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

Background: There is increasing interest and growing demand for nurses to perform colonoscopy. This is, among other factors, driven by the increased endoscopic demand resulting from colorectal cancer screening programs. Nurse endoscopists (NE) have shown to be competent and safe in gastroscopy and sigmoidoscopy. However, to date little is known about the performance of NE in colonoscopy. Aim: To assess endoscopic quality and patient experiences of NE performing full colonoscopy. Methods: Five trained NE were enrolled in a multiCentre prospective study. 100 consecutive colonoscopies of each NE were evaluated for endoscopic quality and patient experiences. The colonoscopies were performed under supervision of a gastroenterologist, using techniques and protocols of the participating hospitals. Patient experiences were measured using a questionnaire. Descriptive statistics were used to report the data. Results: Five NE; all women, median age 47 years (range 36-49), median number of performed colonoscopies before the start of the study 550 (range 260-2000). In total 500 colonoscopies were evaluated in 500 patients; mean age 55 years (SD±15), 61% women, and 98% ASA I or II. 97% of patients received conscious sedation with midazolam. Colonoscopies were performed for screening or surveillance in 39%, and for symptomatic indications in 61% of patients. The un-assisted cecal intubation rate was 92%, mean cecal intubation time was 15 minutes (SD±9), and mean withdrawal time was 10 minutes (SD±3). Adenoma detection rate was 24.8%. In 154 out of 500 procedures (31%) the NE required assistance for an advice, or help with a polypectomy or loop. Complication rate was 0.2%; one perforation. 363/500 patients (73%) completed the questionnaire. Overall, 345/363 patients (95%) were satisfied with the endoscopic procedure. 243/363 (67%) experienced no pain during the procedure, whereas 99/363 (27%) experienced moderate and 20/363 (6%) experienced substantial pain. Respondents were satisfied with the communicative and technical skills of the nurse endoscopists in 358/363 (99%) and 343/363 (95%) of cases, respectively. 259/363 respondents (71%) had no specific preference for a physician or nurse endoscopist, whereas 56/363 (15%) preferred a physician endoscopist and 48/363 (13%) preferred a nurse endoscopist. Considering colonoscopy waiting time for a NE and hereafter for a physician endoscopist to be 2 weeks shorter, respectively 246/363 (68%) and 234/363 (65%) of respondent preferred the colonoscopy at a shorter time interval.
Conclusion: Nurse endoscopists perform colonoscopies according to the international recognized quality standards, with high patient satisfaction.

Self-assessment in colonoscopy, a novel tool for assessment of skills

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

Introduction: Colonoscopy is a key diagnostic and therapeutic modality in gastro-enterology. Proficiency in advancing a colonoscope is usually obtained by structured skills training and performing several hundred procedures. To date there has been little attempt to comprehensively assess both generic and specific technical skills in flexible endoscopy. This study reports the results of a newly developed assessment tool for colonoscopy training. The purpose of this tool is to gain insight in individual learning curves and to create a self-awareness of individual strong and weak points.Methods: The Rotterdam Assessment Form (RAF) consists of a series of identical questionnaires that are filled out, each immediately following every colonoscopy. The questionnaire is divided in 3 parts. The first part covers objective data on depth of intubation and time taken. The second part invites trainees to subjectively judge their own performance on a visual analogue scale. The third part is repeated every 10 colonoscopies and encourages the trainee to extrapolate an improvement plan. Gastroenterology trainees performing colonoscopy in the Erasmus MC participated in this study. Filled out questionnaires are entered into a database and pooled in sets of 20 colonoscopies for each trainee.Results: A total of 1860 colonoscopies were self-assessed by 12 trainees. Seven trainees were evaluated from the start, 5 trainees were already in their last years of training. Initial adherence to self-assessment varied strongly among trainees ranging from 38 to 100% but increased after feedback to a median of 90%. The RAF took a median 36 seconds to complete. Cecal intubation rate was calculated and plotted in a learning curve as well as intubation time. The mean cecal intubation rate improved from 65% (range 45-80%) to 78% (range 65-95%) and 85% (range 80-90%) after performing 100 and 200 colono-scopies respectively. Cecal intubation time improved from 13:10 minutes (range 9-19) to 9:30 (range 7-13) and 8:30 (range 7-10). Trainers picked up problems sooner by studying the individual learning curves.
Conclusions: This novel self-assessment form provides insight in individual learning curves of colonoscopists in training. It provides data on the development of dexterity skills and stimulates trainees to develop steps for self-improvement.

Genomic and signal transduction events promoting insulinoma

E-J.M. Speel, Dept. of Molecular Cell Biology, GROW-School for Oncology & Developmental Biology, Maastricht University Medical Centre, The Netherlands

Insulinomas are the most common functioning endocrine pancreatic tumors (EPTs). They present with clinical symptoms as a consequence of hypoglycemia induced by inappropriate insulin secretion. The etiology of these tumors is poorly understood. Approximately 30% of the tumors are unresectable, and they often show different growth rates, which hampers treatment. Currently, no reliable clinical tests are available to differentiate benign from malignant tumors. Therefore, a better understanding of the molecular processes underlying insulinoma development and progression is required to improve diagnosis, prognosis and therapy.So far molecular studies from our research group have revealed that 1) only few sporadic tumors harbor mutations in the susceptibility gene of the multiple endocrine neoplasia type 1 (MEN1) syndrome, whereas most cases show wildtype MEN1, and neither promotor hypermethylation nor deregulated gene expression; 2) chromosome 9q gain is the most frequent, recurrent chromosomal abnormality in both benign and malignant insulinomas and pinpoints candidate genes that are overexpressed in insulinomas, including ABL1 and SHCc; 3) insulin-like growth factor (IGF) signalling appears to be more important than EGFR and Ras-ERK signalling in insulinoma tumorigenesis; and 4) chromosomal instability is the most powerful predictor of metastatic disease and poor survival.
In conclusion, the identification of genomic and signal transduction events is increasing our understanding of the molecular pathways involved in insulinoma tumorigenesis. In addition, these findings will pave the way for the identification of novel targets for therapeutical intervention and more reliable markers for clinical diagnosis and prognosis.

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Reduced small intestinal function in essential fatty acid (EFA) deficiency

S. Lukovac, E.H.H.M. Rings, H.J. Verkade, Pediatric Gastroenterology, Dept. of Pediatrics, Beatrix Children's Hospital, Groningen University Institute for Drug Exploration (GUIDE), Centre for Liver, Digestive and Metabolic Diseases, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

EFA deficiency is common in pediatric patients with cholestasis, where it is associated with fat malabsorption and severely impaired nutritional status. Often, EFA deficiency aggravates the cholestasis induced failure to thrive (CIFTT) in pediatric patients. In our laboratory, a mouse model for EFA deficiency has been developed. In mice and other species it has become apparent that EFA deficiency likely affects the small intestine. However, detailed information about the effects of EFA deficiency on the small intestine remained scarce. In order to improve the nutritional status of pediatric patients encountering EFA deficiency, insight into the pathophysiology of EFA deficiency, regarding the small intestinal function is essential. In mouse model for EFA deficiency, we analyzed the effects of EFA deficiency on the absorption and digestion of several nutrients and on the enterohepatic circulation of bile salts by means of a stable isotope dilution technique. Furthermore, we determined the effects of EFA deficiency on the small intestinal morphology. Finally, we performed in vitro experiments to determine the intracellular effects of EFA deficiency and to analyze whether some of the symptoms of EFA deficiency can be reversed. Our studies clearly show that EFA deficiency leads to a variety of functional changes in the small intestine. More specifically, lipid malabsorption and disaccharide digestion are impaired during EFA deficiency in mice. Increased intestinal reabsorption of bile salts is insufficient to normalize the decreased lipid absorption, underscoring previous implications that intracellular rather than intraluminal steps of fat absorption are impaired during EFA deficiency in mice. Short term supplementation of linoleic acid does not seem to reverse the effects of EFA deficiency on the small intestinal enterocytes as revealed by our in vitro study. In order to improve the nutritional strategies of CIFTT patients with EFA deficiency, studies on the effects of EFA deficiency on the intestinal function are warranted as the follow up to our presently obtained results in mice. Patients studies using stable isotope-labeled macronutrients, i.e. lipids, carbohydrates and proteins, will further assess nutritional status of children with CIFTT. We expect that these mechanistic nutritional studies will help to develop and improve nutritional therapies for pediatric patients with CIFFT awaiting liver transplantation.

Food matrix effects on bio-accessibility of β-carotene can be measured in an in-vitro gastrointestinal model

C.A. van Loo-Bouwman[1], T.H.J. Naber[1,2], M. Minekus[3], R.B. van Breemen[4], T. van Roekel-Jansen[5], P.J.M. Hulshof[5], G. Schaafsma[5,6], [1]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, [2]Dept. of Internal Medicine, Tergooi hospitals, Hilversum, [3]TNO Quality of Life, Zeist, The Netherlands, [4]Dept. of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois, Chicago, IL, USA, [5]Division of Human Nutrition, Wageningen University, Wageningen, [6]Research group on Sports, Nutrition and Lifestyle, HAN University, Nijmegen, The Netherlands

There is a need for a simple, quick and realistic in-vitro model to measure the effect of the food matrix on the digestion and absorption of nutritional components. The food matrix is an important determinant of the availability of β-carotene for intestinal absorption (bio-accessibility). In-vivo, the studies are biased by the metabolism of the nutrient. By application of an in-vitro model, only the bio-accessibility can be studied.The aim of this study was to investigate the food matrix effects on the bio-accessibility of β-carotene from the two diets by using an in-vitro gastrointestinal model and to compare the results with those of an in-vivo study. In that study, the ratio of apparent absorption of β-carotene was 1.9 between both diets. Further, the study offered the opportunity to investigate if extrinsically labelled β-carotene could be used as a tracer method for measurement of absorption in-vivo. The isotopic enrichment of β-carotene should be the same in the feeding sample as in the bio-accessible fractions.Two diets with different matrices were investigated: the 'mixed diet', containing β-carotene-rich vegetables and the 'oil diet', containing for 85% supplemental β-carotene in oil. A computer-controlled dynamic in-vitro gastric small-intestinal model was selected, which comprises four connected compartments that represent the stomach, duodenum, jejunum, and ileum. The total bio-accessible β-carotene amount over 6 hours as fraction of the amount of β-carotene in the feeding is the bio-accessibility of β-carotene. The bio-accessibility of β-carotene was 28% for the 'mixed diet' and 53% for the 'oil diet'. Supplemental β-carotene in the 'oil diet' was thus 1.9-fold more bio-accessible than β-carotene in the 'mixed diet' derived from β-carotene-rich vegetables. This ratio between the two diets confirmed the results from a diet-controlled experiment in humans. The labelled b-carotene was not equally distributed over time in the bio-accessible fractions, which meant that it did not fully mix with the β-carotene in the food matrix or follows a different micellarization pattern.In conclusion, the food matrix effects on bio-accessibility of β-carotene can be measured in this in-vitro model and was consistent with in-vivo data. The extrinsic labelling technique is not suitable for the measurement of matrix effects in-vivo.

Multiple common genetic variants for coeliac disease influencing immune gene expression

G Trynka[1], P.C.A. Dubois[2], L. Franke[1], C.J. Mulder[3], G.J. Tack[3], W.H.M. Verbeek[3], V.M. Wolters[4], R.H.J. Houwen[4], M.L. Mearin[5], Coeliac Disease Genetics Consortium[6], R. McManus[7],D. Barisani[8], P. Saavalainen[9], D.A. Van Heel[2], C. Wijmenga[1], [1]Genetics Department, University Medical Centre and Groningen University, The Netherlands, [2]Centre for Gastroenterology, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, UK, [3]Dept. of Gastroenterology, VU Medical Centre, Amsterdam, [4]Dept. of Paediatric Gastroenterology, University Medical Centre Utrecht, Utrecht, [5] Dept. of Paediatric Gastroenterology, Leiden University Medical Centre, Leiden, [6]The Celiac Disease Genetics Consortium, Groningen, The Netherlands and London, United Kingdom, [7]Dept. of Clinical Medicine, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland, [8]Dept. of Medical Sciences, University of Milan, Italy, [9]Dept. of Medical Genetics, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland

Coeliac disease is highly heritable. Our previous genome wide association study (GWAS) and follow-up studies identified 13 non-HLA celiac genomic risk regions. Known variants, including HLA variants, collectively explain around 35% of heritability. We proposed that additional common genetic variants underlie a further component of unexplained celiac heritability and that their identification would provide new insights into genes and pathways underlying coeliac susceptibility and pathogenesis. We performed a new coeliac disease GWAS in 4,533 cases and 10,750 controls from 4 populations of european descent. We integrated data from our first GWAS and expanded genomic coverage in new samples to 523,749 SNPs passing quality controls. In stage 2 we tested 131 SNPs from 14 previously reported, and 79 possible new coeliac risk loci obtaining $P_{GWAS} < 10^{-4}$ in a further 4,918 cases and 5,684 controls. We report variants from 13 new regions obtaining genome wide significance ($P_{combined} < 5 \times 10^{-8}$), including regions containing TNFRSF14, RUNX3, CCR4, CD80, BACH2, THEMIS, ZMIZ1, ETS1, CIITA/SOCS1/CLEC16A, ICOSLG. A further 13 regions had suggestive association evidence ($10^{-6}<P_{combined}<5x10^{-8}$, and/or $P_{follow-up} <0.01$). Genes from most regions influence aspects of immune function, the TNFRSF14, RUNX3, ETS1 and THEMIS associations intriguingly point to a role for thymic T cell selection. To investigate the function of coeliac variants we performed a genome-wide expression quantitative trait meta-analysis of 1,469 whole blood samples, demonstrating that variants at 53% of 38 tested non-HLA celiac loci, correlate with cis gene expression.
Conclusions: We report multiple new common variants for celiac disease and show that genetic determination of cis gene expression is a major mechanism by which these variants influence celiac susceptibility.

Survival in Enteropathy Associated T-cell lymphoma: type of lymphoma is not a prognostic factor

LR de Baaij[1], J.M.W. van de Water[1], W.H.M. Verbeek[1] and C.J.J. Mulder[1], [1]Gastro-enterology and Hepatology, VU University Medical Centre Amsterdam, The Netherlands

Background: Although the WHO classification of Enteropathy Associated T-cell Lymphoma (EATL) only distinguishes between two types of EATL (i.e. Type I is associated with celiac disease, Type II is not), in practice it appears that EATL Type I may present itself in two different forms. For one, there is the EATL that develops after a period of refractory celiac disease type II (EATL after RCDII). In the second form, EATL develops in patients with uncomplicated celiac disease, which is frequently diagnosed shortly before or at the same time as EATL (EATL de novo). So far, data about survival rates in both groups are limited. Hitherto only one study has been performed to investigate the survival rate according to the associated type of enteropathy, concluding that survival is significantly shorter in EATL after RCDII (Malamut et al, Gut 2009). Aims: To investigate the survival rates in EATL after RCDII and in EATL de novo. Materials and Methods: A retrospective study was performed of the medical files of 38 patients with EATL. Patients with EATL Type II were excluded (n=2). Kaplan-Meier curves and the Log-rank test were used to compare survival between the two groups. Results: From a total of 36 patients, 18 patients developed an EATL after RCD II (9M/9F) and 18 patients presented with EATL de novo (12M/6F). Mean age at diagnosis of EATL was 63 and 64 years respectively. In the group of 18 EATL after RCD II, 16 patients died. In the group of EATL de novo, 14 of 18 patients died. In both groups, 3 patients were treated with experimental stem cell transplantation, 5 of these patients died (after 6, 8.75, 11, 14.5, and 15 months). This experimental treatment did not influence the survival rate within the groups significantly (p= 0.246 and p= 0.686). The median survival time in EATL after RCD II and EATL de novo is 5.0 months (95% CI: 0.63-9.4) and 9.5 months (95% CI:1.8-17.2) respectively. Two-year survival in the EATL after RCDII group is 18%, whereas in EATL de novo this is 25%. The difference in survival rate between the two groups is not significant (p=0.351).
Conclusions: In contrast to other recently published data, we have found no significant difference in survival rates between EATL after RCDII and EATL de novo.

Prediction model for the diagnosis chronic upper gastrointestinal ischemia: diagnostic value of symptoms, radiological imaging and gastrointestinal tonometry

A. Sana[1], D. van Noord[1], Y. Vergouwe[2] , L.M.G. Moons[1], H.J.M. Verhagen[3], P.M.T. Pattynama[4] , E.J. Kuipers[1], P.B.F. Mensink[1], Dept. of Gastroenterology and Hepatology[1], Centre for Medical Decision Sciences[2], Vascular Surgery[3], Interventional Radiology[4] Erasmus MC - University Medical Centre, Rotterdam, The Netherlands

Diagnosing chronic upper gastrointestinal ischemia (CUGI) remains a clinical challenge. CUGI can develop in patients with gastrointestinal arterial stenosis, but most subjects with gastrointestinal arterial stenosis do not necessarily have symptoms because of abundant collateral circulation. The varying presenting symptoms are one of the factors hampering the establishment of a correct diagnosis in these patients. We therefore aimed to assess the added predictive value of visualization of the gastrointestinal arteries and tonometry (TM) for diagnosing CUGI on top of clinical parameters such as symptoms, medical history and physical examination. Patients referred for evaluation of suspected CUGI were consecutively included. All patients were asked to fill out a questionnaire concerning symptoms, risk factors and family history of cardiovascular disease. The gastrointestinal arteries were visualized using CT angiography, MR- angiography or conventional angiography. TM was used for evaluation of mucosal ischemia. After assessment of all diagnostics, a consensus diagnosis was reached in a multidisciplinary team. The used reference standard, i.e. definite diagnosis of CUGI, was persistent clinical response after adequate therapy at one year follow-up. Multivariable logistic regression was used to estimate the association between the predictors and the reference standard. First a model was fitted with clinical parameters, and subsequently, radiological imaging (model 2) and TM (model 3) were added to assess the added value of these tests. Discrimination was assessed with the concordance statistic (c-statistic). The clinical usefulness of the three models was assessed with the net reclassification index (NRI). In 2 ½ years time 186 patients were included. CUGI was diagnosed in 125 (67%) patients. Postprandial pain, weight loss, ever smoking, concomitant cardiovascular disease and presence of an abdominal bruit were the strongest predictors in the first model (c-statistic 0.66). Adding only radiological imaging to the prediction model (second model) improved the discriminative ability (c-statistic 0.82), while adding TM (third model) to the prediction model further improved the discriminative ability of the model (c-statistic 0.94). The third model classified patients with or without CUGI in 52% better than the first model.
Conclusion: Clinical parameters alone have a low predictive value for the correct diagnosis of CUGI. Addition of radiological imaging of the gastrointestinal arteries and gastrointestinal tonometry, both significantly improve the discriminative ability of the prediction model for the correct diagnosis of CUGI.

Loss of the guardians at the intestinal barrier: paneth cell apoptosis as a new phenomenon in human intestinal ischemia-induced bacterial translocation

J. Grootjans[1], C. Hodin[1], J.J. de Haan[1], K. Lenaerts[1], M. Hadfoune[1], J. Derikx[2], A.P. de Bruïne[3], R. van Dam[1], C.H.C. Dejong[1], W. Buurman[1], [1] Surgery, Maastricht University Medical Centre, Maastricht, [2]Surgery, Orbis Medical Centre, Sittard, [3]Pathology, VieCuri Medisch Centrum, Venlo, The Netherlands

Paneth cells (PCs), highly specialized cells in the crypts of the small intestine, actively sense bacterial presence and release anti-microbial proteins to prevent bacterial penetration. We hypothesized that PC viability is compromised during intestinal ischemia-reperfusion (I-IR), a phenomenon strongly associated with bacterial translocation. PC viability was studied using a unique human I-IR model. In 30 patients, 6 cm of healthy jejunum, to be removed for surgical reasons, was exposed to 30, 45, or 60 minutes of ischemia followed by 30 and 120 minutes of reperfusion (n=10 for each ischemic period). Tissue was collected at all timepoints. Double staining for lysozyme (PCs) and M30 (apoptosis) was performed to assess PC apoptosis. PC apoptosis was quantified by two independent observers. To investigate the consequences of PC apoptosis during I-IR, we studied bacterial translocation after selective PC-ablation in a rat intestinal hypoperfusion (IH) model. Male Sprague-Dawley rats were subjected to IH by withdrawal of 30-40% of their circulating volume (n=12). In 6 rats, PCs were selectively ablated by administering the zinc-chelator dithizone (0.1mg/g BW i.v.) prior to IH. Paneth cell ablation was confirmed with Western blot and immunohistochemistry for lysozyme, and bacterial translocation to mesenteric lymph nodes (MLN) was assessed. Bonferroni's multiple comparison (after significant one-way ANOVA) or Mann-Whitney-U test was used when appropriate.Double stainings revealed that 45 and 60 minutes of ischemia with 30 minutes of reperfusion resulted in PC apoptosis ($p<0.01$ and $p<0.001$, respectively), whereas other crypt cells were hardly affected. The number of apoptotic PCs correlated significantly with ischemia-time ($r^2=0.51$, $p<0.0001$). Apoptotic PCs were shed into the intestinal lumen, resulting in decreased PC numbers at 120 minutes of reperfusion ($p<0.01$). Using a rat IH model with selective PC ablation we found that absence of PCs during IH led to significantly more bacterial penetration to MLN ($p<0.01$) compared to IH alone, which was independent from physical barrier integrity damage.
In conclusion, we describe for the first time the occurrence of PC-apoptosis during human I-IR. The importance of this finding was demonstrated in a rat IH-model with selective PC-ablation, which revealed a crucial role for PCs in limiting bacterial translocation during intestinal ischemia.

Vitamin B_{12} deficiency in Patients with Chronic Pancreatitis: Not as rare as previously thought

R.C.G. Biesmans[1], A.G.H. Kessels[2], J.H.M. Brouns[3], P.P.C.A. Menheere[4], A.A.M. Masclee[1], Y.C.A. Keulemans[1], [1]Gastroenterology, Maastricht Universitary Medical Centre, Maastricht, [2]Epidemiology, Maastricht Universitary Medical Centre, Maastricht, [3]Dietetics and Nutrition, Maastricht Universitary Medical Centre, Maastricht, [4]Clinical Chemistry, Maastricht Universitary Medical Centre, Maastricht, The Netherlands

Background: Vitamin B_{12} (B_{12}) deficiency can cause a variety of symptoms including anemia and multiple neurological disorders. Clinical guidelines suggest determining B_{12} levels in all patients with chronic pancreatitis (CP) because of an increased risk for B_{12} deficiency. However, this advice is not evidence based because the scarce literature indicates that B_{12} deficiency is not a relevant problem in CP-patients with a prevalence of less than 6 percent[1]. Objectives: To determine the prevalence of B_{12} deficiency in a cohort of CP-patients and to investigate by which mechanisms these B_{12} deficiencies could be explained. Methods: Seventy-two CP-patients (48 males, 24 females; mean age 56.2 years) visiting our outpatient clinic were reassessed for serum B_{12} levels. A B_{12} level below 150 pmol/l was considered deficient according to regional age-matched controls. Faecal elastase and steatocrit measurements were examined as markers for respectively protease and lipase efficiency. We achieved anti-gastric parietal cell antibodies (AGPA) in B_{12} deficient patients to exclude intrinsic factor deficiency. Dietary intake of B_{12} was also recorded. Results: In our group of 72 CP-patients, 23 patients had a B_{12} deficiency (31.9 percent). We found an association between serum B_{12} and faecal elastase ($p = 0.01$). There was no association found between B_{12} and steatocrit ($p = 0.3$). B_{12} deficiency was more common in patients that had undergone pancreatic surgery (43.5 vs. 23.1 percent) but this difference was not significant ($p = 0.09$). Daily dietary B_{12} intake was sufficient in most B_{12} deficient patients (82.6 percent) and only three subjects in the B_{12} deficient group had positive AGPA (13.0 percent).
Conclusions: B_{12} deficiency in CP-patients is not as rare as suggested in past literature and is related to pancreatic protease deficiency. Lipase insufficiency and intestinal bacterial overgrowth play a less important role since we found no significant correlation. A deficient dietary intake and pernicious anemia were factors contributing to only a few B_{12} deficiencies. Based on this study we advise health care professionals to regularly check B_{12} levels in CP-patients – especially when faecal elastase is decreased – and supplement both B_{12} as well as pancreatic enzymes accordingly. 1. Glasbrenner B et al. Vitamin B12 and Folic Acid Deficiency in Chronic Pancreatitis: A Relevant Disorder? Klin Wochenschr 1991; 69:168-72.

Endoglin as indicator of metastatic neuroendocrine tumors of the pancreas

P. Kuiper[1], H.W. Verspaget[1], E.S.M. de Jonge-Muller[1], L.J.A.C. Hawinkels[2], I. Biemond[1], C.B.H.W. Lamers[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Molecular Cell Biology and Centre for Biomedical Genetics, Leiden University Medical Centre, Leiden, The Netherlands

Introduction & Aim. Neuroendocrine tumors of the pancreas are rare, highly vascularized tumors. Endoglin, a Transforming Growth Factor-β co-receptor, is a marker for angiogenic endothelial cells. Angiogenesis is required for tumor progression and the development of metastases. Recently, endoglin expression was found to be a prognostic marker in pancreatic carcinomas. However, the role of endoglin in neuroendocrine pancreas tumors has not been studied so far. The aim of the present study was to evaluate the expression and localization of endoglin in pancreatic neuroendocrine tumors, and to assess the role of this angiogenic marker in the prognosis of the patients.Materials & Methods. Tumor tissues (n=26) obtained from 21 patients with functional (n=16) and non-functional (n=10) pancreatic neuroendocrine tumors were subjected to endoglin immunostaining. Levels of endoglin were determined in tissue extracts (n=27) and pre- (n=16) and postoperative (n=14) serum samples of the patients.Results. High endoglin expression was observed in endothelial cells of newly formed blood vessels in all tumor samples. Tissue levels of endoglin were significantly increased in tumor tissues (n=19) compared to (associated) normal tissues (n=8), median 17.7 versus 1.9 ng/mg protein, p=0.03. Furthermore, primary tumor tissues of patients who had developed (lymph node or liver) metastases (n=8) showed higher endoglin levels than from those without metastases (n=6), median 18.5 versus 3.5 ng/mg protein, p=0.02. Moreover, metastatic tumor samples (n=5) showed higher endoglin levels compared to primary lesions (n= 14), median 44.4 versus 16.3 ng/mg protein. Immunostaining of endoglin demonstrated a similar pattern, with a higher expression on tumors with metastatic development. Endoglin expression and tissue levels did not show a relationship with survival of the patients. We also analyzed the soluble form of endoglin, which is considered to have anti-angiogenic properties, in the circulation of these patients, which revealed that post-operative serum endoglin levels are increased compared to preoperative levels, median 5.3 versus 4.4 ng/ml. Both showed, however, no significant relation with the presence of metastases.
Conclusion. Expression of the angiogenic cell marker endoglin is increased in patients with neuroendocrine pancreas tumors and a high expression was related to the presence of metastatic disease. Therefore, we conclude that increased endoglin expression is indicative of metastatic pancreatic neuroendocrine tumors.

Smoking induces pancreatic fibrosis in humans

E.J.M. van Geenen[1,2], M.M. Smits[1], T.C.M.A. Schreuder[1,5], D.L. van der Peet[4], E. Bloemena[3], C.J.J. Mulder[1], [1]Dept. of Gastroenterology & Hepatology, VU University Medical Centre, Amsterdam, [2]Dept. of Gastroenterology & Hepatology, Bronovo Teaching Hospital, The Hague, [3]Dept. of Pathology, VU University Medical Centre, Amsterdam, [4]Dept. of Gastrointestinal Surgery, VU University Medical Centre, Amsterdam, [5]Dept. of Gastroenterology & Hepatology, Slingeland Ziekenhuis, Doetinchem, The Netherlands

Introduction: Smokers are at risk for pancreatic cancer and other pancreatic diseases. Cigarette smoking also aggravates the risk of pancreatic cancer in patients with hereditary and chronic pancreatitis and results in a higher incidence of acute pancreatitis and relapses in chronic pancreatitis. Both pancreatic cancer and chronic pancreatitis are characterized by a progressive fibrosis. Recently, two studies on rats reported that tobacco smoking is associated with chronic pancreatic inflammation with fibrosis, and scarring of pancreatic acinar structures. In this study we aim to confirm a relation between cigarette smoking and pancreatic fibrosis (PF) in humans. Methods: In this retrospective study, pancreatic tissue acquired during autopsy was collected and revised. Pancreatic fibrosis (PF) was gradually scored by analyzing intra-lobular, extra-lobular and total PF: grade 0 (normal or mild; 0-25% PF), grade 1 (moderate; 25-50% PF), grade 2 (severe; >50%). Information on smoking habits was extracted from (electronic) medical files. Results: Of 900 autopsies, performed from January 2005 till December 2007, the minority of available histology material (n=111) was of significant quality to be included for analysis. Grade 2-3 total PF and intra-lobular PF was significantly more present in “smokers” versus “never smokers” (total: 42.9% vs 26.5%, p=0,027 and intra-lobular: 39.3% vs 15.6%, p=0.013), whereas no differences could be found between “never smokers” and “abstinent smokers” and “abstinent smokers” and “smokers”. When taking into account interlobular PF, no differences between all groups were observed.
Conclusion: To date no human study studied the effect of tobacco smoking on pancreatic tissue. We demonstrate for the first time that current cigarette smoking is associated with total pancreatic fibrosis and more specific intra-lobular pancreatic fibrosis, compared to non-smokers.

Does consultation of a dietician in chronic pancreatitis patients with exocrine insufficiency make a difference? a dutch national survey

E.C.M. Sikkens[1], D. Cahen[1], C.H. van Eijk[2], E.J. Kuipers[1], M.J. Bruno[1], [1]Dept. of Gastroenterology, Erasmus Medical Centre, Rotterdam, [2]Dept. of Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

Little is known about the enzyme dose, dietary behaviour/restrictions, and outcome after consultation of a dietician in patients with exocrine pancreatic insufficiency (EPI) due to chronic pancreatitis (CP). An anonymous questionnaire was distributed in August 2009 by the Dutch Association of Patients with Pancreatic Disorders to their members. Until October 2009, 348 questionnaires were returned. Outcomes of patients who reported to have had consultation of a dietician were compared to those who had not.333 patients completed the questionnaire and 225 (67.7%) suffered from CP of whom 142 (63%) had EPI. Of these, 26% (n=37, mean age 57±10 yrs) consulted a dietician (group A) and 74% (n=105, mean age 56±12 yrs) did not (group B). In group A, patients used a median dose of 150.000 FIP-E units of lipase per day (25th % 77.500, 75th % 200.000), equivalent to 6 capsules of 25.000 FIP-E units of lipase, while in group B this was 137.500 FIP-E units of lipase per day (25th % 75.000, 75th % 150.000), equivalent to 5.5 capsules of 25.000 FIP-E units of lipase ($p>0.05$). All preparations were enteric coated. The mean difference between the lowest ever reported and current bodyweight was 13.5±10.5 kg in group A vs. 10.7±9.0 kg in group B ($p>0.05$). In group A, 78.4% reported steatorrhea related complaints with a median score of 3 (25th % 1, 75th % 5) on a 7 point rating scale compared to 66.7% in group B with a median score of 3 (25th % 1, 75th % 4) ($p>0.05$). Both groups reported to have equal difficulties in maintaining weight (37.8% vs 43.8%, $p>0.05$). In both groups, the majority of patients had some kind of food restriction imposed by a dietician, physician or themselves (76% vs 64%, $p>0.05$); of fat (60% vs 54%), spicy food (11% vs 16%), sugar (19% vs 9%), and/or proteins (8% vs 9%). Patients in group A were significantly more satisfied with information they received about the use of enzymes than patients in group B ($p<0.005$). Apart from a higher patient satisfaction there are no apparent differences in the enzyme dose, weight increase, steatorrhea associated complaints, difficulties in maintaining weight, and food restrictions between patients who did or did not had consulted a dietician. Surprisingly, even in patients who consulted a dietician about 60% reported a restriction of fat intake, while this is hardly ever indicated with modern enzyme preparations provided the proper dose is prescribed. Given the observation that many patients continue to report steatorrhea associated complaints and difficulties maintaining weight, this questions the quality of dietary consultation and the advised enzyme dose.

Lipid-rich nutrition reduces enterocyte damage and controls inflammation in murine gram-negative sepsis

T. Lubbers[1], J.J. De Haan[1], M. Hadfoune[1], Y. Zhang[4], M.D. Luyer[1,2], D. Grundy[4], W.A. Buurman[1], J.W. Greve [1,3], [1]Dept. of Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre+, Maastricht, [2]Dept. of surgery, Maasland Hospital, Sittard, [3]Dept. of Surgery, Atrium Medical Centre, Heerlen, The Netherlands, [4]Dept. of Biomedical Science, University of Sheffield, Sheffield, United Kingdom

Aim: Loss of intestinal integrity has been attributed a prominent role in the dysregulated inflammatory state of sepsis. Previously, our group demonstrated in a rat hemorrhagic shock model that lipid-rich enteral nutrition preserves intestinal integrity and reduces inflammation via a neuroimmune pathway in which cholecystokinin (CCK)-receptors and nicotinic receptors are involved. The current study investigates the potential of lipid-rich nutrition to attenuate enterocyte damage and inflammation in a murine model of gram-negative sepsis and delineates the mode of action. Materials: Male C57bl6 mice were subjected to a bolus of lipopolysaccharide (LPS) derived from E. Coli (2 mg/kg, i.p.). Prior to LPS administration, mice were fasted or fed lipid-rich nutrition enriched with 30% phospholipids or control low-lipid nutrition. Mesenteric afferent discharge was measured in response to both nutritional compositions ex vivo to investigate activation of the autonomic nervous system. Antagonists to the cholecystokinin receptor and nicotinic receptor were administered 30 minutes prior to LPS challenge. Blood and tissue samples were collected at 90 minutes to investigate intestinal epithelial cell damage, determined as plasma levels of ileum-lipid binding protein (I-LBP) and inflammation. A Mann-Whitney U test was used for between group comparisons. A spearman's correlation was used to assess the association between plasma levels of I-LBP and TNF-α, n≥6 for all groups. Results: Administration of lipid-rich nutrition effectively prevented LPS-induced damage to small intestinal epithelium (I-LBP; 8.3 ± 2.3 ng/ml vs [fasted] 27.1 ± 3.0 ng/ml and [low-lipid] 18.5 ± 3.2 ng/ml; both $p<0.05$). In line, lipid-rich nutrition attenuated systemic levels of TNF-α (1.5 ± 0.2 ng/ml) compared with fasted (3.7 ± 0.5 ng/ml; $p<0.01$) and low-lipid treated mice (2.5 ± 0.3 ng/ml; $p<0.05$). Enterocyte damage and circulating levels of TNF-α were highly correlated ($r^2 = 0.74$, $p<0.001$). Lipid-rich nutrition activated the autonomic nervous system more efficiently ($p<0.05$) than low-lipid nutrition. Moreover, administration of cholecystokinin receptor antagonists and nicotinic receptor antagonists blunted the anti-inflammatory effect of lipid-rich nutrition compared with vehicle (both $p<0.01$).
Conclusion: The current study demonstrates that enteral nutrition enriched with lipids attenuates enterocyte damage and reduces inflammation during gram-negative sepsis via a recently discovered neuroimmune axis, the so-called nutritional anti-inflammatory pathway. These findings implicate lipid-rich nutrition as a promising intervention to control inflammation during septic conditions.

Long-term efficacy of infliximab treatment in pediatric Crohn's disease in The Netherlands

C.I. de Bie[1], T.Z. Hummel[2], A. Kindermann[2], F.T.M. Kokke[3], G.M. Damen[4], C.M.F. Kneepkens[5], P.F. van Rheenen[6], J.J. Schweizer[7], J.H. Hoekstra[8], O.F. Norbruis[9], W.E. Tjon a Ten[10], A.C. Vreugdenhil[11], J.M. Deckers-Kocken[12], C. Gijsbers[13], J.C. Escher[1], L. de Ridder[1], [1]Dept. of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, [2]Dept. of Pediatric, Gastroenterology, Emma Children's Hospital/Academic Medical Centre, Amsterdam, [3]Dept. of Pediatric Gastroenterology, Wilhelmina Children's Hospital/Utrecht Medical Centre, Utrecht, [4]Dept. of Pediatric Gastroenterology, University Medical Centre St Radboud, Nijmegen, [5]Dept. of Pediatric Gastroenterology, VU University Medical Centre, Amsterdam, [6] Dept. of Pediatric Gastroenterology, Beatrix Children's Hospital/University Medical Centre Groningen, Groningen, [7]Dept. of Pediatric Gastroenterology, Leiden University Medical Centre, Leiden, [8]Dept. of Pediatric Gastroenterology, Hieronymus Bosch Hospital, 's-Hertogenbosch, [9]Dept. of Pediatric Gastroenterology, Isala Klinieken, Zwolle, [10]Dept. of Pediatric Gastroenterology, Maxima Medical Centre, Veldhoven, [11]Dept. of Pediatric Gastroenterology, University Hospital Maastricht, Maastricht, [12]Dept. of Pediatric Gastroenterology, Flevoziekenhuis, Almere, [13]Dept. of Pediatric Gastroenterology, Juliana Children's Hospital, The Hague, The Netherlands

Infliximab (IFX) is effective for induction and maintenance of remission in children with moderately to severely active Crohn's disease (CD). Little is known about the efficacy of IFX after more than three years of treatment. The primary aim of this study was therefore to assess the long-term efficacy of IFX treatment in pediatric CD. In this retrospective, multiCentre study, all Dutch pediatric CD patients treated with IFX from October 1992 to October 2009 and with a minimal follow-up (FU) of three months since start of IFX, were studied. Patients were categorized according to duration of FU: 3 – 12 mo (n=34), 1 – 3 yr (n=74), 3 – 5 yr (n=36) and ≥5 yr (n=37). Treatment outcome was considered successful when good clinical response was maintained minimally 90 days after IFX stopped or when repeated IFX infusions were needed to maintain clinical response. 181 CD patients (101M/80F) were treated with IFX by pediatric gastroenterologists in 13 hospitals. Mean age at start of IFX treatment was 14.5 years (range, 5.9 – 18.9 years) after a mean disease duration of 2.3 years (range, 0 – 10.1 years). A total of 2811 infusions was administered (mean, 15.5 infusions). Success of treatment was seen in respectively, 30/34 (88.2%), 45/74 (60.8%), 25/36 (69.4%) and 14/37 (37.8%) of patients in the FU categories 3 – 12 mo, 1 – 3 yr, 3 – 5 yr and ≥ 5 yr. Adjustments in treatment schedule (dosage increase to 10 mg/kg and/or shortening of the interval between two infusions) were needed in respectively, 26.7%, 44.4%, 63.6% and 50.0% of patients on maintenance treatment in the FU categories 3 – 12 mo, 1 – 3 yr, 3 – 5 yr and ≥ 5 yr. In total, 67 patients were (eventually) unsuccessfully treated with IFX. The majority of these patients underwent surgery (65.7%), followed by treatment with adalimumab (40.3%), corticosteroids (16.4%) and/or restart of IFX (14.9%; unsuccessful in seven patients).
Conclusions: IFX is effective in refractory pediatric CD. However, the therapeutic effect decreases over time with lost response to IFX treatment in approximately 60% of patients after five years. In addition, the number of patients that requires adjustment in treatment schedule to maintain clinical response increases to more than 60% after three to five years of treatment. These data emphasize the need for developing an effective, long-term treatment strategy for pediatric CD.

Multichannel intraluminal impedance base values in infants before and during proton pump inhibitor therapy

C.M. Loots[1,3], M.J. Smits[1], M.P. van Wijk[1,3], T.G. Wenzl[2], M.A. Benninga[1], T.I. Omari[3]
[1]Paediatric Gastroenterology and Nutrition, Emma Children's Hospital / Academic Medical Centre, Amsterdam, The Netherlands, [2]Klinik für Kinder- und Jugendmedizin, Universitätsklinikum der RWTH , Aachen, Germany, [3]Centre for Paediatric and Adolescent Gastroenterology, CYWHS, Women's and Children's Hospital, Adelaide, SA, Australia

Esophageal Multichannel Intraluminal Impedance(MII) has been used extensively for the detection of gastroesophageal reflux(GER) events. MII base values, which are typically above 1250 Ohms in healthy infants, have not been studied in detail. We hypothesized that abnormally low baselines would increase during PPI treatment. 24-hour MII studies were performed in 21 infants with symptoms of GER disease (mean age: 7.4 ± 4.2 weeks) before and after a week of 0.5 mg/kg esomeprazole therapy. Using purpose built software (Sandhill Scientific, USA), twenty hours of raw MII base values for the two most distal MII segments were extracted (0.1 Hz) and compared between the two studies. All datapoints above 5000 Ohms were excluded, as these are thought to represent presence of gas in the esophagus. An initial base less than 1250 Ohms was considered low. All data are given for the most distal segment only, since results did not differ between the two analysed segments. Data are shown as medians (25th–75th percentile). Comparisons were made using Wilcoxon's signed rank test and Pearson's correlation statistics. In infants with low initial baselines(n=15), the base increased during treatment (830(567-989) vs. 1831(1302-1980)Ohms, p=0.001; difference of means: 916(95%CI:654 to 1179)Ohms). In patients with normal baselines(n=6), no change in base was seen (2231(1331-2631) vs. 2289(1933-2903)Ohms, p=0.249; difference of means: 241(95%CI:-171 to -652)Ohms). In addition a correlation was found between the initial impedance base and the change in base during PPI treatment: Pearson r=-0.59 (95%CI:-0.81 to -0.21), p=0.005. No difference was found in the number of impedance detected bolus GER events before and during treatment, however acid exposure (reflux index) was significantly lower during treatment (p<0.001). No correlation was found between baselines and the reflux index, nor between the change in base and change in reflux index.
Conclusion: In infants with GER disease who show low MII baselines values during initial testing, an increase of this base is seen with PPI treatment. The increase is larger when initial values are lower. Whilst low impedance does not correlate with the degree of esophageal acid exposure, PPI therapy normalizes impedance baselines. We hypothesize that low impedance baselines may be a marker of abnormal levels of esophageal secretions due to inflammation and/or mucosal damage. Further research is needed to test this. However, it suggests a potential role for MII in detection and/or exclusion of mucosal damage in infants with GER disease.

The Role of Endoscopy of the Upper Gastrointestinal Tract in the diagnostic assessment of Childhood Inflammatory Bowel Disease

T.Z. Hummel[1], F.J.W. ten Kate[2], M.A. Benninga[1], A. Kindermann[1], Dept. of Pediatric Gastroenterology[1], Dept. of Pathology[2]Amsterdam Medical Centre, The Netherlands

Introduction Upper gastrointestinal tract (UGT) endoscopy has become part of routine evaluation of children with suspected inflammatory bowel disease (IBD) in the Netherlands. No consensus exists with respect to diagnostic criteria of IBD of the UGT. Objectives: to describe the histological UGT abnormalities in children with Crohn disease, Ulcerative Colitis and non-IBD patients and to establish the role of UGT involvement in children with IBD at diagnosis. Methods Biopsies from children suspected for IBD who underwent endoscopy during the last 6-years were reassessed by a blinded, expert pathologist. Histological findings of the UGT were compared with the diagnosis based on ileocolonic biopsies. Histology of the UGT showing granulomas confirmed the diagnosis of Crohn disease. Final diagnosis was based on endoscopic findings, histologic interpretation, imaging studies and follow-up data. Results A total of 172 children were enrolled in this study. Of these children, 70 had Crohn disease, 33 Ulcerative Colitis, 1 Indeterminate Colitis and 68 had no IBD. Granulomas in the UGT were found in 21 (30%) children with Crohn disease; 3 esophageal, 19 gastric and 2 duodenal. Focally enhanced gastritis (defined as presence of at least one foveolum/gland surrounded and infiltrated by inflammatory cells) was seen in 43 (61%) children with Crohn disease, compared to 6 (18%) children with Ulcerative Colitis and 5 (7%) non-IBD children. Specificity and positive predictive value of focal gastritis in Crohn disease were 89% and 80%, respectively. Cryptabscesses were only found in 6 (9%) children with Crohn disease, 5 gastric and 2 duodenal. Focal duodenitis was seen in 13 (19%) children with Crohn disease and in 1 child with no IBD. In 8 (11%) children with Crohn disease the diagnosis was solely based on UGT abnormalities; granulomas (n=5) and histiocytic infiltrates (n=3).
Conclusion: Focally enhanced gastritis, formerly suggested as a diagnostic marker for patients with Crohn disease, can also be found in children with Ulcerative Colitis and in non-IBD children. This finding does not differentiate between Crohn disease and Ulcerative Colitis. Granulomas infiltrates are exclusive found in children with Crohn disease. In 11% of the children with Crohn disease in our study the diagnosis was solely based on the detection of these findings in the UGT. We confirm that UGT endoscopy has an important role in the investigation in children suspected of IBD.

Sacral nerve neuromodulation therapy; a promising new treatment for children with refractory functional constipation

B.P.W. van Wunnik[2], B. Peeters[1], W. van Gemert[2], M.A. Benninga[1], C.G.M.I. Baeten[2], [1]Dept. of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre Amsterdam, [2]Dept. of Surgery, University Medical Centre Maastricht, The Netherlands

Background Sacral nerve neuromodulation (SNM) therapy has been successfully applied in adult patients with urinary and fecal incontinence. Recently, SNM therapy showed good results in adults with functional constipation not responding to intensive conservative treatment. No data, however, are available of SNM therapy as a treatment option in children with refractory functional constipation. Aim To describe the preliminary results of SNM therapy in children with chronic functional constipation refractory to intensive conservative treatment. Material and methods Children with functional constipation according to the ROME III criteria not responding to intensive conservative treatment (laxatives, enemas and colonic lavage) were assigned for SNM therapy. When improvement of symptoms was seen during the percutaneous nerve evaluation (PNE) with a permanent electrode in the 3 weeks testing phase, a permanent sacral nerve neuromodulator was implanted. Patients were prospectively followed up to at least six months after implantation of the permanent neuromodulator by interviews and bowel diaries. Improvement was defined as spontaneous defecation ≥ 3 times a week.Results A total of 5 patients (all females) 14 – 18 years old with functional constipation were included in this study. None of them had spontaneous defecation at presentation or felt urge to defecate. Duration of symptoms varied from 6 - 18 years and the duration of treatment differed from 1 -17 years. All 5 patients suffered from chronic abdominal pain and only one out of five patients reported fecal incontinence. Absenteeism from school on a regularly basis was present in 2 out of 5 patients. In all patients, PNE in the testing phase led to spontaneous defecation ≥ 3 times a week without pain or discomfort. After implantation of the permanent neuromodulator, all children had a normal spontaneous defecation pattern of ≥ 3 times a week without further medication and felt urge to defecate without any problems up till 6 months after implantation. Abdominal pain and fecal incontinence disappeared. The position of the neuromodulator was changed in 1 patient after 6 months due to pain at the implantation site. No other complications occurred.
Conclusion Sacral nerve neuromodulation therapy is a promising new treatment option in children with refractory functional constipation not responding to intensive conservative therapy. However, larger prospective studies with long-term follow up are required.

A novel mouse model for celiac disease reveals that gluten feed does not abide the rules of oral tolerance

J.N. Samsom[1], M. F. du Pré[1], L. A. van Berkel[1], M. N. ter Borg[1], L. Torp Jensen[2], Y. Kooy-Winkelaar[3], F. Koning[3], L. M. Sollid[4], E. E. S. Nieuwenhuis[1], L. A. Fugger[5], [1]Dept. of Pediatrics, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands [2]Clinical Institute, Aarhus University Hospital, Skejby Sygehus, Aarhus, Denmark [3]Dept. Blood Transfusion and Immunohematology, Leiden University Medical Centre, Leiden, The Nederlands [4]Institute of Immunology, University of Oslo, Rikshospitalet-Radiumhospitalet Medical Centre, Oslo, Norway [5]Department of Clinical Neurology & MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, University of Oxford, Oxford, UK

Celiac disease is an inflammatory disease of the small intestine caused by intolerance to gluten-proteins, constituents of wheat and rye. Virtually all patients express HLA-DQ2. This predisposition is explained by the preferential binding of gluten peptides to these HLA-molecules, which triggers an inflammatory $CD4^+$ T-cell response. This T-cell response is non-detectable in gluten-tolerant HLA-DQ2 individuals. Using mice transgenically expressing HLA-DQ2 and a humanized gluten-specific T-cell receptor, we aimed to clarify the regulation of gluten-specific T-cell responses. Previously, we have shown that oral tolerance to food proteins depends on differentiation of $Foxp3^+$ regulatory T-cells in the gut-draining mesenteric lymph nodes (MLN). Surprisingly, gluten feed induced a very dominant T-cell response in the spleen instead of the MLN, implying that the response is not confined to the mucosal immune system. The gluten-reactive T cells had an effector-like phenotype and secreted large amounts of interferon-g but also secreted interleukin-10. Despite their effector-like phenotype, splenic gluten-reactive T cells could suppress gluten-specific immune responses upon adoptive transfer to naive mice. These data demonstrate that gluten feed induces a splenic effector-like regulatory T-cell response in mice. This novel mouse model provides important progress in our understanding of gluten-specific T-cell regulation and the pathogenesis of celiac disease.

A biopsy is not always necessary to diagnose celiac disease

A. Mubarak[1], V.M. Wolters[1], S.A.M. Gerritsen[1], F.H.J. Gmelig-Meyling[2], F.J.W. ten Kate[3], R.H.J. Houwen[1], Dept. of Paediatric Gastroenterology[1], Immunology[2] and Pathology[3], University Medical Centre Utrecht, The Netherlands

Objective Small intestinal histology is the gold standard for the diagnosis of celiac disease (CD). However, results of serological tests such as anti-endomysium antibodies (EMA) and anti-tissue transglutaminase antibodies (tTGA) are becoming increasingly reliable. This raises the question whether a small intestinal biopsy is always necessary. The aim of the present study was therefore to investigate whether a small intestinal biopsy can be avoided in a selected group of patients.Methods Serology and histological slides obtained from 283 paediatric patients suspected of having CD were examined retrospectively. EMA were detected by means of immunofluorescence using sections of distal monkey oesophagus. Serum tTGA were measured by means of ELISA using human recombinant tissue transglutaminase. The positive predictive values (PPVs) of EMA and tTGA were calculated using villous atrophy upon microscopic examination as the gold standard for CD. Subsequently a subgroup of patients with a tTGA ≥100 U/ml was selected, as at this level diagnostic accuracy of serology might be better. Results A total of 163 (57.6%) patients had a small intestinal biopsy diagnostic for CD. The PPV for EMA and tTGA were 79% and 88% respectively. Dual positivity for EMA and tTGA did not lead to an improved diagnostic accuracy as the PPV only slightly increased to 89%. A tTGA level ≥100 U/ml was found in 128 of the 283 patients. Upon microscopic examination of the small intestinal epithelium villous atrophy was found in 124 of these patients, confirming the presence of CD. Three patients had crypt hyperplasia or an increased number of intra-epithelial lymphocytes, which can be compatible with CD too. Therefore two of these patients started a gluten free diet (one symptomatic, one asymptomatic), with good response in the patient who was symptomatic. The third patient did not adhere strictly to a gluten free diet. In the fourth patient no histological abnormalities were found. This patient did not respond to a gluten free diet, while 111/114 symptomatic patients in the high tTGA group, who did adhere to the diet, had a good response. The remaining 14 patients either did not start or adhere to a diet (4), were asymptomatic (4) or were lost to follow-up (6)
Conclusion: In this study all 111 patients with a tTGA level ≥100 U/ml in whom complaints improved upon a gluten free diet had a small intestinal biopsy compatible with CD. Therefore in this group a biopsy to confirm CD might not be necessary.

Constitutive Hedgehog signaling impairs maturation and migration of esophageal epithelial precursor cells

W.A. van Dop[1,2], A. Uhmann[3], V. Jaks[4], J. Offerhaus[5], M.A. van den Bergh Weerman[6], J. Heijmans[7], D.W. Hommes[7], J.C. Hardwick,[7], R. Toftgård[4], H. Hahn[3], G.R. van den Brink[7,1], [1]CEMM, Academic Medical Centre, Amsterdam, [2]Dept. of Gastroenterology & Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [3]Institute of Human Genetics, Georg August University of Göttingen, Göttingen, Germany, [4]Dept. of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden, [5]Dept. of Pathology, University Medical Centre, Utrecht, [6]Dept. of Pathology, Academic Medical Centre, Amsterdam, [7]Dept. of Gastroenterology & Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

Morphogens pattern tissues during development and maintain tissue architecture in rapidly renewing adult organs such as the gastrointestinal tract. In the columnar epithelium of the adult intestine we found that hedgehog signaling is exclusively from the epithelium to the mesenchyme where it induces a secondary signal that negatively regulates intestinal precursor cells. The mechanisms of epithelial renewal of the squamous epithelium of the esophagus have remained virtually unexplored. Here we examined the role of Hedgehog signaling in the esophagus of adult mice using conditional mutant mice. To study the effect of Hedgehog on the esophageal epithelium we used two different strategies for conditional activation of Hedgehog signaling in the esophagus. We used tamoxifen inducible Ptch1flox/flox-Rosa26CreERT2 mice resulting in body wide recombination of Ptch1 and mice carrying tetracyc regulated-GLI1 crossed to K5-rtTA mice for inducible expression of GLI1 in skin and esophagus. We examined expression of Sonic Hedgehog, Indian Hedgehog, Ptch1 and Gli1, by quantitative RT-PCR and in situ hybridization. The phenotype of Ptch1 mutant mice was examined using routine histological techniques, transmission electron microscopy and immuno-histochemical analysis of cellular proliferation and differentiation markers. Cell migration was examined in BrdU pulsed mice. Precursor cells of the esophagus expressed the Hedgehog receptor Ptch1, indicating that they are direct targets of Hedgehog signaling, in contrast to intestinal precursor cells. Sonic Hedgehog was the main Hedgehog produced in the esophagus. Conditional activation of Hedgehog signaling using two different approaches resulted in the same morphological alterations. We observed palisading of the precursor cells in the basal epithelial layer, and failure of epithelial maturation. In some parts of the epithelial layer small epithelial buds were formed that migrated into the underlying mesenchyme. BrdU labeling studies revealed that precursor cells were retained in the basal layer and failed to migrate to the esophageal lumen. Our results suggest that Hedgehog signaling has different functions throughout the gastrointestinal tract. We previously found that Hedgehog signaling negatively regulates the intestinal epithelial precursor cells in a paracrine manner. Here we describe an autocrine role for Hedgehog signaling in the esophageal epithelium. In the esophagus we find that Hedgehog signaling positively regulates precursor cell fate and retention.

Human polycystic liver cyst fluid disturbs cholangiocyte cyclic AMP signaling and proliferation, both processes are normalized by lanreotide treatment in a somatostatin receptor 5 and phosphodiesterase 4D dependent mechanism

J. Woudenberg, M.J. Janssen, I. Worm, R.H. te Morsche, M. Chrispijn, J.P.H. Drenth
Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Polycystic liver disease (PCLD) is a progressive disease, characterized by the development of multiple fluid-filled liver cysts. In cyst epithelium of PCLD patients, intracellular concentrations of the second messenger cyclic AMP (cAMP) are elevated. Increased cAMP levels drive cholangiocyte proliferation and the cAMP effectors protein kinase A (PKA), exchange proteins activated by cAMP (EPACs) and ERK1/2 are involved in this process. The somatostatin analogue lanreotide reduces intracellular cAMP levels and in a randomised clinical trial we showed that lanreotide reduces polycystic liver volume. In order to unravel the intracellular mechanism of lanreotide action, we developed a novel in vitro model for PCLD, i.e. the cultivation of human cholangiocytes in the presence of PCLD patient cyst fluid. Using this model, we explored which somatostatin receptor and which subcellular components are utilized by lanreotide to reduce intracellular cAMP levels and cholangiocyte proliferation. Human Sk-ChA-1 cholangiocytes were treated with 20% (Vol/Vol) PCLD patient cyst fluid in the presence or absence of 20 nM lanreotide, 8 nM BIM23056 (somatostatin receptor 5 inhibitor) and 10 μM rolipram (Phosphodiesterase 4D-PDE4D inhibitor). Cell proliferation and intracellular cAMP levels were measured using commercially available assays. ERK activation was analyzed by western blot analysis of phospho- and total ERK expression. mRNA expression and protein expression of somatostatin receptors, phosphordiesterases, PKAs and EPACs were assessed in Sk-ChA-1 cells by Quantitative Real-Time PCR, western blot or immunohistochemistry. Cyst fluid treatment of human cholangiocytes raises intracellular cAMP levels and cholangiocyte proliferation, which are normalized by lanreotide treatment. EPAC2 levels and ERK phosphorylation are significantly elevated by cyst fluid treatment, both are reduced by lanreotide. We found that somatostatin receptor 5 is the most abundantly expressed somatostatin receptor in human cholangiocytes and induced by lanreotide treatment. Lanreotide significantly induces expression of the cAMP metabolizing enzyme phosphodiesterase PDE4D in cholangiocytes. Blocking of SST5 with 8 nM BIM23056 or inhibition of PDE4D activity with 10 μM rolipram reverses the beneficial effect of lanreotide on cholangiocyte proliferation.
Conclusions: Lanreotide treatment significantly reduces PCLD patient cyst fluid-induced proliferation in a mechanism that depends on the somatostatin receptor 5 and the phosphordiesterase PDE4D. Therefore, induction of PDE4D enzyme activity is an attracttive novel target for the treatment of polycystic liver disease.

Characterization of the liver progenitor cell niche in liver diseases: potential involvement of Wnt and Notch signaling

B. Spee[1], G. Carpino[2], B.A. Schotanus[3], A. Katoonizadeh[1], S. van der Borght[1], E. Gaudio[4], and T. Roskams[1], [1]Dept. of Morphology and Molecular Pathology, University Hospitals Leuven, Leuven, Belgium, [2]Dept. of Health Sciences, University of Rome "Foro Italico", Rome, Italy, [3]Dept. of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, The Netherlands, [4]Dept. of Human Anatomy, Sapienza University of Rome, Rome, Italy

Hepatic progenitor cells (HPCs) hold a great potential for therapeutic intervention for currently untreatable liver diseases. However, in human diseases molecular mechanisms involved in proliferation and differentiation of HPCs are poorly understood. In the present study activated HPCs and its microenvironment (niche) were investigated in acute and chronic human liver disease by gene-expression analysis and immuno-histochemistry/-fluorescence. Cryopreserved liver tissues were used from patients with parenchymal versus biliary diseases: acute necrotising hepatitis (AH), cirrhosis after hepatitis C infection (HCV), and primary biliary cirrhosis (PBC) in order to study differentiation of HPCs towards hepatocytic versus biliary lineage. Keratin 7 (K7) positive HPCs/reactive ductules were captured by means of Laser Capture Microdissection (LCM) and gene-expression profiles were obtained by using a customized PCR Array. Gene expression results were confirmed by immunohistochemistry and immunofluorescence double staining. In all disease groups, microdissected HPCs expressed progenitor cell markers such as *KRT7*, *KRT19*, *NCAM*, *ABCG2*, *LIF*, *KIT*, *OCT4*, *CD44*, and *TERT*. In AH, HPCs were most activated and showed a high expression of prominin-1 (CD133) and alpha-fetoprotein (AFP), and a strong activation of the Wnt-pathway. In contrast to parenchymal diseases, HPCs in PBC (biliary differentiation) showed a high activation of Notch signalling.
Conclusion: A distinct pattern of HPC surface markers was found between acute- and chronic-liver diseases. Similar to what is known from animal experiments, strong evidence has been found signifying the role of Wnt signalling in proliferation of human HPCs whereas Notch signalling is involved in biliary differentiation. These pathways can be targeted in future therapies.

Conditional loss of intestinal Hedgehog signaling results in a regenerative response and subsequently in loss of villi and the spontaneous development of chronic enteritis

W.A. van Dop[1,2], E.A. Wassenberg[1], B. Lanske[3], A.R. Clarke[4], J. Offerhaus[5], D.W. Hommes[6], J.C. Hardwick[6], I. Biemond[6], G.R. van den Brink[1,6], [1]CEMM, Academic Medical Centre, Amsterdam, [2]Dept. of Gastroenterology & Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [3]Dept. of developmental biology, Harvard School of Dental Medicine, Boston, MA, USA, [4]School of Biosciences, University of Cardiff, Cardiff, United Kingdom, [5]Dept. of Pathology, University Medical Centre, Utrecht, [6]Dept. of Gastroenterology & Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

Indian hedgehog (Ihh) is expressed by differentiated intestinal epithelial cells and acts on the subepithelial myofibroblasts. We previously found that this epithelial mesenchymal interaction is part of a negative feedback loop from the differentiated cells to the intestinal epithelial precursor cells. Genetic variants in the hedgehog pathway have recently been linked to the development of inflammatory bowel disease. Here we studied the effect of loss of Hh signaling on the small intestinal epithelium. We conditionally deleted Ihh by injecting naphtoflavone in Cyp1a1-Cre*Ihhfl/fl mice. Deletion of Ihh was confirmed by immunohistochemistry for Ihh and quantitative RT-PCR for targets of Hh signaling. The phenotype of Ihh mutant mice was examined using routine histological and immunohisto-chemical techniques. We found that loss of Hedgehog signaling initially caused a regenerative response of the intestinal epithelium with deepening and fissioning of the crypts and lengthening of the villi. Profound morphological changes were found in the intestinal subepithelial myofibroblasts and smooth muscle cells in the villus core which lost their elongated appearance and rolled up into little balls. Later time points were characterized by complete loss of myofibroblasts and smooth muscle cells from the villus core, loss of small intestinal villi and the development of a chronic inflammatory infiltrate. In chronic intestinal inflammation epithelial regeneration is generally believed to result from epithelial damage by the inflammatory process. Our results show that epithelial regeneration and chronic intestinal inflammation may be separate processes and suggest that we should reappraise our thinking of cause and consequence in chronic intestinal inflammation and epithelial regeneration. Our data provide further evidence for a potential link between aberrant Hh signaling and the development of inflammatory bowel disease.

In autosomal dominant polycystic liver disease (PCLD) cysts develop through a cellular recessive mechanism involving loss of heterozygosity and somatic mutations

M.J. Janssen[1], E. Waanders[1,2], H.B. Dijkman[3], R.H.M. te Morsche[1], J. Woudenberg[1], J.P.H. Drenth[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Human Genetics and [3]Dept. of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Autosomal dominant polycystic liver disease (PCLD) involves abnormal cholangiocyte proliferation and is characterised by multiple liver cysts and hepatomegaly. About 15% of the PCLD patients carry a heterozygous germline mutation in *PRKCSH*. Previous studies show absence of the *PRKCSH* gene product hepatocystin from liver cyst epithelium in these patients. This suggests that cyst formation results from a cellular recessive mechanism affecting the second *PRKCSH* allele. To determine the mechanism of cyst formation in PCLD we determined loss of heterozygosity (LOH) and the presence of additional somatic mutations in cyst epithelium.
We used micro laser dissection to isolate the cyst epithelium of 41 liver cysts from 4 patients with a germline *PRKCSH* mutation, normal liver cells were used as a control. DNA from the cysts was sequenced to identify somatic *PRKCSH* mutations and 4 polymorphic DNA markers spanning 30-70 kb around the *PRKCSH* locus were used to determine the region involved in LOH.
We detected LOH or somatic *PRKCSH* gene mutations in 35/41 cysts (85%). LOH was present in 27/41 cysts (66%), resulting in complete loss of the functional *PRKCSH* allele from the cyst epithelium. The LOH region varied between <30 kb to >70 kb in the different cysts. In 8/41 (19%) of the remaining cysts we identified novel small deletions and base pair substitutions.
These findings establish that cyst formation in PCLD results from a cellular recessive mechanism involving LOH and somatic mutations. The large variety of mutations suggests that each cyst developed independently and was formed through clonal expansion of a single mutated cholangiocyte.

Evaluation of the human hepatoma cell HepaRG for bioartificial liver application

G.A.A. Nibourg[1,2], T.V. van der Hoeven[1,2], M.T. Ackermans[3], R.P.J. Oude Elferink[2], T.M. van Gulik[1], R.A.F.M. Chamuleau[2], R. Hoekstra[1,2], [1]Surgical Laboratory, [2]Tytgat Institute for Liver and Intestinal Research, [3]Laboratory of Endocrinology, Academic Medical Centre, Amsterdam, The Netherlands

We have developed a bioartificial liver (BAL) to bridge acute liver failure patients to liver transplantation or liver regeneration. The BAL consists of a bioreactor loaded with liver cells of preferably human origin and displaying high hepatic functionality. The human hepatoma cell HepaRG (Gripon et al. PNAS. 2002) is known for its high detoxification function, but other hepatic functions relevant to BAL application have never been evaluated. In this study, we investigated the characteristics of HepaRG cells in a BAL.HepaRG cells were cultured for 14 days in laboratory scale BALs (n=11). Proliferation and cell death were studied by total protein content analysis before and after BAL culture, leakage of lactate dehydrogenase (LDH) and aspartate aminotransferase (AST), and histological examination. Transcript levels of cytochrome p450 (CYP) 3A4 and carbamoyl phosphate synthetase (CPS) (urea cycle enzyme), were assessed by qRT-PCR before and after BAL culture. In addition, ureagenesis and ammonia elimination were tested at day 6 and 13 of BAL culture by subjecting the BALs to recirculating culture medium supplemented with 1.5 mM ^{15}N-ammonia. Lastly, the production of the apolipoprotein A-1 (ApoA-1) was analyzed as a marker for synthetic functionality. During 14 days of BAL culture, the total protein content did not significantly change, indicating no net cell growth or cell death. Histological analysis revealed that the entire matrix inside the BAL was completely filled with vital cells, explaining the lack of proliferation. LDH and AST leakage per day were both less than 0.1% of total LDH and AST content of the loaded cell mass, indicating negligible cell death. Transcript levels of CYP3A4 increased significantly from 10% to 102% of human in vivo levels during BAL culture. CPS mRNA levels did not significantly change (from 37% to 44% of in vivo levels). Ammonia elimination remained unaltered during culture and was comparable to the elimination rate of a BAL filled with an equal amount of primary porcine hepatocytes (PPH-BAL) (40 µmol/h). Ureagenesis increased significantly over time from 1.1 ± 0.3 µmol/h at day 7 to 2.1 ± 0.2 µmol/h at day 14, reaching 10% of the production rate of a PPH-BAL. In addition, 31% of the produced urea was formed out of ^{15}N-ammonium chloride, leaving 69% originating from alternative nitrogen sources. The rate of ApoA-1 synthesis did not change during culture and was comparable to the production rate of a PPH-BAL (170 µg/h).
Conclusion: Inside the BAL, HepaRG cells differentiate up to a promising level for BAL application. Currently the HepaRG BAL is tested in a rat model of acute liver failure.

Role of IL-1R-MyD88 signaling in the pathogenesis of postoperative ileus

S.A. Snoek[1], S.H. van Bree[1], F.W. Hilbers[1], O. Welting[1], R.M. van den Wijngaard[1], G.E. Boeckxstaens[1,2], W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, University Hospitals Leuven, Leuven, Belgium

Postoperative ileus (POI) is commonly associated with intestinal stasis and bacterial overgrowth. We have shown that intestinal manipulation (IM) during abdominal surgery induces bacterial translocation. However, we also demonstrated that TLR signaling is not crucial in IM-induced muscular inflammation, excluding bacterial recognition as a triggering factor for postoperative ileus. In this study we assessed whether damage induced inflamemasome activation and IL-1beta production mediates the muscular inflammatory reaction after IM. Experiments were performed in C57Bl/6 (WT) and MyD88-/- mice. Mice underwent laparotomy (L) or L followed by a gentle manipulation of the small bowel (IM). Twenty four hours after surgery, intestinal inflammation was assessed by the number of MPO-positive cells per mm^2 and cytokine production in the muscularis externa of the small intestine. Bacterial translocation was determined at 24h post surgery as colony forming units (CFU) from mesenteric lymph node (MLN). Mice were treated i.p. with the IL-1R antagonist anakinra (100 mg/kg), at 1h before, 20 min. and 6h after IM. IM enhanced bacterial translocation in C57Bl/6 (WT) mice, as indicated by an increase in bacteria cultured from mesenteric lymph nodes (WT, L: 8.8±3.3; IM: 36.4±15.6 CFU/mg). The IM induced bacterial translocation was increased in MyD88-/- mice as compared to WT, but this difference was not significant (MyD88, L: 3.6±2.1; IM: 213.6±105.3 CFU/mg). Irrespectively, IM induced muscular inflammation is crucially dependent on MyD88 signaling, as neutrophil recruitment (IM-WT: 219±24 vs IM-MyD88-/-:80±18 cells/mm^2) as well as production of MCP-1 (IM-WT: 325±59 vs IM-MyD88-/-: 123±19 pg/mg protein) and IL-6 (IM-WT: 11.2±4.4 vs IM-MyD88-/-: 1.2±0.5 pg/mg protein) in the muscularis externa was significantly reduced in mice deficient for MyD88. As MyD88 is crucial in IL-1R signalling, we further studied the role of IL-1R activation in POI. IL-1beta production was increased after IM (WT, L: 17.3±1.6; IM: 28.4±5.7 pg/mg protein). Treatment with the IL-1R antagonist anakinra significantly reduced muscularis IL-6 production (IM-saline: 71.5±7.1 vs IM-anakinra: 50.3±9.0 pg/mg protein). Also, anakinra treatment reduced neutrophil influx and MCP-1 production but this was not significant.

Conclusions: MyD88 signaling is crucial in the IM-induced muscular inflammation resulting in POI. Our results point towards a role for inflammasome-mediated IL-1beta production and subsequent activation of the IL-1R-MyD88 signaling pathway in the pathogenesis of POI.

ATG16L1 and IRGM Contribute to the Regulation of Immune Responses

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

Various polymorphisms in the autophagy related genes ATG16L1 and IRGM have been associated with the development of Crohn's disease (CD). Autophagy is primarily known to be important in the survival of cells during starvation as well as the processing of intracellular bacteria. Although the link between decreased autophagy and an inflammatory disorder like IBD suggests a role for this process in the regulation of immune responses, no data has been available on this topic thus far. Therefore, this study focused on the effects of decreased ATG16L1 and IRGM expression on the immunogenicity of dendritic cells.

Monocytes obtained from healthy volunteers were cultured in the presence of GM-CSF and IL-4 to generate dendritic cells. Gene knockdown was achieved using siRNA technology. Dendritic cell phenotype was studied by flow cytometry, and functionality was tested in mixed lymphocyte reactions, an OVA processing assay and cytometric bead arrays.

Knockdown efficiency achieved ranged from 25-85% in individual experiments. Interestingly, even the lower level knockdown resulted in a clear decrease in functional autophagy, indicating that relatively small changes in the levels of autophagy proteins (e.g. such as those caused by some point mutations) have a strong impact on the pathway as a whole. Decreased levels of autophagy did not decrease viability of dendritic cells under nutrient-rich conditions. Strinkingly, ATG16L1^{low} and IRGM^{low} dendritic cells induced significantly more T-cell proliferation in both an allogeneic mixed lymphocyte reaction and an antigen specific proliferation assay. This finding was consistent in both human and mouse cells, suggesting a conserved role for autophagy in the regulation of the immune reaction.

Flow cytometry showed ATG16L1^{low} and IRGM^{low} dendritic cells to express levels of HLA-DR and co-stimulatory molecules comparable to that of control cells. Furthermore, decreased levels of autophagy did not result in an altered cytokine profile of these cells, indicating that mechanisms other than increased maturation underlie the increased immunoreactivity.

Conclusion: Even a partial decrease in autophagy results in an increased pro-inflammatory capacity in dendritic cells. This phenomenon may contribute to the increased immune activation seen in those CD patients carrying polymorphisms in these genes.

Anti-TNF induced inhibition of T cell proliferation in a mixed lymphocyte reaction is Fc receptor dependent

A.C.W. Vos[1], M.E. Wildenberg[1], M. Duijvestein[1], A.P. Verhaar[1], J. Heijmans[1], G.R. van den Brink[1], D.W. Hommes[1], [1]Dept. of Gastroenterology and Hepatology, Leiden Univeristy Medical Centre, Leiden, The Netherlands

Introduction:Infliximab and adalimumab, monoclonal anti-TNFα antibodies, are effective treatments for Crohn's disease (CD). Although etanercept, a TNF receptor fusion protein, also efficiently neutralizes soluble TNFα, etanercept is not effective in CD, suggesting that neutralizing TNFα is not the primary effector mechanism in CD. The aim of this study was to unravel the mechanism of action of infliximab in CD. Methods:Lymphocytes isolated from healthy donors were activated using αCD3/αCD28 or in an allogeneic mixed lymphocyte reaction (MLR). Cells were treated with anti-TNF compound or IgG control. Proliferation was measured by 3H thymidine incorporation. Monocytes and dendritic cells (DCs) were treated with anti-TNF compounds and costimulatory molecule expression was analyzed by flowcytometry. For mTNF binding assays, anti-TNF compounds were labeled with a fluorescent dye and incubated with activated T cells. Binding to mTNF was measured by flowcytometry. Results:Infliximab and adalimumab bind to mTNF on activated T cells, whereas etanercept does not. In lymphocytes activated with αCD3/αCD28, all TNF agents slightly inhibited T cell proliferation, suggesting a minor effect caused by neutralizing TNFα. However, in an MLR, only infliximab and adalimumab significantly inhibited T cell proliferation but etanercept did not, mimicking the clinical response to these compounds. As an MLR contains not only T cells but also antigen presenting cells (APCs), these data suggest that the presence of APCs is necessary for the inhibition of proliferation observed. However, none of the anti-TNF compounds altered the expression of costimulatory molecules on monocytes and DCs. Interestingly, saturating Fc receptors in an MLR completely abolished the inhibition of proliferation. In addition, infliximab F(ab')2 fragment did not inhibit proliferation, although infliximab F(ab')2 fragment binds mTNF to the same extent as infliximab.
Conclusion: This study shows that both binding to the Fc receptor and binding to mTNF is indispensable for anti-TNF induced inhibition of proliferation.

Immunoglobulin A: FcαRI interactions induce neutrophil migration through release of leukotriene B4

L.P.E. van der Steen[1], C. W. Tuk[1], J.E. Bakema[1], G. Kooij[1], A. Reijerkerk[1], G. Vidarsson[4], G. Bouma[2], G. Kraal[1], H.E. de Vries[1], R.H.J. Beelen[1], M. van Egmond[1,3], [1]Dept. of Molecular Cell Biology and Immunology, VU University Medical Centre, Amsterdam, [2]Dept. of Gastroenterology, VU University Medical Centre, Amsterdam, [3]Dept. of Surgery, VU University Medical Centre, Amsterdam, [4]Dept. of Experimental Immunohematology, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands

Exacerbations of ulcerative colitis (UC) are dominated by massive neutrophil influx in the lamina propria with concomitant mucosal ulceration. The prevalent antibody in this area is immunoglobulin A (IgA). Interestingly, the IgA Fc receptor (FcαRI) potently activates neutrophils. As such, we investigated whether IgA-FcαRI interaction contributes to tissue damage in UC. Response of neutrophils to bovine serum albumin–, IgG-, or IgA-coated beads and Escherichia coli was investigated with 3-dimensional culture systems, real-time video microscopy, and (fluorescence) microscopy. In vivo studies were performed using human FcαRI transgenic mice or nontransgenic littermates. Microscopic slides of UC patients were stained for IgA, FcαRI, and neutrophils. In vitro and in vivo cross-linking of FcαRI on neutrophils by serum IgA or uptake of IgA-coated E coli led to neutrophil migration. The responsible chemotactic factor was identified as leukotriene B4. Moreover, dimeric IgA (dIgA), which is produced in the lamina propria, but neither secretory IgA nor IgG, was equally capable of inducing neutrophil recruitment. We furthermore showed that FcαRI-positive neutrophils in the colon of UC patients had phagocytosed IgA-antigen complexes.
Conclusions: Neutrophils are the first cells that arrive at inflammatory sites once pathogens have crossed the epithelial barrier. FcαRI-dIgA interactions therefore may constitute an essential activation step to recruit more neutrophils, hereby eradicating impending infections. However, excessive IgA-antigen complexes can sustain a perpetuating inflammatory loop in UC, hereby seriously aggravating morbidity. Novel therapeutic strategies that block dIgA-FcαRI interactions, and therefore diminish neutrophil migration and activation, may dampen the uncontrolled inflammatory processes in these patients.

6-thioguanine increases human innate immunity via inhibition of the Rac1 signaling pathway

L. Zhou[1,2], G. Dijkstra[2], K. Parikh[1], L. Visser[3], A. Regeling[2], G.M. Fuhler[1], M.P. Peppelenbosch[1], K.N. Faber [2], [1]Dept. of Gastroenterology, [2]Dept. of Cell biology, [3]Dept. of Pathology, University Medical Centre Groningen, The Netherlands

Background Accumulating evidence suggests that the primary immnue defect in patients with Crohn's disease (CD) lies in impaired innate immunity. Immunosuppressive agents, such as Azathioprine (AZA), are the first medicine for treating CD patiens. We aimed to unravel the effect of AZA on human innate immunity.Methods 6-Thioguanine (6-TG), the active derivative of AZA, was assessed for its effects on E.coli phagocytosis and cytokine production of human primary monocytes from healthy individuals and CD patients, and for its effects on Rac1 signaling pathway.Results 6-TG at 10-60 μM dose-dependently enhances monocyte E. coli phagocytosis. The stimulation of monocyte phagocytosis by 6-TG (10 μM) is confirmed in monocytes from healthy individuals and CD patients ($p<0.001$). 6-TG strongly inhibits the activity of Rac1-GTPase and its downstream kinase PAK2 ($p<0.05$) in monocytes. E. coli phagocytosis of monocytes is enhanced by the unrelated Rac1 inhibitor NSC23766, confirming that Rac1 inhibition leads to enhanced monocyte phagocytosis. In CD patients, the Rac1 pathway is hyperactivated in both peripheral monocytes and in the intestinal mucosa ($p<0.05$), which is suppressed by 6-TG. Moreover, 6-TG increases interleukin-8 production while slightly reducing IL-10 production in monocytes.
Conclusions: 6-TG enhances monocyte capability of bacterial clearance, which directly overcomes the impairment of innate immunity in CD patients. This is in with the long-term remission maintenance effect of AZA. Furthermore, we propose that Rac1 hyper-activation leads to defective innate immunity in CD, thus defining a novel therapeutic target.

Monocytes from chronic HCV patients are functionally altered with distinct regulation of bacterial and viralrecognition pathways

B. Liu, H.L.A. Janssen, A. Boonstra, Dept. of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

There are indications that the innate immune response in patients with chronic HCV infections is suppressed. In this, dendritic cells have been studied most extensively, while monocytes have received less attention. However, monocytes play an important role in the defense to viral and bacterial infections by secreting numerous cytokines and by serving as the precursors of dendritic cells and macrophages. Aim of this project was to study whether monocytes from chronic HCV infected patients are affected in their response to diverse pathogen-derived products. Monocytes were purified from peripheral blood collected from 23 chronic HCV patients and 23 healthy individuals. Monocytes isolated from HCV patients showed significantly higher spontaneous production of TNF, IL-12p40 and IL-10 (2 to 3-fold higher) as compared to healthy individuals, suggesting that monocytes from patients were at a higher activation state. In line with the enhanced activation state of monocytes from chronic HCV patients, also their response to the TLR7/8 ligand R848 -a mimic for viral single-stranded RNA- was enhanced as compared to controls. Cytokine measurements in cultures stimulated with the TLR7/8 ligand demonstrated 3 to 4-fold higher TNF, IL-12p40, IL-12p70 and IL-10 production *in vitro*, by monocytes from chronic HCV patients as compared to healthy individuals. In sharp contrast, monocytes from HCV patients did not respond to pathogen-derived products from bacteria, such as LPS, to increase their TNF and IL-12p40 production (average TNF production, n=14; med: 751 pg/ml; LPS: 701 pg/ml). However, monocytes from healthy individuals were highly responsive (average TNF production, n=14; med: 255 pg/ml; LPS: 2224 pg/ml). Importantly, the levels of LPS-induced IL-10 did not differ between patients and healthy controls, indicating that the observed differences are not a consequence of impaired responsiveness to the TLR4 ligand, but suggests modulated signaling events leading to suppressed production of pro-inflammatory cytokines. This is supported by our findings that TLR4 mRNA expression by highly purified monocytes from chronic HCV patients was similar to expression by monocytes from healthy controls.
In summary, our data indicate that monocytes from patients chronically infected with HCV are functionally altered as compared to control subjects. Although monocytes from HCV patients strongly respond to TLR8 triggering (mimic of pathogen-derived product from viruses), they are less responsive to bacterial products. Our data highlight the importance of studying bacterial infections in chronic HCV patients. In addition, functional modulation of monocytes may contribute to the establishment and maintenance of persistence as observed in the majority of patients after HCV infection.

Potent in vivo inhibition of hepatitis C virus replication by mycophenolic acid in mice

P. de Ruiter[1], Q. Pan[2], H.J. Metselaar[2], J. Kwekkeboom[2], G. Kazemier[1], H.W. Tilanus[1], H.L.A. Janssen[2], L.J.W. van der Laan[1], Depts. of [1]Surgery and [2]Gastroenterology & Hepatology, Erasmus MC - University Medical Centre, Rotterdam, The Netherlands

Background: Chronic hepatitis C virus (HCV) infection is the leading indication for liver transplantation, and particular immunosuppressants can have an influence on HCV recurrence. We previously showed that Mycophenolic Acid (MPA) has antiviral activity in a subgenomic HCV replication model (Hu7-ET) in vitro. In this study, we further investigated the effect of MPA in the JFH1-derived infectious model in vitro, and the replicon-based Huh7-ET model in mice. Methods and Results: Treatment with clinically relevant concentrations of MPA (1-5µg/ml) significantly inhibited viral replication in Huh7-ET replicon cells up to 77% ± 4.5 SD after 24 hours. MPA treatment had no effect on luciferase activity in control Huh7 cells constitutively expressing luciferase (Huh7-Luc). In a JFH1-derived infectious model, 5µg/ml MPA resulted in 86% ± 1 inhibition of viral replication as well as 79 ± 6% reduction of de novo virion production. In vivo, MPA treatment (50 mg/kg, intraperitoneally) of NOD/SCID mice engrafted subcutaneously with Huh7-ET led to robust inhibition of HCV replication (86% ± 12, n=7, p=0.006) after 24 hours as compared to vehicle-control treated animals. No effect was observed on the signal from Huh7-Luc cells co-transplanted at an adjacent side in the same mice (see Figure), confirming antiviral specificity of MPA in vivo.
Conclusion: This study demonstrates the potent antiviral activity of MPA in vitro and in mice. MPA was shown to have a distinct anti-HCV mechanism of action, independent of cell proliferation and guanosine depletion (shown previously), and may contribute in reducing HCV recurrence after liver transplantation.

5-Aminosalicylic acid induces colorectal cancer cell death in vitro and in vivo

P.J. Koelink, A.I.M.J. Langers, W.H. De Vos tot Nederveen Cappel, M.A.C. Mieremet-Ooms, D.W. Hommes, C.B.H.W. Lamers, H.W. Verspaget, Dept. of Gastro-enterology-Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

5-Aminosalicylic acid (5-ASA) has colorectal cancer (CRC)-preventive properties in inflammatory bowel disease (IBD) patients, although the mechanism is largely unknown. We aimed to determine the ability of 5-ASA to induce cell death in colorectal cancer cells *in vitro* and *in vivo.* HT29 cells were treated with 5-ASA *in vitro*. Thirty-one patients with a colorectal neoplasm were treated with 5-ASA enemas for 14 consecutive days. Neoplastic and normal tissue biopsies were taken before and after 5-ASA treatment. Apoptosis was assessed by determination of caspase-3 activity, caspase-degraded cytokeratin 18 (M30 antigen) and total cytokeratin 18 (CK18) levels. 5-ASA induced caspase-3 activity *in vitro* in a concentration and time-dependent manner, indicating classical caspase-dependent apoptosis. However, blocking caspase-3 was not able to completely inhibit the cell death inducing effects of 5-ASA, suggesting the contribution of non-caspase mediated cell death mechanisms, besides apoptosis. 5-ASA also induced caspase-3 activity in homogenates of colorectal carcinomas (Wilcoxon signed rank test, $p=0.03$) and normal mucosa, ($p=0.006$) but not significantly in adenomas ($p=0.81$), revealing the induction of apoptosis also *in vivo*. Moreover, 5-ASA significantly decreased CK18 levels in carcinomas ($p=0.04$), indicating the loss of epithelial cancer cells.

Conclusions: We conclude that 5-ASA induces caspase-dependent apoptosis in CRC cells, both *in vitro* and *in vivo*. Moreover, 5-ASA is also capable of inducing caspase-independent cell death *in vitro*, which might have contributed to the *in vivo* loss of cancer cells in colorectal carcinomas.

Preoperative calorie restriction reduces hepatic tumour load after exposure to circulating coloncarcinoma tumorcells in a mouse model

T.M. van Ginhoven[1], J.W. van den Berg[1,2], W.A. Dik[2], J.N.M. IJzermans[1], R.W.F. de Bruin[1], [1]Dept. of Surgery, Erasmus MC, Rotterdam, [2]Dept. of Immunology, Erasmus MC, Rotterdam, The Netherlands

The inflammatory response after surgery contributes to tumour metastasis by increasing the expression of cellular adhesion molecules. We have recently shown that short-term calorie restriction (CR), a 30% reduction in daily calorie intake during two weeks, is able to reduce the expression of adhesion molecules and confer protection against surgically induced inflammation. We therefore hypothesized that preoperative CR reduces expression of adhesion molecules and subsequent tumour take and growth in a mouse model of colorectal liver metastases. Male BALB/c mice were subjected to two weeks of CR (30% reduction in calorie intake) prior to the inoculation of tumour cells. Intrasplenic injection of $5x10^5$ c26-coloncarcinoma cells was followed by removal of the spleen. Animals were allowed to eat ad libitum postoperatively and were sacrificed after ten days. Hepatic tumour load was scored as a percentage (tumour surface/total liver surface) on haematoxylin and eosin stained sections. In addition, serum from CR mice was used in experiments assessing the effects on in vitro tumour growth and adhesion capacity. Liver mRNA expression of adhesion molecules was determined. Preoperative DR led to a significant reduction in tumour growth ten days after tumour inoculation ($p=0.0355$). In vitro experiments showed no influence of CR serum on the growth of c26 cells. CR significantly reduced in vitro adhesion of c26 cells to endothelial cells. mRNA expression levels of E-selectin in the liver were significantly lower after CR when compared to the ad libitum fed group.
Conclusions: Preoperative calorie restriction reduces hepatic tumour load ten days after injection of tumour cells. The significantly reduced in vitro adhesion and reduced mRNA expression of E-selectin suggest that CR reduced tumour load by lowering the adhesion of circulating tumour cells to hepatic vascular endothelium.

Distinct pathways leading to colorectal cancer are prevalent in hyperplastic polyposis syndrome

K.S. Boparai[1], E. Dekker[1], M. Polak[2], A. Musler[2], S. van Eeden[2], C.J.M. van Noesel[2], [1]Dept. of Gastroenterology & Hepatology, Academic Medical Centre, Amsterdam, [2]Dept. of Pathology, Academic Medical Centre, Amsterdam, The Netherlands

Introduction:Hyperplastic polyposis syndrome (HPS) is characterized by the presence of multiple colorectal hyperplastic polyps, sessile serrated adenomas and conventional adenomas and is associated with an increased colorectal cancer (CRC) risk. Although a serrated pathway leading to CRC has been proposed in HPS, a classical Wnt-pathway can not be disregarded considering the common presence of conventional adenomas. Hence, it is unknown to what extent either of these pathways plays a role in CRC development in HPS. Accordingly the clinical relevance of polyps with different histologies is unknown. Aims and methods:To establish what pathways leading to CRC play a role in HPS we identified from a cohort of HPS patients at our centre 15 patients with CRC. In these patients we analyzed the morphological and molecular characteristics of polyps (n=74) and CRCs (n=16) compared to control groups of various sporadic polyps (n=59) and sporadic microsatellite stable CRCs (n=16). In the case of a CRC with an identified mutation, ≥5 polyps found in the same HPS patient, were subsequently analyzed. Somatic mutation analysis was performed in the APC (mutation cluster region), K-ras (exon 2) and BRAF (exon 15) genes. Results: Molecular analysis in HPS polyps and control group polyps showed APC mutations exclusively in adenomas and BRAF mutations exclusively in serrated polyps. BRAF mutations were detected in 43/54(80%) of HPS serrated polyps compared to 20/42 (48%) in control group serrated polyps (p=0.001). APC mutations were detected in 9/20(45%) HPS adenomas compared to 7/17(41%) control group adenomas (ns).In 6/16(38%) cases, HPS CRCs were identified within a serrated polyp. Mutation analysis performed in both the CRC and the serrated component of these lesions showed the same BRAF mutation. In 1/16(6%) cases, HPS CRC was identified within an adenoma which showed an identical APC mutation in both components. Overall, 9/16 (56%) HPS CRCs carried a BRAF mutation compared to 1/16(6%) in control group CRCs (p=0.006). In 2/16(13%) HPS CRCs an APC mutation was identified. One of these had both a BRAF mutation and an APC mutation.
Conclusion: This study provides histological and molecular evidence that both a serrated pathway and a classical Wnt pathway to CRC are prevalent in HPS. A seemingly predominant serrated pathway in HPS could be explained by the reported numerical prevalence of serrated polyps compared to conventional adenomas in the literature. However an increased intrinsic malignant potential in serrated polyps can not be excluded. To prevent malignant progression we propose annual endoscopic surveillance with removal of all polyp types in HPS patients.

Successful prevention of surgery-induced liver metastases development after anti-tumor monoclonal antibody therapy is mediated by the innate mononuclear phagocyte network

S. Grewal[1], M. Bögels[2], G.J. Van der Bij[1,2], M.A. Otten[1], S.J. Oosterling[2], S. Meijer[2], R.H.J. Beelen[1], M. van Egmond[1,2], [1]Dept. of Molecular Cell Biology and Immunology, VU University Medical Centre, Amsterdam, [2]Dept. of Surgical Oncology, VU University Medical Centre, Amsterdam, The Netherlands

Liver metastases are a frequent complication of colorectal cancer (CRC), even after successful resection of the primary tumor. Post-operative adjuvant may help prevent secondary disease. We studied the potential of therapeutic antibodies to prevent outgrowth of liver metastases in mice and rats.Liver metastases were induced in mice via injection of murine B16F10 melanoma cells into the spleen or by injection of rat CC531s colon carcinoma cells into the mesenterial vene in rats. Wild type, FcgRI$^{-/-}$, FcgRIII$^{-/-}$, FcgRI/III$^{-/-}$ or FcgRI/II/III$^{-/-}$ mice were treated with anti-gp75 antibody (TA99). Alternatively, rats were treated with a low or high dose of anti-CC531s antibodies of different isotypes (MG4-γ1 (mIgG1), MG4-γ2a (mIgG2a) and MG4-γ2b (mIgG2b)). Kupffer cells (KC) were depleted in mice and rats. The number of liver metastases was determined 3 weeks after tumor cell inoculation. To study short term events after surgery, animals were sacrificed 24 hours after injection of fluorescently-labeled tumor cells. We showed that anti-tumor antibodies efficiently prevent liver metastases outgrowth. Additionally, efficacy of antibody therapy was dependent on the presence of the IgG receptors FcγRI and FcγIV. Because these receptors are exclusively expressed by cells of the innate mononuclear phagocyte network, we further investigated the role of both monocytes and macrophages in antibody therapy of liver metastases. Less tumor cells were present in livers of control rats that had been treated with antibody 24 hours after tumor cells injection. However, after KC depletion no difference was observed in tumor cell numbers in antibody-treated or non-treated rats, supporting a prominent role for KC. Moreover, treatment with a low antibody dose was sufficient to prevent liver metastases outgrowth in control rats, but therapeutic efficacy was completely abrogated in KC depleted animals. Interestingly, when high doses were injected in KC depleted rats, antibody treatment still partly prevented metastases outgrowth, which was due to phagocytosis of tumor cells by monocytes. Antibody treatment after surgery can efficiently prevent the development of liver metastases. The protective effect of antibodies is mainly mediated by KC. The discovery that KC and monocytes can eliminate tumor cells after surgery through antibody-dependent cellular cytotoxicity has promising clinical implications for designing new adjuvant therapies for patients with CRC.

C-terminal phosphorylation of β-catenin increases its downstream signaling and contributes to intestinal carcinogenesis

W. van Veelen[1], N.H. Le[2], W. Helvensteijn[1], L. Blonden[2], M. Theeuwes[1], E. Bakker[1], L. van Gurp[3], F. Meijlink[3], E.J. Kuipers[1], R. Fodde[2], R. Smits[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, [2]Dept. of Pathology, Josephine Nefkens Institute, Erasmus Medical Centre, Rotterdam, The Netherlands

Colorectal cancer (CRC) is caused by mutations in the APC or b-catenin genes, both leading to increased Wnt signaling. The hallmark of aberrant Wnt signaling is represented by the nuclear accumulation of b-catenin, as observed in virtually all CRC specimens. Various in vitro experiments have shown that activated receptor tyrosine kinases can phosphorylate tyrosine 654 (Y654) at the C-terminus of b-catenin, which could evoke a switch in its function as an adhesion molecule to activation of gene transcription. This suggests that Y654 phosphorylation of b-catenin could contribute to intestinal carcinoma formation.To investigate the in vivo relevance of Y654 phosphorylation of b-catenin, we have generated a conditional knock-in mouse model expressing a modified b-catenin from its endogenous promoter. In this model, Y654 is replaced by glutamic acid (E) which mimicks a phosphorylated tyrosine. We have observed that homozygous b-catenin$^{E654/E654}$ animals are embryonically lethal, caused by anterior truncation, which is associated with increased Wnt signaling. A subset of heterozygous b-catenin$^{Y654/E654}$ animals spontaneously developed intestinal tumors at the age of 16-18 months. Inducing heterozygous intestinal-specific expression of b-catenin-E654 in an Apc mouse model, severely increased the incidence of intestinal adenocarcinomas at the age of 8 months, without obvious effects on tumor grade, suggesting that the Y654E mutation in b-catenin contributes to activation of Wnt signaling. This was confirmed by a significant increase in percentage of cells expressing nuclear b-catenin in tumors isolated from Apc;b-catenin$^{Y654/E654}$ mice compared to tumors from Apc mice. Using mouse embryonic fibroblasts with endogenous expression of either wild-type b-catenin or b-catenin-E654, we could show a reduced interaction of b-catenin-E654 with cadherins compared to wild-type b-catenin. In addition, cells expressing b-catenin-E654 showed an increase in active Wnt signaling as observed by increased expression of the specific target gene Axin2. We have observed that the phosphorylation of S675 in the C-tail of b-catenin, was increased in b-catenin-E654 compared to wild-type b-catenin. S675 is a phosphorylation site for PKA, and its phosphorylation is associated with increased stabilization, binding to co-activators of gene transcription and increased Wnt signaling. Together, we conclude that Y654 phosphorylation of b-catenin contributes to APC-induced intestinal tumor formation through enhancing C-terminal phosphorylation and downstream signaling.

Plattegrond

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Acertys	B 21
Alvleesklliervereniging	B 34
AstraZeneca BV & Abbott BV	B 19
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B.Braun Medical B.V.	B 7
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Cablon Medical b.v.	B 23
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Cook Nederland B.V.	B 15
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Dörr Kampen B.V.	K 13
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