Programma voorjaarsvergadering 17 en 18 maart 2011

NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

Sectie Gastrointestinale Endoscopie
Netherlands Society for Parenteral and Enteral Nutrition
Sectie Neurogastroenterologie en Motiliteit
Sectie Experimentele Gastroenterologie
Sectie Kinder-MDL
V & VN MDL

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

NVGIC Nederlandse Vereniging GastroIntestinale Chirurgie

NEDERLANDSE VERENIGING VOOR GASTROINTESTINALE CHIRURGIE

MDL

NEDERLANDSE VERENIGING VAN MAAG-DARM-LEVERARTSEN

Locatie:

NH KONINGSHOF VELDHOVEN

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Tijdstippen diverse ledenvergaderingen donderdag:

Nederlandse Vereniging voor Gastroenterologie	*17 maart,*	*11.30 uur – Brabantzaal*
Juniorvereniging – NVMDL (MDL-artsen i.o.)	*17 maart*	*12.00 uur – Zaal 83*
Nederlandse Vereniging voor Hepatologie	*17 maart,*	*15.00 uur – Baroniezaal*

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Tijdstippen diverse ledenvergaderingen vrijdag:

Sectie Experimentele Gastroenterologie	*18 maart, 08.00 uur – Baroniezaal*
ALV NVMDL, met lunch	*18 maart, 12.00 uur – Genderzaal*
V & VN MDL	*18 maart, 11.50 uur – Diezezaal*
Sectie Kinder-MDL	*18 maart, 13.30 uur - Zaal 82*

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 17 en 18 maart a.s. in Congrescentrum Koningshof te Veldhoven.
Zoals gebruikelijk wordt onze tweedaagse wetenschappelijke voorjaarsvergadering vooraf gegaan door het cursorisch onderwijs in MDL-ziekten (zie programma pag. 6).

Het programma gaat op donderdag om 10.00 uur van start gaan met drie parallelle sessies van de NVGE in de Brabantzaal, het Auditorium en de Parkzaal. In de Baroniezaal start de Dutch Experimental Gastroenterology and Hepatology Meeting, een gezamenlijk initiatief van de sectie experimentele gastroenterologie van de NVGE en de sectie basale hepatologie van de NVH. Vanaf 12.00 organiseert de DEGH postersessies in de Meierijfoyer.

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 vindt na de lunch een symposium plaats, getiteld: 'Centralisatie van zorg: noodzakelijk, nuttig of (on)aangenaam?'
Later in de middag zijn er vrije voordrachten te volgen van de Sectie Neurogastroenterologie en Motiliteit, en de Nederlandse Vereniging voor Gastroenterologie in respectievelijk Auditorium en Parkzaal. Om 17.00 uur vindt in de Brabantzaal een lecture plaats, verzorgd door prof. dr. M.A. Cuesta. De lezing is getiteld: 'Laparoscopische chirurgie 1990-2010'. Aansluitend daaraan om 17.30 uur de President Select, 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 ruim gelegenheid is voor diner en ontspanning.

Op vrijdagochtend vanaf 08.30 uur vrije voordrachten van de Sectie Gastrointestinale Endoscopie en parallel daaraan in de vrije voordrachten van de Nederlandse Vereniging voor Gastroenterologie in de Parkzaal. Na de koffiepauze abstracts van de Sectie Kinder-MDL en NESPEN in respectievelijk de Parkzaal en zaal 80. Gedurende de gehele vrijdag zijn er behalve de sessies met genodigde sprekers en vrije voordrachten van de DEGH, ook vrije voordrachten van de Nederlandse Vereniging voor Gastroenterologie. In de Diezezaal wordt door de Vereniging Verpleegkundigen en Verzorgenden Nederland MDL (V&VN MDL, voorheen SEVA en VMDLV) eigen programma's met lezingen verzorgd. In de middag is er tot slot in de Brabantzaal een programma rond de herziene richtlijn oesophaguscarcinoom.

Mede namens het bestuur wens ik u een nuttig congres toe!

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 de Geneesmiddelenwet die per 1 juli 2007 in werking is getreden is een hoofdstuk Geneesmiddelenreclame (hoofdstuk 9) opgenomen waarin de regels hieromtrent zijn vastgelegd. Daarnaast gelden per 1 juli 2007 de 'Beleidsregels nadere invulling begrip gunstbetoon'. 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)
Drs. M. Bargeman (aios MDL, UMCG)
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. J. Bosman (aios MDL, UMCU)
Dr. R. Timmer (MDL-arts, Antonius Nieuwegein)

Onderwerp: **Dunne darm en pancreas**

Voorzitter: R. Timmer

15.00 – 15.15 Evaluatie toets

15.15 – 15.45 Diagnostiek en classificatie van acute pancreatitis
Dr. Th. Bollen, radioloog, St. Antonius Ziekenhuis, Nieuwegein

15.45 – 16.15 Behandeling acute pancreatitis
Dr. M.G.H. Besselink, chirurg i.o., St. Antonius Ziekenhuis, Nieuwegein

16.15 – 16.45 Diagnostiek en endoscopische behandeling chronische pancreatitis
Dr. J.W. Poley, MDL-arts, Erasmus MC Rotterdam

16.45 – 17.15 Pauze

Voorzitter: E. van der Harst

17.15 – 17.45 Chirurgische behandeling van chronische pancreatitis, pijnbestrijding en lange termijn prognose
Dr. M.A. Boermeester, chirurg, Academisch Medisch Centrum, Amsterdam

17.45 – 18.15 Dunne darm diagnostiek
Dr. M.A.M.J. Jacobs, MDL-arts, VU medisch centrum, Amsterdam

18.15 – 18.45 Short bowel syndrome
Dr. G.J.A. Wanten, MDL-arts, UMC St. Radboud, Nijmegen

18.45 – 20.00 Dinerbuffet

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

Voorzitter: P.D. Siersema

20.00 – 20.30 Ischemie
Dr. J. Kolkman, MDL-arts, Medisch Spectrum Twente, Enschede

20.30 – 21.00 Chronische niet infectieuze diarree
Prof. dr. J.H. Kleibeuker, MDL-arts UMC Groningen

Voorzitter: P.D. Siersema

21.00 – 22.10 Paneldiscussie met M. Boermeester, J. Kolkman, J.H. Kleibeuker en G. Wanten aan de hand van casuïstiek
1. Short bowel syndrome PTV en dunne darm transplantatie (UMCG)
2. Chronische pancreatitis endoscopisch/chirurgisch (MUMC)
3. Acute on chronic ischemia (Antonius Nieuwegein)

22.10 – 22.30 Afsluitende kennistoets

De cursuscommissie verwacht van de MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie (die deel uitmaakt van de Dutch Liver Week van de Nederlandse Vereniging voor Hepatologie) éénmaal bezoeken in het tweede deel van de MDL-opleiding (jaar vier tot zes).

Programma donderdag 17 maart 2011

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
10.00 – 12.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie gevolgd door ALV 11.30 p. 10	DEGH-Meeting v.a. 10.30 Gastspreker: Prof. dr. N. Barker p. 14	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 23	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 11	Geen programma in deze zaal op donderdag
12.00 – 13.00	Lunchbuffet expositiehal	Lunchbuffet- postersessie			
13.00 – 15.00	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 15	DEGH-Meeting v.a. 13.30 p. 27	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 25	Symposium Centralisatie van Zorg: noodzakelijk, nuttig of (on)aangenaam? p. 20	
15.00 – 15.30	Theepauze	Theepauze & NVH ALV		Theepauze	
15.30 – 17.00	Vrije voordrachten Ned. Ver. voor Gastroenterologie en Gastrointestinale Chirurgie p. 17	DEGH-Meeting (vervolg) Gastspreker: Dr. J. Banales p. 28	15.00 uur: Programma Leververpleegkundigen Netwerk p. 30	Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit p. 21	
17.00 – 17.30	**Invited Lecture** Prof. dr. M.A. Cuesta	Einde programma deze zaal	Vervolg programma tot 17.45	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 18 maart 2011

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	ZAAL 80	DIEZEZAAL
08.30 – 09.00	Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 31	DEGH Meeting Gastspreker: Prof. dr. J. McKeating p. 39	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 36		
09.00 – 10.30	Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 31	Vervolg programma DEGH Meeting p. 40	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 36		Programma V&VN MDL (aanvang 10.15) p. 49
10.30 – 11.00	Koffiepauze	Koffiepauze	Koffiepauze		Koffiepauze
11.00 – 12.00	Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 30	DEGH Meeting (tot 12.30) Gastspreker: Prof. dr. L. Dieleman p. 40	Vrije voordrachten Sectie Kinder-MDL p. 38	Vrije voordrachten van NESPEN p. 34	Vervolg Programma V&VN MDL p. 49
12.00 – 13.30	Lunchbuffet expositiehal Ledenvergadering NVMDL	Lunchbuffet- postersessie	Lunchbuffet expositiehal	Netwerk lunch NESPEN	Lunchbuffet expositiehal
13.30 – 15.30	Symposium rond herziene richtlijn oesophagus carcinoom (tot 15.00 uur) p. 42	DEGH Meeting gevolgd door prijsuitreikingen p. 43	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 44	Symposium: 'Body composition, body function and energy expenditure' (vanaf 13.00) p. 47	Vervolg Programma V&VN MDL p. 49
15.30	Koffie/thee expositiehal	Koffie/thee expositiehal	Koffie/thee expositiehal	Einde programma 15.30	Einde programma 15.15

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

09.30 Inschrijving, koffie

Voorzitters: M.J. Bruno en J.M. Conchillo

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

10.00 Trademark and generic acid suppressive drugs more than 10 years after the endoscopical diagnosis of reflux oesophagitis (p. 60)
G.M.H.E. Dackus, S.M.L.A. Loffeld, R.J.L.F. Loffeld, Medical students University of Maastricht, Dept of Internal Medicine Zaans Medisch Centrum, Zaandam, The Netherlands

10.10 Complaints in patients with reflux oesophagitis more than 10 years after the diagnosis (p. 61)
S.M.L.A. Loffeld, G.M.H.E. Dackus, R.J.L.F. Loffeld, Medical students University of Maastricht, Dept of Internal Medicine Zaans Medisch Centrum, Zaandam, The Netherlands

10.20 Risk factors for prevalent adenocarcinomas in patients with high-grade dysplasia in Barrett's esophagus: a Dutch population-based study (p.62)
R.E. Verbeek[1], M.G.H. van Oijen[1], F.J. ten Kate[2], F.P. Vleggaar[1], M.E.I. Schipper[2], J.W.P.M. van Baal[1], P.D. Siersema[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Pathology, University Medical Center Utrecht, The Netherlands

10.30 Inter- and intra observer variability in pH-impedance measurements between10 experts in pediatric gastroesophageal reflux and automated analysis (p.63)
C.M. Loots[1], M.P. van Wijk[1], K. Blondeau[4], K. Dalby[5], L. Peeters[1], R. Rosen[6], S. Salvatore[7], T.G Wenzl[8], Y. Vandenplas[9], M.A. Benninga[1], T.I. Omari[2,3], [1]Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands, [2]Women's and Children's Hospital, Adelaide, SA, Australia, [3]University of Adelaide, Adelaide, SA, Australia, [4]Centre for Gastroenterological Research, KU Leuven, Leuven, Belgium, [5]H.C Andersen children's hospital, Odensee, Denmark, [6]Children's Hospital Boston, Boston, MA, United States, [7]Università dell'Insubria, Varese, Italy, [8]Universitätsklinikum der RWTH Aachen, Germany, [9]Universitair Ziekenhuis Brussel, Brussels, Belgium

10.40 Screening for dysplasia in idiopathic achalasia using Lugol staining (p.64)
W.O.A. Rohof[1], J.J. Bergman[1], J.F. Bartelsman[1], D.P. Hirsch[1], G.E.E. Boeckxstaens[1,2] , [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Gastroenterology, University Hospital of Leuven, Leuven, Belgium

10.50 Adherence to gastroprotective agents and the risk of upper gastrointestinal complications in coxib users (p.65)

V.E. Valkhoff[1,2], E.M. van Soest[1], G. Mazzaglia[3], R.K.F. Schade[1], M. Molokhia[4], J.L. Goldstein[5], S. Hernandez-Diaz[6], G. Trifirò[1], J.P. Dieleman[1], E.J. Kuipers[2], M.C.J.M. Sturkenboom[1,7], [1]Dept of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology, Rotterdam Erasmus University Medical Center, The Netherlands, [3]Health Search, Italian College of General Practitioners, Florence, Italy, [4]Dept of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom, [5]University of Illinois at Chicago, Chicago, USA, [6]Dept of Epidemiology, Harvard School of Public Health, Boston, USA, [7]Dept of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands

11.00 Gastric acid suppressive therapy and community-acquired pneumonia, etiology and outcome (p.66)

R. Laheij[1], P. de Jager[2], E. Gemen[3], M. van Oijen[1], R. van Gageldonk-Lafeber[5] , P. Siersema[1], R. Kusters[3], P. Wever[4], [1]Gastroenterology and Hepatology, UMC Utrecht, Utrecht, [2]Intensive Care, Jeroen Bosch Hospital, 's Hertogenbosch, [3]Clinical Chemistry, Jeroen Bosch Hospital, 's Hertogenbosch, [4]Microbiology, Jeroen Bosch Hospital, 's Hertogenbosch, [5]National Institute for Public Health and the Environment, Bilthoven, The Netherlands

11.10 Functional dyspepsia patients have lower mucosal cholecystokinin concentrations in response to duodenal lipid (p.67)

O.S. van Boxel[1], J.J.M. ter Linde[1], J. Oors[1, 5], B. Otto[3], B.L.A.M. Weusten[4], C. Feinle-Bisset[2], A.J.P.M. Smout[1, 5], P.D. Siersema[1], [1]Departement of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands, [2]University of Adelaide Discipline of Medicine and Centre of Clinical Research Excellence in Nutritional Physiology, Interventions and Outcomes, Royal Adelaide Hospital, Adelaide, Australia, [3]Dept of Gastroenterology, Medizinische Klinik - Campus Innenstadt, München, Germany, [4]Dept of Gastroenterology, St. Antonius Hospital Nieuwegein, The Netherlands, [5]Dept of Gastroenterology, Academic Medical Center Amsterdam, The Netherlands

11.20 The quality of prediction scores in gastrointestinal bleeding: a systematic review and quantitative appraisal (p.68)

N.L. de Groot[1], P.D. Siersema[1], M.G.H. van Oijen[1], [1]University Medical Center Utrecht, Dept of Gastroenterology and Hepatology, The Netherlands

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 en J.Ph. Kuijvenhoven

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

10.00 Risk factors for metachronous advanced colorectal neoplasia in a cohort of adenoma patients: advanced morphology and multiplicity (p.69)

E.M.B. van Heijningen[1], I. Lansdorp-Vogelaar[1], V. de Jonge[2], E.W. Steyerberg[1], E.J. Kuipers[2, 3], M. van Ballegooijen[1], [1]Dept of Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Dept of Gastroenterology and Hepatology and [3]Dept of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

10.10 Detection of proximal serrated polyps is dependent on quality of bowel prep and the endoscopist (p.70)

T.R. de Wijkerslooth[1], E.M. Stoop[2], P.M. Bossuyt[3], K.M.A.J. Tytgat[1], J. Dees[2], E.M.H. Mathus-Vliegen[1], E.J. Kuipers[2,4], P. Fockens[1], M.E. van Leerdam[2] and E. Dekker[1], [1]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [3]Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, [4]Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

10.20 Influence of body mass index on outcome in advanced colorectal cancer patients receiving chemotherapy with or without targeted therapy (p.71)

L.H.J. Simkens[1], M. Koopman[2], L. Mol[3], G.J. Veldhuis[4], D. ten Bokkel Huinink[5], E.W. Muller[6], V.A. Derleyn[7], S. Teerenstra[8], C.J.A. Punt[1], [1]Radboud University Nijmegen Medical Centre, Dept of Medical Oncology, Nijmegen, [2]University Medical Centre Utrecht, Dept of Medical Oncology, Utrecht, [3]Comprehensive Cancer Centre East (IKO), Nijmegen, [4]Antonius Hospital, Dept of Internal Medicine, Sneek, [5]Diakonessenhuis, Dept of Internal Medicine, Utrecht, [6]Slingeland Hospital, Dept of Internal Medicine, Doetinchem, [7]Elkerliek Hospital, Dept of Internal Medicine, Helmond, [8]Radboud University Nijmegen Medical Centre, Dept of Epidemiology, Biostatistics, and HTA, Nijmegen, The Netherlands

10.30 Microsatellite instability screening in young colorectal cancer patients in the Mid-Netherlands in the period 1999-2008 (p.72)

K. Kessels[1,2], N.L. de Groot[2], M.G.H. van Oijen[2], M. Brink[3], T.G. Letteboer[4], R. Timmer[1], M.F. Stolk[1], C.A. Seldenrijk[5], T. van Dalen[6], J. van Gorp[7], E.C. Consten[8], M.L.R. Tjin-A-Ton[9], H. Vente[10], D.R. de Vries[1], H.H. Fidder[2], G.J. Offerhaus[11], P.D. Siersema[2], [1]Dept of Gastroenterology and hepatology, Sint Antonius Hospital, Nieuwegein, [2]Dept of Gastroenterology and hepatology, University Medical Center Utrecht, Utrecht, [3]Comprehensive Cancer Center Mid-Netherlands, Utrecht, [4]Dept of Clinical Genetics, University Medical Center Utrecht, Utrecht, [5]Dept of Pathology, Sint Antonius Hospital, Nieuwegein, [6]Dept of Surgery, Diakonessenhuis Hospital, Utrecht, [7]Dept of Pathology, Diakonessenhuis Hospital, Utrecht, [8]Dept of Surgery, Meander Medical Center, Amersfoort, [9]Dept of Internal Medicine, Rivierenland Hospital, Tiel, [10]Dept of Surgery, Zuwe Hofpoort Hospital, Woerden, [1]Dept of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

10.40 Risk factors for the combined adenoma-serrated phenotype: a population-based study (p.73)

M. Bouwens[1], E. Rondagh[1], M. Weijenberg[2], B. Winkens[3], A. Masclee[1], S. Sanduleanu[1], [1]Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, [2]Dept of Epidemiology, Maastricht University Medical Center, [3]Dept of Methodology and Statistics, Maastricht University Medical Center, The Netherlands

10.50 Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) for colorectal polyp and cancer detection: a prospective feasibility study (p.74)

A.M. Leufkens[1], T.C. Kwee[2], M.A.A.J. van den Bosch[2], W.P.Th.M. Mali[2], T. Takahara[2], P.D. Siersema[1], [1]Dept of Gastroenterology, University Medical Center Utrecht, Utrecht, [2]Dept of Radiology, University Medical Center Utrecht, The Netherlands

11.00 Can an individual risk profile for CRC be used as triage test in CRC screening (p.75)

I. Stegeman[1, 4], T.R. de Wijkerslooth[2], E.M. Stoop[3], M. van Leerdam[3], E. Dekker[2], E.J. Kuipers[3], P. Fockens[2], R.A. Kraaijenhagen[4], P.M. Bossuyt[1], [1]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academical Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [3]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, [4]Research and Development, NDDO Institute for Prevention and Early Diagnostics, Amsterdam, The Netherlands

11.10 The incidence and prediction of carcinomatosis peritonei in patients with a T4 colorectal carcinoma (p.76)

N.R. Koning[1], K.R. Spekreijse[1], H.C. van Santvoort[1], P.C. de Bruin[2], B. van Ramshorst[1], A.B. Smits[1], T.S. de Vries Reilingh[1], M.J. Wiezer[1], St. Antonius Hospital, Nieuwegein, Dept of [1]Surgery and [2]Pathology

11.20 Rage signaling promotes intestinal tumorigenesis (p.77)

N.V.J.A. Büller[1], J. Heijmans[1], E. Hoff[2], A.A. Dihal[2], I. Biemond[2], D.W. Hommes[2], V. Muncan[1], G.R. van den Brink[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands

Einde abstractsessie

11.30 **Ledenvergadering NVGE in de Brabantzaal**

12.00 Lunchbuffet in expositiehal

Donderdag 17 maart 2011

DEGH-Meeting **Baroniezaal**

Voorzitters: N. Barker en E.H.H.M. Rings

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

Theme: Stem cell biology

10.30 Non-canonical Bone Morphogenetic Protein signaling induces Epithelial to Mesenchymal Transition in SMAD4 deficient colorectal cancer (p.78)
P.W. Voorneveld[1], L.L. Kodach[1], R.J. Jacobs[1], D.W. Hommes[1], G.R. van den Brink[2], M.P. Peppelenbosch[3] and J.C.H. Hardwick[1], [1]Dept of Gastroenterology & Hepatology, Leiden University Medical Center, Leiden, [2]Tytgat Institute for Liver & Intestinal Research, Academic Medical Center, Amsterdam, [3]Dept of Gastroenterology & Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

10.42 ER-stress is sufficient for intestinal stem cell differentiation (p.79)
J. Heijmans[1, 2], V. Muncan[1, 2], T.C. Wielengajs[1], L.L. Kodach[2], J. van der Zon[2], I. Biemond[2], J.C. Hardwick[2], A.S. Lee[3] , J. Paton[4], A. Paton[4], D.W. Hommes[2], G.R. van den Brink[1, 5], [1]Tytgat Institute for Liver and Intestinal Research, AMC, Amsterdam, [2]Dept of Gastroenterology and Hepatology, LUMC, Leiden, [3]University of Southern California Keck School of Medicine, Los Angeles, CA, United States, [4]School of Molecular and Biomedical Science, University of Adelaide, Adelaide, SA, Australia, [5]Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands

10.54 Intestinalization of esophageal squamous cells depends on a synergistic collaborative interaction between the BMP4/PSMAD pathway and CDX-2 (p.80) *F. Milano[1], A. Pacha[1], K.A. Hoebe[2], J. Van Marle[2], R. Versteeg[3], K.K. Krishnadath[4], [1]Dept of Experimental Internal Medicine, Academic Medical Center, Amsterdam, [2]Dept of Cell Biology and Histology, Academic Medical Center, Amsterdam, [3]Dept of Antropogenetics, Academic Medical Center, Amsterdam, [4]Dept of Gastroenterology and Hepathology, Academic Medical Center, Amsterdam, The Netherlands*

11.06 Local administration of bone marrow-derived mesenchymal stromal cells induces normal liver regeneration in liver fibrosis (p.81) *E.S.M. de Jonge-Muller, B. van Hoek, B.F. de Rooij, M. Duijvestein, M.J. Coenraad, D.W. Hommes, H.W. Verspaget, Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands*

11.18 Adverse effects of mTOR inhibition on liver regeneration and autophagy (p.82) *S.M.G. Fouraschen[1], J. de Jonge[1], R.W.F. de Bruin[1], H.J. Metselaar, G. Kazemier[1], J. Kwekkeboom[2], H.W. Tilanus[1] and L.J.W. van der Laan[1], Depts of [1]Surgery and [2]Gastroenterology & Hepatology, Erasmus MC-University Medical Center Rotterdam, The Netherlands*

11.30 **Invited Speaker: Prof. dr. Nick Barker**
"Lgr5 Stem Cells in Epithelial Renewal and Disease".

Postersessie DEGH **Meierij 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. Vier posters per categorie, 7 min. per poster, zie pag. 50.

13.30 Vervolg DEGH-programma in de Baroniezaal.

Ned. Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

Voorzitters: M. Bemelmans en F. Holman

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

13.00 Quality of life after surgery for colon cancer in patients with Lynch syndrome, partial versus (sub)total colectomy (p.83)

J.F. Haanstra[1], W.H. de Vos tot Nederveen Cappel[1], J. Vecht[1], S.A.L.W. Vanhoutvin[2], A. Cats[2], J.H. Kleibeuker[3], A.M.J. Langers[4], P.C. van de Meeberg[5] , E. Dekker[6] , J.H.W. Bergmann[7], H.F.A. Vasen[8], F.M. Nagengast[9], P. van Duijvendijk[9], [1]Isala clinics, Zwolle, The Netherlands, [2]Cancer Institute Antoni van Leeuwenhoek hospital, Amsterdam, [3]University Medical Centre Groningen, Groningen, [4]Leids University Medical Centre, Leiden, [5]Slingeland hospital, Doetinchem, [6]Academic Medical Centre, Amsterdam, [7]Martini hospital, Groningen, [8]Netherlands Foundation for the Detection of Hereditary Tumors (NFDHT), Leiden, [9]Radboud University Medical Centre Nijmegen, Nijmegen, The Netherlands

13.10 Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicenter randomized trial (Stent-in 2 study) (p.84)

J.E. van Hooft[1,5], W.A. Bemelman[2], B. Oldenburg[3], A.W. Marinelli[4], M. Lutke Holzik[6], M.J. Grubben[7], M.A. Sprangers[8], M.G. Dijkgraaf[9], P. Fockens[1] for the collaborative Dutch Stent-In study group, [1]Dept of Gastroenterology and Hepatology and [2]Dept of Surgery, Academic Medical Centre, University of Amsterdam, [3]Dept of Gastroenterology and Hepatology, University Medical Centre, Utrecht, [4]Dept of Surgery, Medical Centre Haaglanden, Den Haag, [5]Dept of Gastroenterology and [6]Dept of Surgery, Medisch Spectrum Twente, Enschede, [7]Dept of Gastroenterology, Sint Elisabeth Hospital, Tilburg, [8]Dept of Medical Psychology, Academic Medical Centre, Amsterdam, [9]Clinical Research Unit, Academic Medical Centre, Amsterdam, The Netherlands

13.20 Outcomes of patients undergoing repeated cytoreductive surgery and peri-operative chemotherapy for recurrent colorectal cancer peritoneal carcinomatosis (p.85)

Y.L.B. Klaver[1,2], T.C. Chua[2], I.H.J.T. de Hingh[1], D.L. Morris[2], Dept of Surgery[1], Catharina Hospital, Eindhoven, The Netherlands, Dept of Surgery[2], St. George Hospital, University of New South Wales, Sydney, Australia

13.30 Neoadjuvant short course radiotherapy followed by transanal endoscopic microsurgery six weeks later for T2N0 or T3N0 rectum carcinoma in frail elderly patients: a pilot study (p.86)

I.D. Ayodeji[1], S. Vennix[2], E.R. Manusama[3], M.L. Smidt[2], C. Hoff[3], [1]Dept of General surgery, VU medical center Amsterdam, [2]Dept of General surgery, Maastricht Medical Center, [3]Dept of General surgery, Leeuwarden medical center, The Netherlands

13.40 Adherence to adjuvant treatment guidelines in high risk stage II colonic cancer patients (p.87)

B. Koebrugge[1], V.E.P.P. Lemmens[2], D.J. Lips[1], J.F.M. Pruijt[3], J.C. van der Linden[4], M.F. Ernst[1], K. Bosscha[1], [1]Depts of Surgery, [3]Oncology, [4]Pathology, Jeroen Bosch Hospital, [2]Eindhoven Cancer Registry, Eindhoven, The Netherlands

13.50 Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study (p.88)

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

14.00 Colonoscopy after conservative treated diverticulitis: sense or non-sense? (p.89)

E.M.B.P. Reuling[1], B.J.M. van de Wall[1], W.A. Draaisma[1], J.H.J. van Grinsven[1], M.P. Schwartz[2], I.A.M.J. Broeders[1], E.C.J. Consten[1], Dept of [1]Surgery and [2]Gastroenterology, Meander Medical Center, Amersfoort, The Netherlands

14.10 Short-term outcomes of ligation anopexy in combination with transanal hemorrhoidal dearterilisation (THD) for the treatment of mucosal rectal prolapse and hemorrhoids (p.90)

S.M.J. ter Veldhuis[1], J.M. Klaase[1], R. Koop[1], J. van der Palen[2], M.F. Lutke Holzik[1], Depts of [1]Surgery and [2]Epidemiology, Medical Spectrum Twente, Enschede, The Netherlands

14.20 Alternative specimen extraction techniques after laparoscopic emergency colectomy in Inflammatory Bowel Disease (p.91)

T.J. Gardenbroek[1,2], E.J. Eshuis[1,2], G.J.D. van Acker[3], P.J. Tanis[1], W.A. Bemelman[1], Depts of [1]Surgery and [2]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept of Surgery, Medical Center Haaglanden, The Hague, The Netherlands

14.30 Ileocolic resection: a safe and durable option for limited Crohn's disease of the terminal ileum (p.92)

E.J. Eshuis[1,2], A. Kraima[1], C.P. Ponsioen[2], P.C.F. Stokkers[2,3], W.A. Bemelman[1], [1]Dept of Surgery, Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept of Gastroenterology and Hepatology, St Lucas Andreas Hospital, Amsterdam, The Netherlands

14.40 MRI features associated with acute appendicitis (p.93)

M.M.N. Leeuwenburgh[1,2], M.E. Thieme[3], B.M. Wiarda[3], S. Bipat[2], P.M.M. Bossuyt[4], J. Stoker[2], M.A. Boermeester[1], Depts of [1]Surgery, [2]Radiology and [4]Clinical epidemiology, Academic Medical Centre Amsterdam, Amsterdam, [3]Dept of Radiology, Alkmaar Medical Center, Alkmaar, The Netherlands

14.50 Longitudinal health-related quality of life and self-reported treatment preference of patients scheduled for pancreatoduodenectomy with or without preoperative biliary drainage (p.94)

N.A. van der Gaag[1], S.M.M. de Castro[1], M.A. Sprangers[2], O.R. Busch[1], E.A. Rauws[3], M.J. Bruno[4], T.M. van Gulik[1], P.M.M. Bossuyt[5], D.J. Gouma[1], Depts of [1]Surgery, [2]Medical Psychology and [3]Gastroenterology, Academic Medical Center, Amsterdam, Depts of [4]Gastroenterology and [5]Clinical Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

15.00 Locally advanced pancreatic and periampullary cancer – is palliative resection justified? (p.95)

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

15.10 Theepauze

Voorzitters: M.I. van Berge Henegouwen en E. Uludag

15.30 Preconditioning in patients undergoing esophagectomy: A randomized controlled pilot study (p.96)

H. Heynen[1], C. de Jonge[1], J.Willms[2], H. Kerkkamp[1], M.N. Sosef[1], Depts of [1]Surgery and [2]Physical Therapy, Atrium Medical Centre, Heerlen, The Netherlands

15.40 Implementation of an enhanced recovery program in esophageal surgery (p.97)

R.L.G.M. Blom[1], M. van Heijl[1], W.A. Bemelman[1], M.W. Hollmann[2], R. Tepaske[2], J.H.G. Klinkenbijl[1], O.R.C. Busch[1], M.I. van Berge Henegouwen[1], Depts of [1]Surgery and [2]Anesthesiology, Academic Medical Center, Amsterdam, The Netherlands

15.50 Results of the introduction of a minimally invasive esophagectomyprogram in a tertiary referral center (p.98)

R.L.G.M. Blom[1], J.H.G. Klinkenbijl[1], M.W. Hollmann[2], O.R.C. Busch[1], M.I. van Berge Henegouwen[1], Depts of [1]Surgery and [2]Anesthesiology, Academic Medical Center, Amsterdam, The Netherlands

16.00 Low impact of staging EUS for determining surgical resectability of esophageal cancer (p.99)

M. van Zoonen[1], M.S. van Leeuwen[2], R. van Hillegersberg[3], M.G.H van Oijen[1], P.D Siersema[1], F.P. Vleggaar[1], [1]University Medical Center Utrecht, Dept of Gastroenterology and Hepatology, [2]University Medical Center Utrecht, Dept of Radiology, [3]University Medical Center Utrecht, Dept of Surgery, The Netherlands

16.10 High expression of the mammalian target of rapamycin is associated with poor survival in patients diagnosed with esophageal adenocarcinoma, is there a role for rapamycin targeted therapy? (p.100)

M.J.D Prins[1], R.J.J. Verhage[1], F.J.W. ten Kate[2], R. van Hillegersberg[1], Depts of [1]Surgery and [2] Pathology, University Medical Center Utrecht, The Netherlands

Donderdag 17 maart 2011

16.20 Assessment of hepatic function using hepatobiliary scintigraphy in patients with parenchymal liver disease (p.101)

W. de Graaf[1], J.J.T.H. Roelofs[2], L.T. Hoekstra[1], R.J. Bennink[3] and T.M. van Gulik[1], Depts of [1]Surgery, [2]Pathology, [3]Nuclear Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

16.30 Metastatic lymph nodes in hilar cholangiocarcinoma: does size matter? (p.102)

A.T. Ruys[1], F.J. TenKate[2], M.R. Engelbrecht, O.R. Busch[1], D.J.Gouma[1] , T.M. van Gulik[1], Depts of [1]Surgery, [2]Pathology and [3]Radiology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands

16.40 Improved liver regeneration and functional recovery after partial hepatectomy in fatty livers treated with omega-3 fatty acids in rats (p.103)

H.A. Marsman[1], W. de Graaf[1], M. Heger[1], F.J.W. ten Kate[2], R. Bennink[3], T.M. van Gulik[1], Depts of [1]Surgery, [2]Pathology and [3]Nuclear Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

16.50 Pancreatic neuroendocrine Tumors (PNETs): diagnostic and operative results (p.104)

E.J.M. Nieveen van Dijkum[1], P.H.L.T. Bisschop[2], P. Fockens[3], E.A.J. Rauws[3], O.R.C. Busch[1], T.M. van Gulik[1], D.J. Gouma[1], Depts of [1]Surgery, [2]Endocrinology and Metabolism and [3]Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands

17.00 **Invited Lecture prof. dr. M.A. Cuesta**
'Laparoscopische chirurgie 1990-2010'

President Select (plenaire sessie) — Brabantzaal

Voorzitter: C.J.J. Mulder

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

17.30 Endoscopic closure of iatrogenic perforations of the gastrointestinal tract using the over-the-scope-clip: a prospective multicenter human trial (p.105)

R.P. Voermans[1], P. Deprez[2], O. Le Moine[3], Th. Ponchon[4], A. Larghi[5], J.J.G.H. Bergman[1], M. Giovannini[7], J. Haringsma[8], M. Bruno[8], D. von Renteln[9], H. Neuhaus[6], B. Weusten[10], J. Deviere[3], G. Costamagna[5], P. Fockens[1], Dept of Gastroenterology, AMC[1], Amsterdam & EMC[8], Rotterdam & St. Antonius Hospital[10], Nieuwegein, The Netherlands, Cliniques Universitaires Saint-Luc[2] & Erasme University Hospital[3] , Brussels, Belgium, Hôpital Edouard Herriot[4], Lyon, France, Catholic University of Rome[5], Italy, Evangelisches Krankenhaus[6], Düsseldorf & Universitätsklinikum Hamburg[9], Germany, Paoli-Calmettes Institute[7], Marseille, France

17.45 Chemoprevention in Barrett's esophagus with non-steroidal anti-inflammatory drugs and statins: results of a large multicenter prospective cohort study (p.106)

F. Kastelein[1], M.C.W. Spaander[1], K. Biermann[2], E.W. Steyerberg[3], H. Geldof[5], P.C.J. ter Borg[6], W. Lesterhuis[7], E.C. Klinkenberg[8], F. ter Borg[9], J.J. Kolkman[10], B. den Hartog[11], A.J.P. van Tilburg[12], T.G. Tan[13], F.T.M. Peters[14], B.E. Schenk[15], L.G.J.B. Engels[16], E.J. Kuipers[1,4], M.J. Bruno[1], Dept of [1]Gastroenterology & Hepatology, [2]Pathology, [3]Public health and [4]Internal medicine, Erasmus Medical Center, Rotterdam, [5]Dept of Gastroenterology & Hepatology , IJsselland Hospital, Capelle a/d IJssel, [6]Dept of Gastroenterology & Hepatology , Ikazia Hospital, Rotterdam, [7]Dept of Gastroenterology & Hepatology, Albert Schweitzer Hospital, Dordrecht, [8]Dept of Gastroenterology & Hepatology, VU Medical Center, Amsterdam, [9]Dept of Gastroenterology & Hepatology , Deventer Hospital, Deventer, [10]Dept of Gastroenterology & Hepatology , Medisch Spectrum Twente, Enschede, [11]Dept of Gastroenterology & Hepatology, Rijnstate Hospital, Arnhem, [12]Dept of Gastroenterology & Hepatology , Sint Franciscus Gasthuis, Rotterdam, [13]Dept of Gastroenterology & Hepatology, ZGT Hospital, Hengelo, [14]Dept of Gastroenterology & Hepatology, University Medical Center, [15]Dept of Gastroenterology & Hepatology , Isala Clinics, Zwolle, [16]Dept of Gastroenterology & Hepatology, Orbis Medical Center, Sittard, The Netherlands

18.00 Exosomes can mediate transmission of Hepatitis C Virus in the presence of neutralizing antibodies: relevance for Hepatitis C recurrence? (p.107)

V. Ramakrishnaiah[1], P. de Ruiter[1], R. Willemsen[1], J. Demmers[1], H.W Tilanus[1], D. Diederick[1], G. Jenster[1], J. de Jonge[1], G. Kazmier[1], J. Kwekkeboom[1], H.J Metselaar[1] and L.J.W Van der Laan[1], Erasmus MC-University Medical Centre, Rotterdam, The Netherlands

18.15 High incidence of a second primary esophageal squamous cell carcinoma in patients with previous head-and-neck cancer: a nationwide population-based study (p.108)

C.A.I. Schotborgh[1], L. Liu[2,3], V.E.P.P. Lemmens[3], I. Soerjomataram[2], J.J.G.H.M. Bergman[4] and E.J. Schoon[1], [1]Dept of Gastro-enterology, Catharina Ziekenhuis, Eindhoven, [2]Dept of Public Health, Erasmus MC, Rotterdam, [3]Integraal Kankercentrum Zuid, IKZ, Eindhoven, [4]Dept of Gastro-enterology, Academisch Medisch Centrum Universiteit van Amsterdam, Amsterdam, The Netherlands

18.30 Einde programma, congresborrel in de expositiehallen

19.30 Diner in de Genderzaal

Donderdag 17 maart 2011

Symposium **Auditorium**

Voorzitters: J.P.H. Drenth en H.J. Verkade

Centralisatie van Zorg: noodzakelijk, nuttig of (on)aangenaam?

Sedert publicatie van studies die wijzen op het verband tussen operatievolume en sterfte zijn artsen, politici en patiënten in debat over het centraliseren van zorg. Zeldzame operaties met een hoog risico zouden thuishoren in ziekenhuizen met veel ervaring. Nu de discussie over de al dan niet afgedwongen centralisatie van het slokdarmcarcinoom is uitgewoed, kan de aandacht worden verlegd naar andere verrichtingen zoals de ERCP. Bij minder dan 20 ERCP's per jaar geen certificaat? Is er een plaats voor minimale volumenormen, en zo ja, welke? De Inspectie voor Gezondheidszorg heeft de wetenschappelijke verenigingen uitgenodigd hierover hun gedachten te ontwikkelen en vervolgens vast te leggen. Er ligt op dit vlak nog wel een reeks aan vragen. Is het bewijs voor centralisatie sterk, en geldt het voor chirurgische als niet-chirurgische ingrepen, en ook voor endoscopische handelingen? Wat zijn (wetenschappelijk verantwoorde) afkappunten? Gelden de volumenormen per centrum of per specialist? Hoe verhoudt zich een handeling/ingreep in het totaal van de ketenzorg bij een aandoening, bijvoorbeeld bij een maligniteit, en hoe zou je idealiter de kwaliteit van de onderdelen willen vaststellen en bewaken?

13.00	Volume en kwaliteit: het standpunt van de Inspectie *W. Schellekens, hoofdinspecteur Curatieve Gezondheidszorg, Inspectie Gezondheidszorg (IGZ), Den Haag*
13.30	Relatie tussen volume en kwaliteit bij ERCP *Dr. E.A.J. Rauws, maag-darm-leverarts, AMC, Amsterdam*
14.00	Wetenschappelijke analyse van kwaliteit van zorg: de (on)mogelijkheden *Prof. dr. J. Kievit, chirurg, Leids Universitair Medisch Centrum, Leiden*
14.30	Forumdiscussie met, naast bovengenoemde sprekers, *Prof. dr. C.J.J. Mulder, maag-darm-leverarts, (VUmc, Amsterdam) en* *Prof. dr. C.H.C. Dejong, chirurg, (Maastricht UMC)*
15.00	Einde symposium, theepauze

Sectie Neurogastroenterologie en Motiliteit **Auditorium**

Voorzitters: J.W. Straathof en R. van den Wijngaard

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

15.30 Reduction of rectal distensibility and external anal sphincter function after radiation therapy for localized prostate cancer (p.109)

R. Krol[1], W.P.M. Hopman[1], R.J. Smeenk[2], E.N.J.Th. Van Lin[2], Depts of [1]Gastroenterology and Hepatology and [2]Radiation Oncology, Radboud University Nijmegen Medical Centre, The Netherlands

15.40 Assessment of pain perception in irritable bowel syndrome: towards an optimal definition of rectal hypersensitivity (p.110)

S. Ludidi, J.M. Conchillo, D. Keszthelyi, M. van Avesaat, D. Jonkers, A. Masclee, Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, The Netherlands

15.50 The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients (MLDS-project MWO 05-42) (p.111)

T.K. Klooker[1], K.E.M. Leliefeld[1], R.M.van den Wijngaard[1], G.E.E. Boeckxstaens[1,2]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands. [2]Gastroenterology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium.

16.00 The role of esophageal acid exposure on esophageal baseline impedance levels (p.112)

B.F. Kessing[1], A.J. Bredenoord[1], P.W. Weijenborg[1], G.J.M. Hemmink[2], C.M.Loots[3], A.J.P.M. Smout[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, Amsterdam, [2]Dept of Gastroenterology, Sint Antonius Hospital Nieuwegein, Nieuwegein, [3]Dept of Pediatric Gastroenterology and Nutrition, Emma Children Hospital, Academic Medical Centre, Amsterdam, The Netherlands

16.10 Effect of Transoral Incisionless Fundoplication 2.0 on esophagogastric junction distensibility in GERD patients: a study using an endoscopic functional luminal imaging probe (EndoFLIP) (p.113)

D.W. Bruls[1], F.G. Smeets[1], B.P. Witteman[2], G.H. Koek[1], A.A. Masclee[1], N.D. Bouvy[2], J.M. Conchillo[1], [1]Dept of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [2]Dept of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

16.20 Impaired distensibility of the esophagogastric junction in patients with achalasia and persistent symptoms (p.114)

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

16.30 Effect of stepwise gastric band adjustment on esophageal motility in obese patients (p.115)

J.S. Burgerhart[1,4], E.O. Aarts[2], P.C. van de Meeberg[3,4], P.D.Siersema[1], A.J.P.M. Smout[5], [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, [2]Dept of Surgery, Rijnstate Hospital Arnhem, [3]Dept of Gastroenterology and Hepatology, Slingeland Hospital Doetinchem, [4]Dutch Obesity Clinic Hilversum, [5]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

16.40 Azitromycin reduces the number of acid reflux episodes by changing the position of the gastric acid pocket (p.116)

A.A. de Ruigh[1], W.O. Rohof[1], R.J. Bennink[2], D.P.Hirsch[1], G.E.Boeckxstaens[1,3], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept of Gastroenterology, University Hospital, Leuven, Belgium

16.50 Response of chronic constipation symptoms to prucalopride treatment and relationship with patient satisfaction (p.117)

R. Kerstens[1], L. Vandeplassche[1], D. Dubois[2], L. Wouters[3], [1]Movetis NV, Turnhout, [2]Patient Value Solutions, Huldenberg, [3]I-BioStat, Hasselt University, Diepenbeek, Belgium

17.00 Best response distribution of 12-week treatment with prucalopride (Resolor) in patients with chronic constipation: combined results of three randomised, double- blind, placebo-controlled phase III trials (p.118)

V. Stanghellini[1], L. Vandeplassche[2], R. Kerstens[2], [1]Dept of Clinical Medicine, University of Bologna, Bologna, Italy, [2]Movetis NV, Turnhout, Belgium

17.10 Tissue damage and brain activation in postoperative ileus (p.119)

S.H. van Bree[1], J. van der Vliet[1], S. el Temna[1], L. Costes[1], C. Cailotto[1], G.E. Boeckxstaens[1,5]. [1]Tytgat institute of Liver and Intestinal Research, Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, the Netherlands. [2]Dept of Gastroenterology, University Hospital Leuven, Leuven, Belgium

17.20 Effect of probiotic treatment on visceral hypersensitivity in Irritable Bowel Syndrome (p.120)

A.Y. Thijssen[1], D.M.A.E. Jonkers[1], C.H.M. Clemens[2], A.A.M. Masclee[1], [1]Dept of Internal Medicine, Division of Gastroenterology & Hepatology, Maastricht Univ. Medical Center, The Netherlands, [2]Dept of Internal Medicine, Diaconessen Hospital Leiden, The Netherlands

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

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

Voorzitters: D.J. de Jong en C.J. van der Woude

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

10.00 HSPA6 and HSPA1B are smoke inducible genes that reside in Ulcerative Colitis susceptibility loci (p.121)

F. Imhann[1], E.M.J. van der Logt[1], T. Blokzijl[1], V.W. Bloks[2], K.N. Faber[1] G. Dijkstra[1], [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, [2]Dept of Pediatrics, University Medical Center Groningen, The Netherlands

10.10 Tissue factor-dependent chemokine production aggravates experimental colitis (MLDS project WO 06-02) (p.122)

K.C. Queiroz, H.L. Aberson, A.P. Groot, M.I. Verstege, J.J. Roelofs, A.A. te Velde, C. van 't Veer, C.A. Spek, [1]Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, [2]Laboratory of Experimental Gastroenterology, Academic Medical Center, University of Amsterdam, [3]Dept of Pathology Academic Medical Center, University of Amsterdam, The Netherlands

10.20 Formation of tertiary lymphoid tissue in dextran sulfate sodium induced colitis is partially dependant on $LTa_1 b_2$-LTbR axis (p.123)

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

10.30 Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease (p.124)

F.D.M. van Schaik[1], H.M. Smeets[2,3], G.J.M.G. van der Heijden[2], P.D. Siersema[1], M.G.H. van Oijen[1] and B. Oldenburg[1], [1]University Medical Center Utrecht, Dept of Gastroenterology and Hepatology, The Netherlands, [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands, [3]Agis Health Insurance Company, Amersfoort, The Netherlands

10.40 Different Risk Factors for Colitis Associated Colorectal Cancer in Ulcerative Colitis and Crohn's Disease (p.125)

M.W.M.D. Lutgens[1], P.D.Siersema[1], F.P.Vleggaar[1], M.Broekman[1], M.G.H. van Oijen[1], A.A. van Bodegraven[2], G.Dijkstra[3], D.W. Hommes[4], D.J. de Jong[5], C.I.J. Ponsioen[6], C.J. van der Woude[7], B. Oldenburg[1], On behalf of the Initiative on Crohn and Colitis in The Netherlands: [1]University Medical Center Utrecht, Dept of Gastroenterology and Hepatology, [2]VU University Medical Center, Dept of Gastroenterology and Hepatology, [3]University Medical Center Groningen, Dept of Gastroenterology and Hepatology, [4]Leiden University Medical Center, Dept of Gastroenterology and Hepatology, [5]University Medical Center Nijmegen, Dept of Gastroenterology and Hepatology, [6]Academic Medical Center Amsterdam, Dept of Gastroenterology and Hepatology, [7]Erasmus Medical Center Rotterdam, Dept of Gastroenterology and Hepatology, The Netherlands

10.50 5-ASA inhibits Phospolipase D-dependent mammalian Target of Rapamycin signaling in colorectal cancer (p.126)

B. Baan[1,6], A.A. Dihal[1], E. Hoff[1], C.L. Bos[2], P.W. Voorneveld[1], P.J. Koelink[1], H.W. Verspaget[1], D.J. Richel[3], J.C.H. Hardwick[1], D.W. Hommes[1], M.P. Peppelenbosch[4], G.R. van den Brink[1,5,6], [1]Dept of Gastroenterology & Hepatology, Leiden University Medical Center, Leiden, [2]Dept of Pathology, VU University Medical Center, [3]Dept of Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, [4]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, [5]Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, [6]Tytgat Institute for Liver & Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

11.00 Transcriptomic profiles in colon tissue from inflammatory bowel diseases patients in relation to N-nitroso compound exposure and colorectal cancer risk (p.127)

D.G.A.J. Hebels[1], K.M. Sveje[1], M.C. de Kok[1], M.H.M. van Herwijnen[1], G.G.C. Kuhnle[2, 3], L.G.J.B. Engels[4], M.J.L. Romberg-Camps[4], W.G.N. Mares[4, 5], M. Pierik[5], A.A.M. Masclee[5], J.C.S. Kleinjans[1], T.M.C.M. de Kok[1], [1]Dept of Health Risk Analysis and Toxicology, Maastricht University, Maastricht, [2]MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, United Kingdom, [3]Dept of Food and Nutritional Sciences, University of Reading, Reading, United Kingdom, [4]Dept of Gastroenterology, Orbis Medical Center, Sittard, [5]Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, The Netherlands

11.10 Colorectal cancer surveillance in patients with longstanding ulcerative colitis and colonic Crohn's disease: actual practice does not match surveillance guidelines (p.128)

J.E. van Rooij, J. van der Palen, J. van Baarlen, J.J. Kolkman, G.H. van Olffen, M.G.V.M. Russel, Medisch Spectrum Twente, Enschede, The Netherlands

11.20 Osteoporosis in adult patients with inflammatory bowel disease is more related to classical than to disease-specific risk factors (p.129)

P.H.A. Bours[1], J.R. Vermeijden[1], A. van de Wiel[2], [1]Dept of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, [2]Dept of Internal Medicine, Meander Medical Center, Amersfoort, The Netherlands

11.30 Ledenvergadering in de Brabantzaal,
aansluitend lunchpauze in de expositiehal.

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

Voorzitters: G.R. Dijkstra en B. Oldenburg

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

13.00 Tolerability and safety of conventional thiopurines concomitantly with allopurinol in IBD-patients with a skewed thiopurine metabolism (p.130)
M.L. Seinen, D.P. van Asseldonk, N.K.H. de Boer, K. Smid, G.J. Peters, C.J.J. Mulder, G. Bouma, A.A. van Bodegraven, VU University medical center, Amsterdam, The Netherlands

13.10 Crohn's disease patients treated with adalimumab benefit from co- treatment with immunomodulators: results from a nationwide study in The Netherlands (p.131)
M.E. van der Valk, M.G.H. van Oijen, P.D. Siersema, M. Ammerlaan, B. Oldenburg B, [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, [2]ApotheekZorg, Elsloo, The Netherlands

13.20 Quantitative comparison of the neutralizing capacity of therapeutic anti-TNF-a drugs and the cross-reactivity of anti-anti-TNF-a antibodies (p.132)
D.J. Buurman[1], B.T. Pham[1], E.M.J. van der Logt[1], T. Blokzijl[1], K.N. Faber[1], S. Arends[2], E. Brouwer[2], M.P. Peppelenbosch[3], J.H. Kleibeuker[1], G. Dijkstra[1], [1]University Medical Center Groningen, Dept of Gastroenterology and Hepatology, [2]University Medical Center Groningen, Dept of Rheumatology and Clinical Immunology, [3]Erasmus Medical Center Rotterdam, Dept of Gastroenterology and Hepatology, The Netherlands

13.30 Naturally-occurring autoantibodies against TNF-alpha are present in sera of inflamematory bowel disease patients and influence the response to adalimumab (p.133)
Z. Zelinkova, M.P. Peppelenbosch, A. van Liere-Baron, C. de Haar, C.J. van der Woudem Dept of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, The Netherlands

13.40 Tolerability of shortened infliximab infusion times in patients with inflammatory bowel diseases: a single center cohort study (p.134)
C. Breynaert[1], M. Ferrante[1], H. Fidder[2], K. Van Steen[3], M. Noman[1], V.Ballet[1], S. Vermeire[1], P. Rutgeerts[1], G. VanAssche[1], [1]Leuven University Hospitals, Leuven, Belgium, [2] UMC, Utrecht, The Netherlands, [3] University of Liege, Liege, Belgium

13.50 Effectiveness and tolerability of maintenance methotrexate therapy in Crohn's disease patients, analysis of a referral hospital-based10-years intercept cohort (p.135)
M.L. Seinen, N.K.H. de Boer, C.J.J. Mulder, G. Bouma, A.A. van Bodegraven, VU University Medical Center, Amsterdam, The Netherlands

Donderdag 17 maart 2011

14.00 Primary sclerosing cholangitis is associated with pancolitis and not back-wash ileitis (p.136)

K. Boonstra[1], K.J. van Erpecum[2], C.M.J. van Nieuwkerk[3], J.P.H. Drenth[4], A.C. Poen[5], B.J.M. Witteman[6], H.A.R.E. Tuynman[7], U. Beuers[1], C.Y. Ponsioen[1], [1]Academic Medical Center, Amsterdam, [2]University Medical Center Utrecht, Utrecht, [3]VU Medical Center, Amsterdam, [4]St. Radboud University, Nijmegen, [5]Isala clinics, Zwolle, [6]Gelderse Vallei hospital, Ede, [7]Medical Center Alkmaar, The Netherlands

14.10 Immune-mediated diseases in primary sclerosing cholangitis (p.137)

L.E. Lamberts, M. Janse, E.B. Haagsma, A.P. van den Berg, R.K. Weersma, Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, The Netherlands

14.20 Arthropathies in inflammatory bowel disease patients (p.138)

L.K.P.M. Brakenhoff[1] , R. van der Berg[2] , D.M. van der Heijde[2], D.W. Hommes[1], T.W.J. Huizinga[2], H.H. Fidder[1,3], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [2]Dept of Rheumatology, Leiden University Medical Center, Leiden, [3]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands

14.30 Work disability in inflammatory bowel disease: first results from the COIN study (p.139)

M.E. van der Valk[1], M.J.J. Mangen[2], M.G.H. van Oijen[1], P.D. Siersema[1], B. Oldenburg[1], [1]Dept of Gastro-enterology and hepatology, University Medical Center Utrecht, [2] Medical Technology Assessment, Julius Centre for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

14.40 Large part of poor Health Related Quality of Life in IBD patients explained by Fatigue, Depression and IBS (p.140)

B.A. Franke[1], M.G. Russel[1], Y. van Oossanen[2], A. Eroglu – Berger[1], J. van der Palen[1], M.H. Otten[2], [1]Medisch Spectrum Twente, Enschede, [2]Meander Medisch Centrum, Amersfoort, The Netherlands

14.50 Identification of the gene underlying Congenital Short Bowel Syndrome, pointing to its major role in intestinal development (p.141)

C.S. van der Werf[1], T.D. Wabbersen[2], N.H. Hsiao[3], J. Paredes[4], H.C. Etchevers[5], P.M. Kroisel[6], D. Tibboel[7], R.A. Schreiber[8], E.J. Hoffenberg[9], S.L. Zeder[10], I. Ceccherini[11], S. Lyonnet[5], A.S. Ribeiro[4], R. Seruca[4], G.J. te Meerman[1], S.C.D. van IJzendoorn[3], I.T. Shepherd[2], J.B.G.M. Verheij[1], R.M.W. Hofstra[1]. [1]Dept of Genetics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands [2]The Dept of Biology, Emory University, Atlanta, USA, [3]The Membrane Cell Biology section, Dept of Cell Biology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [4]The Cancer Genetics Group, the Institute of Molecular Pathology and Immunology of the University of Porto, Porto, Portugal, [5]INSERM, U781, Hôpital Necker-Enfants Malades, Université Paris Descartes, Paris, France, [6]Institute of Human Genetics, Medical University of Graz, Graz, Austria, [7]The Dept of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, [8]The Division of Gastroenterology, BC Children's Hospital, Vancouver, [9]The Dept of Pediatrics, Section of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Colorado, Denver, USA, [10]The Dept of Pediatric Surgery, Medical University of Graz, Graz, Austria, [11]Laboratorio di Genetica Molecolare, Istituto Giannina Gaslini, Italy

15.00 Koffie/thee in de expositiehal

Voorzitters: R. van Tol en A.A. te Velde

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

Theme: Epithelial barrier function

13.30 The human colon is capable of limiting epithelial damage and inflammation following ischemia-reperfusion (p.142)

I.H.R. Hundscheid[1], J. Grootjans[1], J.G. Bloemen[1], M.F. Von Meyenfeldt[1], G.L. Beets[1], W.A. Buurman[1], [1]Dept of Surgery, NUTRIM School for Nutrition, Toxicology & Metabolism, Maastricht University Medical Center, Maastricht, The Netherlands

13.42 The human small intestine is equipped with a unique mechanism to reduce wound size and rapidly restore ischemia-induced damage to the epithelial lining (p.143)

J. Grootjans[1], G. Thuijls[2], J.P.M. Derikx[2], R.M. van Dam[1], C.H.C. Dejong[1], W.A. Buurman[1], [1]Dept of Surgery, NUTRIM School for Nutrition, Toxicology & Metabolism, Maastricht University Medical Center, Maastricht, [2]Dept of Surgery, Orbis Medical Center, Sittard, The Netherlands

13.54 Modulation of intestinal epithelial barrier function by fatty acid ethyl esters in a three dimensional (3D) epithelial cell culture model: role of nonoxidative ethanol metabolism (p.144)

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

14.06 The serotonin precursor 5-hydroxytryptophan reinforces intestinal barrier function (p.145)

D. Keszthelyi[1,2], F.J. Troost[1,2], H. van Eijk[3], E. Schaepkens[1,2], P. Lindsey[4], D. Jonkers[1,2], W.A. Buurman[3], J. Dekker[1] and A.A.M. Masclee[1,2], [1]Top Institute Food and Nutrition, Wageningen, [2]Division of Gastroenterology-Hepatology, Dept of Internal Medicine, Maastricht University Medical Centre+, Maastricht, [3]Dept of Surgery, Maastricht University Medical Centre+, Maastricht, [4]Dept of Clinical Genomics, Maastricht University Medical Centre+, Maastricht, The Netherlands

14.18 ATP8B1-deficiency reduces the functional CFTR pool in intestinal T84 cells (p.146)

V.A. van der Mark[1], H.R. de Jonge[1], S. Duijst[1], R.P.J. Oude Elferink[1], C.C. Paulusma[1], [1]Tytgat Institute for Liver and Intestinal Research, Amsterdam, The Netherlands

14.30 Reduced Paneth cell antimicrobial protein levels correlate with activation of the unfolded protein response in the gut of obese individuals (p.147)

C. Hodin[1], F. Verdam[1], J. Grootjans[1], S. Rensen[1], C. Dejong[1], W. Buurman[1], J.W. Greve[1,2], K. Lenaerts[1] , [1]NUTRIM School for Nutrition, Toxicology and Metabolism, Dept of Surgery, Maastricht University Medical Centre, Maastricht, [2]Currently at Dept of Surgery, Atrium Medical Center, Heerlen, The Netherlands

14.42 Oral availability of cefadroxil depends on Abcc3 and Abcc4 (p.148)

D.R. de Waart[1], K. van de Wetering[2], C. Kunne[1], S. Duijst[1], C.C. Paulusma[1], and R.P.J. Oude Elferink[1], [1]Tytgat Institute, Academic Medical Center, Amsterdam, [2]Division of Molecular Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

14.54 Theepauze en Ledenvergadering NVH

DEGH-Meeting, vervolg programma **Baroniezaal**

Voorzitters: K.N. Faber en G. Bouma

ZonMw

Theme: Cholangiocyte biology

15.30 **Invited Speaker: Dr. Jesus Banales**
Role of cholangiocyte primary cilium in polycystic liver diseases

16.00 Loss of heterozygosity in liver cysts of autosomal dominant polycystic liver disease (PCLD) depends on germline mutation of the patient (p.149)

M.J. Janssen[1], J. Woudenberg[1], R.H.M. te Morsche[1], J.P.H. Drenth[1], [1]Gastroenterology & Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

16.12 Dynamic changes in the biliary glycocalyx impact cholangiocyte resistance to bile salt induced toxicity (p.150)

L. Maillette de Buy Wenniger[1], S. Hohenester[1], S.J. van Vliet[2], R. Oude Elferink[1], U. Beuers[1], [1]Academic Medical Center of the University of Amsterdam, Dept of Gastroenterology and Hepatology, Tytgat Institute of Liver and Intestinal Research, Amsterdam, [2]VU University Medical Center, Dept of Molecular Cell Biology and Immunology, Amsterdam, The Netherlands

16.24 Three genetic susceptibility loci indicate a role for IL2, REL and CARD9 in primary sclerosing cholangitis (p.151)

M. Janse[1], L.E. Lamberts[1], L. Franke[2], S. Raychaudhuri[3,4,5], E. Ellinghaus[6], K.M. Boberg[7], E. Melum[7], E. Schrumf[7], A. Bergquist[8], E. Björnsson[9], H.J. Westra[2], H.J.M. Groen[10], R.S.N. Fehrmann[2], J. Smolonska[2], L.H. van den Berg[11], R.A. Ophoff[12], R.J. Porte[13], T.J. Weismüller[14,15], J. Wedemeyer[14,15], C. Schramm[16], M. Sterneck[16], R. Günther[17], F. Braun[18], S. Vermeire[19], L. Henckaerts[19], C. Wijmenga[2], C.Y. Ponsioen[20],

S. Schreiber[6], T.H. Karlsen[7], A. Franke[6], and R.K. Weersma[1], [1]Dept of Gastroenterology and Hepatology, University Medical CenterGroningen and University of Groningen, [2]Dept of Genetics, University Medical Center Groningen and University of Groningen, [3]Division of Genetics, Brigham and Women's Hospital, Boston, Massachusetts, 02115, USA, [4]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, Massachusetts, 02115, USA[5] Broad Institute, Cambridge, Massachusetts, 02142 USA, [6]Institute of Clinical Molecular Biology, Christian- Albrechts- University, Kiel, Germany, [7]Norwegian PSC Research Center, Clinic for Specialized Surgery and Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [8]Dept of Gastroenterology and Hepatology, Karolinska University Hospital,Huddinge, Stockholm, Sweden, [9]Section of Gastroenterology and Hepatology, Dept of Internal Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden, [10]Dept of Pulmonology, University Medical Center Groningen and University of Groningen, [11]Dept of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, [12]Dept of Medical Genetics and Rolf Magnus Institute, University Medical Center Utrecht, [13]Dept of Hepato-Pancreatico-Biliary Surgery and Liver Transplantation, University Medical Center Groningen and University of Groningen, [14]Dept of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany, [15] Integrated Research and Treatment Center – Transplantation (IFB-Tx), Hannover Medical School, Hannover, Germany, [16]1st Dept of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [17]1st Dept of Medicine, University Medical Centre Schleswig-Holstein (UK S-H), Campus Kiel, Germany, [18]Dept of General and Thoracic Surgery, University Medical Centre Schleswig- Holstein (UK S-H), Campus Kiel, Germany, [19]Dept of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium, [20]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

16.36 A HCO_3^- umbrella protects human biliary epithelia against bile acid-induced injury (p.152)

S. Hohenester, L. Maillette de Buy Wenniger, R.P. Oude-Elferink, U. Beuers, Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, The Netherlands

16.48 Significant Contribution of the Portal Vein to Blood Flow through the Common Bile Duct (p.153)

J.C. Slieker[1], W.R.R. Farid[1], C.H.J. van Eijck[1], J.F. Lange[1], J. van Bommel[2], H.J. Metselaar[3], J. de Jonge[1] and G. Kazemier[1], Depts of [1]Surgery, [2]Intensive Care Medicine, [3] Gastroenterology & Hepatology Erasmus MC - University Medical Center, Rotterdam, The Netherlands

17.00 Einde van het programma in deze zaal, voor de lezing van prof. dr. M.A. Cuesta en de aansluitende President Select kunt u zich begeven naar de Brabantzaal

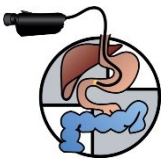
18.30 Borrel in expositiehallen

19.30 Diner Genderzaal

Donderdag 17 maart 2011

Programma Leververpleegkundigen Netwerk **Parkzaal**

v&vn
Beroepsvereniging van zorgprofessionals
Maag Darm Lever



De hepatologie patiënt is meer dan alleen een hepatitis behandeling….

15.00	Woord van welkom Anja Nijmeijer, MDL-verpleegkundige Medisch Spectrum Twente, Enschede
15.10	NASH Drs. T.C.M.A Schreuder, MDL-arts / hepatoloog Slingeland Ziekenhuis / Medisch Centrum de Veluwe
15.40	NASH, vertaalslag naar de verpleegkundige praktijk Ton van der Meijden, verpleegkundig consulent hepatologie VUmc Amsterdam
16.10	Pauze
16.30	Wat kunnen we leren van het Herstel- en Balans programma in de oncologie? Mw. H. Janssen, psychisch hulpverlener, Kenniscentrum Oncologie Deventer Ziekenhuis
17.00	Ervaringsdeskundige tevens MDL-verpleegkundige maakt vertaalslag naar de hepatitis-praktijk Christa Vermeer, MDL-verpleegkundige Meander Medisch Centrum, Amersfoort
17.15	Revalidatie voor hepatitis C patiënten na behandeling, zinvol? Spreker van patiëntenvereniging
17.30	Vragen en discussie
17.45	Afsluiting Anja Nijmeijer, MDL-verpleegkundige, Medisch Spectrum Twente

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

08.30 Quality of colonoscopy from a patient's perspective using the Global Rating Scale (p.154)

J. Sint Nicolaas[1], V. de Jonge[1], O. van Baalen[2], F. ter Borg[3], J.T. Brouwer[4], D.L. Cahen[5], E.E. Colpaert[6], W. Lesterhuis[7], W. Moolenaar[8], R.J.Th. Ouwendijk[9], M.J.F. Stolk[10], T.J. Tang[11], A.J.P. van Tilburg[12], E.J. Kuipers[1,13], M.E. van Leerdam[1], Depts of Gastroenterology and Hepatology of [1]Erasmus MC University Medical Center, Rotterdam, [2]Beatrix Hospital, Gorinchem, [3]Deventer Hospital, Deventer, [4]Reinier de Graaf Hospital Group, Delft, [5]Amstelland Hospital, Amstelveen, [6]Maasstad Hospital, Rotterdam, [7]Albert Schweitzer Hospital, Dordrecht, [8]Medical Center Alkmaar, Alkmaar, [9]Ikazia Hospital, Rotterdam, [10]Sint Antonius Hospital, Nieuwegein, [11]IJsselland Hospital, Capelle aan den IJssel, [12]Sint Franciscus Gasthuis, Rotterdam, and [13]Dept of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

08.40 Quality of colonoscopy reporting and performance (p.155)

V. de Jonge[1], J. Sint Nicolaas[1], O. van Baalen[2], F. ter Borg[3], J.T. Brouwer[4], D.L. Cahen[5], M. Hadithi[6], W. Lesterhuis[7], W. Moolenaar[8], R.J.Th. Ouwendijk[9], M.J.F. Stolk[10], T.J. Tang[11], A.J.P. van Tilburg[12], E.J. Kuipers[1,13], M.E. van Leerdam[1], Depts of Gastroenterology and Hepatology of [1]Erasmus MC University Medical Center , Rotterdam, [2]Beatrix Hospital, Gorinchem, [3]Deventer Hospital, Deventer, [4]Reinier de Graaf Hospital Group, Delft, [5]Amstelland Hospital, Amstelveen, [6]Maasstad Hospital, Rotterdam, [7]Albert Schweitzer Hospital, Dordrecht, [8]Medical Center Alkmaar, Alkmaar, [9]Ikazia Hospital, Rotterdam, [10]Sint Antonius Hospital, Nieuwegein, [11]IJsselland Hospital, Capelle aan den IJssel, [12]Sint Franciscus Gasthuis, Rotterdam, and [13]Dept of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

08.50 Interval colorectal cancers frequently have subtle macroscopic appearance: a 10 year-experience in an academic center (p.156)

C. le Clercq[1], E. Rondagh[1], R. Riedl[2], F. Bosman[2], G. Beets[3], W. Hameeteman[1], A. Masclee[1], S. Sanduleanu[1], Dept of Internal Medicine, Division of Gastroenterology and Hepatology[1], Dept of Pathology[2] and Dept of Surgery[3], Maastricht University Medical Center, The Netherlands

09.00 Adenoma detection with cap-assisted colonoscopy versus regular colonoscopy: a randomized controlled trial (p.157)

T.R. de Wijkerslooth[1], E.M. Stoop[2], P.M. Bossuyt[3], E.M.H. Mathus-Vliegen[1], J. Dees[2] , K.M.A.J. Tytgat[1], M.E. van Leerdam[2], P. Fockens[1], E.J. Kuipers[2,4], E. Dekker[1], [1]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [3]Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, [4]Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

09.10 The occurrence of adeverse events in a 30-day period after colonoscopy (p.158)

V. de Jonge[1], J. Sint Nicolaas[1], O. van Baalen[2], F. ter Borg[3], J.T. Brouwer[4], D.L. Cahen[5], S. Ganesh[6], W. Lesterhuis[7], W. Moolenaar[8], R.J.Th. Ouwendijk[9], M.F.J. Stolk[10], T.J. Tang[11], A.J.P. van Tilburg[12], E.J. Kuipers[1,13], M.E. van Leerdam[1], Depts of Gastroenterology and Hepatology of [1]Erasmus MC University Medical Center, Rotterdam, [2]Beatrix Hospital, Gorinchem, [3]Deventer Hospital, Deventer, [4]Reinier de Graaf Hospital Group, Delft, [5]Amstelland Hospital, Amstelveen, [6]Maasstad Hospital, Rotterdam, [7]Albert Schweitzer Hospital, Dordrecht, [8]Medical Center Alkmaar, Alkmaar, [9]Ikazia Hospital, Rotterdam, [10]Sint Antonius Hospital, Nieuwegein, [11]IJsselland Hospital, Capelle aan den IJssel, [12]Sint Franciscus Gasthuis, Rotterdam, and [13]Dept of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

09.20 Clipped versus standard nasoenteral feeding tubes: a randomized controlled trial (p.159)

M.M.C. Hirdes[1], J.F. Monkelbaan[1], J.J. Haringman[2], P.D. Siersema[1], J. Kesecioglu[2], F.P. Vleggaar[1], Depts of Gastroenterology and [1]Hepatology and [2]Intensive Care Medicine, University Medical Center Utrecht, The Netherlands

09.30 Prague C & M classification in Barrett's esophagus: is it really reliable in daily practice? (p.160)

L. Alvarez Herrero[1,2], W.L. Curvers[2], F.G.I. van Vilsteren[2], B.L.A.M. Weusten[1,2], J.J.G.H.M. Bergman[2], [1]Dept of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, [2]Academic Medical Center, Amsterdam, The Netherlands

09.40 Sampling bias/misclassification in the diagnosis of high-grade dysplasia in Barrett's esophagus: a Dutch population-based study (p.161)

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

09.50 Validation of a DNA FISH biomarker set in a random Barrett's esophagus surveillance population (p.162)

A.F. Pacha[1,2], A.M Rygiel[1,2], W.M. Rosmolen[1], B. Elzer[1], H. Verhulst[1], M. Visser[1], F.J.W. ten Kate[3], B.A. Hutten[4], R.C. Mallant-Hent[5,11], A.H.J. Naber [6,11], A.H.A.M. van Oijen[7,11], L.C. Baak[8,11], P. Scholten[9,11], C.J.M. Böhmer[10,11], J.J Bergman[1,11], K.K. Krishnadath[1,2,11], [1]Dept of Gastroenterology and Hepatology , [2]Center for Experimental Molecular Medicine, [3]Dept of Pathology , Clinical Epidemiology, [4]Biostatistics and Bioinformatics , Academic Medical Center, Amsterdam, The Netherlands, [5]Dept of Gastroenterology , Flevoziekenhuis, Almere, [6]Dept of Gastroenterology , Tergooi ziekenhuizen, Hilversum, [7]Dept of Gastroenterology , Medisch Centrum Alkmaar, [8]Dept of Gastroenterology , Onze Lieve Vrouwe Gasthuis, Amsterdam, [9]Dept of Gastroenterology , Sint Lucas Andreas Ziekenhuis, Amsterdam, [10]Dept of Gastroenterology , Spaarneziekenhuis, Hoofddorp, [11]The Amsterdam Gastroenterological Association, The Netherlands

10.00 Radiofrequency Ablation +/- Endoscopic Resection for Barrett's Esophagus with High-Grade Dysplasia and/or Early Cancer: Durability of the Post-Treatment Neosquamous Epithelium at 5-year Follow-up (p.163)

K.Y.N. Phoa[1], R.E. Pouw[1], F.G.I. van Vilsteren[1], C.M.T. Sondermeijer[1], L. Alvarez Herrero[2], F.J.W. Ten Kate[3], M. Visser[3], M.I. van Berge Henegouwen[4], B.L.A.M. Weusten[2], R.C. Mallant-Hent[5], J.J.G.H.M. Bergman[1], [1]Depts of Gastroenterology, [3]Pathology and Surgery[4], Academic Medical Center, Amsterdam, [2]Dept of Gastroenterology , St. Antonius hospital, Nieuwegein, [5]Dept of Gastroenterology, Flevoziekenhuis, Almere, The Netherlands

10.10 The learning curve of endoscopic resection of esophageal neoplasia is associated with significant complications even in a structured training program (p.164)

F.G.I. van Vilsteren[1], R.E. Pouw[1], L.A. Herrero[2], F.P. Peters[1], R. Bisschops[3], M. Houben[4], F.T.M. Peters[5], B.E. Schenk[6], B.L.A.M. Weusten[2], M. Visser[7], F.J.W. Ten Kate[7], P. Fockens[1], E.J. Schoon[8], J.J.G.H.M. Bergman[1], Dept of Gastroenterology of [1]Academic Medical Center, Amsterdam, [2]St. Antonius Hospital, Nieuwegein, [3]University Medical Center Gasthuisberg, Leuven, [4]Haga Teaching Hospital, Den Haag, [5]University Medical Center Groningen, [6]Isala Klinieken, Zwolle, Dept of Pathology of [7]Academic Medical Center, Amsterdam, [8]Catharina Ziekenhuis Eindhoven, The Netherlands

10.20 First prospective assessment of multiband mucosectomy for endoscopic resection of mucosal squamous neoplasia in the esophagus (p.165)

D.F. Boerwinkel[1], Y.M. Zhang[2], B.L.A.M. Weusten[1,3], S.M. Dawsey[4], D.E. Fleischer[5], N. Lu[6], L. Xue[6], S. He[2], G.Q. Wang[2] , J.J.G.H.M. Bergman[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [2]Dept of Endoscopy, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, P.R. China, [3]Dept of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, The Netherlands, [4]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA, [5]Dept of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA, [6]Dept of Pathology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, P.R. China

10.30 Koffiepauze in expositiehal

11.00 Expandable Metal Stents for Malignant Esophageal Stenosis: a randomized controlled comparison of the new Evolution stent versus the Ultraflex stent (p.166)

N.C.M. van Heel[1], J. Haringsma[1], H. Boot[2], A. Cats[2], S. Vanhoutvin[2], EJ. Kuipers[1], [1]Erasmus MC - Universitair medisch centrum Rotterdam, [2]Antoni van Leeuwenhoek Ziekenhuis Amsterdam, The Netherlands

11.10 Partially versus fully covered self-expandable stent for esophageal perforations and fistula: a randomized controlled study (p.167)

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

11.20 Long term efficacy and safety of biodegradable stent placement for refracttory benign esophageal strictures: a prospective follow-up study (p.168)

M.M.C. Hirdes[1], P. G. van Boeckel[1], P.D. Siersema[1], F.P Vleggaar[1], Dept of Gastroenterology and Hepatology[1], University Medical Center Utrecht, The Netherlands

11.30 Feasibility and accuracy of a new 19G EUS histology needle: an international multicenter prospective study (p.169)

J.W. Poley[1], M.C. Petrone[2], J.Iglesias-Garcia[3], A. Larghi[4], M. Giovannini[5], G. Costamagna[4], Paolo Arcidiaccono[2], E. Bories[5], M.J. Bruno[1], [1]Dept of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, [2]Dept of Gastroenterology , San Raffaele University, Milan, Italy, [3]Dept of Gastroenterology , University Hospital of Santiago de Compostela, Spain, [4]Digestive Endoscopy Unit , Catholic University Rome, Italy, Endoscopy Unit[5] , Institute Paoli-Calmettes, Marseille, France

11.40 Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis, long-term outcome (p.170)

D.L. Cahen[1,2], D.J. Gouma[3], P. Laramée[4], Y.Nio[5], E.A.J. Rauws[2], M.A. Boermeester[3], O.R. Busch[3], P. Fockens[2], E.J. Kuipers[1], S.P. Pereira[6], D. Wonderling[4], M.G.W. Dijkgraaf[7], M.J. Bruno[1], [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept of Surgery , Academic Medical Center, Amsterdam, [4]National Clinical Guideline Center , Royal College of Physicians, London, United Kingdom, [5]Dept of Radiology, Academic Medical Center, Amsterdam, [6]Institute of Hepatology, University College London, London, United Kingdom, [7]Clinical Research Unit , Academic Medical Center, Amsterdam, The Netherlands

11.50 The first prospective, group sequential study evaluating a new type of fully covered self-expandable metal stent for the treatment of benign biliary strictures (p.171)

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

12.00 Einde programma

Nederlandse Vereniging van Maag-Darm-Leverartsen — Genderzaal

12.00 Ledenvergadering *(met lunchbuffet in de zaal)*

Netherlands Society of Parenteral and Enteral Nutrition — Zaal 80

Voorzitters: C.F. Jonkers en G.J.A. Wanten

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

11.00 **Abstractmeeting NESPEN**

11.00 Enteropathy Associated T-cell Lymphoma. a clinical prognostic model to identify high risk patients (p.172)

L.R. de Baaij[1], J.M.W. van de Water[1], W.H.M. Verbeek[1], O.J. Visser[2], D.J. Kuik[3], J.J. Oudejans[4,5], C.J.L.M. Meijer[4], C.J.J. Mulder[1], S.A.G.M. Cillessen[4], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Hematology, [3]Dept of Clinical Epidemiology and Biostatistics, [4]Dept of Clinical Pathology, VU University Medical Center Amsterdam, [5]Dept of Clinical Pathology, Diakonessenhuis, Utrecht, The Netherlands

11.10 The origin of aberrant IEL in RCD II patients (p.173)

R.L.J. van Wanrooij[1], G.J. Tack[1], A.W. Langerak[2], B.M.E. von Blomberg[3], D.A.M. Heideman[3], F. Koning[4], G. Bouma[1], C.J.J. Mulder[1], M.W.J. Schreurs[2,3], [1]Gastro-enterology and Hepatology, VU University Medical Center, [2]Immunology, Erasmus University Medical Center, [3]Pathology, VU University Medical Center, [4]Immunohaematology and Blood Transfusion, Leiden University Medical Centre, The Netherlands

11.20 Multi-sugarpermeability test: a promising new tool for accurate gut permeability assessment in health and disease (p.174)

K. van Wijck[1,2,3], T. Verlinden, J. Dekker[1], W.A. Buurman[1,2,3], C.H.C. Dejong[1,2,3], K. Lenaerts[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, The Netherlands

11.30 Pregabalin for pain treatment in chronic pancreatitis (p.175)

S.S. Olesen[1], S.A.W. Bouwense[2], O.H.G. Wilder-Smith[3, 4], H. van Goor[2] & A.M. Drewes[1,4], [1]Mech-Sense, Dept of Gastroenterology, Aalborg Hospital, Aarhus University Hospital, Denmark Pain and Nociception Neuroscience Research Group, [2]Dept of Surgery and [3]Dept of Anaesthesiology, Pain and Palliative Care, Radboud University Nijmegen Medical Center, The Netherlands, [4]Center for Sensory-Motor Interaction (SMI), Dept of Health Science and Technology, Aalborg University, Denmark

11.40 Lipid- and protein-enriched enteral nutrition attenuates the innate immune response during human experimental endotoxemia (p.176)

T. Lubbers[1], M. Kox[2], J.J. de Haan[1], J.W. Greve[3], J.C. Pompe[2], B.P. Ramakers[2], P. Pickkers[2], W.A. Buurman[1], [1]Dept of Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre+, Maastricht, [2]Dept of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, [3]Dept of Surgery, Atrium Medical Center, Heerlen, The Netherlands

11.50 Assessment of small bowel function in critically ill MODS patients using the citrulline generation test (p.177)

M.B. Keur[1], N.J. Wierdsma[2], J.H.C. Peters[3], A.R.J. Girbes[1], A.A van Bodegraven[4], A. Beishuizen[1], [1]Intensive Care Unit, [2]Dept of Nutrition and Dietetics, Depts of [3]Gastroenterology and [4]Hepatology, [1,2,4]VU University Medical Center, Amsterdam, [3] Red Cross Hospital, Beverwijk, The Netherlands

12.00 Network lunch frontroom Parkzaal
NESPEN members, research dietitians and nurse practitioners

Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie — Parkzaal

Voorzitters: J.H. Kleibeuker en E.J. Kuipers

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

08.30 Gender disparities in performance of a fecal immunochemical test for detection of advanced neoplasia (p.178)

S.T. van Turenhout[1], F.A. Oort[1], J.S. Terhaar sive Droste[1], A.P. Visscher[1,2], V.M.H. Coupé[3], R.W.M. van der Hulst[2], P.C. Stokkers[4], A.A. Bouman[5], G.A. Meijer[6], L.G.M. van Rossum[1,7], and C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [4]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [5]Clinical Chemistry, VU University Medical Center, Amsterdam, [6]Pathology, VU University Medical Center, Amsterdam, [7]Epidemiology, Biostatistics and HTA, Radboud University Medical Center, Nijmegen, The Netherlands

08.40 Attendance and diagnostic yield of repeated fecal immunochemical test screening with intervals of 1, 2, or 3 years: a comparative population-based colorectal cancer screening trial (p.179)

A.H.C. van Roon[1], S.L. Goede[2], M. van Ballegooijen[2], J.C.I.Y. Reijerink[3], H. 't Mannetje[3], A.J. van Vuuren[1], A.C.M. van der Togt[4], J.D.F. Habbema[2], Ernst J. Kuipers[1,5], and M.E. van Leerdam[1], [1]Depts of Gastroenterology and Hepatology, [2]Public Health, and [5]Internal Medicine, Erasmus University Medical Centre, Rotterdam, [3]Cancer Screening Organization for the South-Western, Vlaardingen, The Netherlands [4]Comprehensive Cancer Centre, Rotterdam, The Netherlands

08.50 FOBT accuracy in subjects using acetylsalicylic acid, non-steroidal anti-inflammatory drugs and warfarin: a meta-analysis (p.180)

K. Soufidi[1], R.J.F. Laheij[1], M.G.H. van Oijen[1], P.D. Siersema[1], [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands

09.00 Antithrombotic and/or anticoagulant use is not associated with a higher false positivity rate in FIT screening (p.181)

M.J. Denters[1], M. Deutekom[2], A.F. van Rijn[1], P.M. Bossuyt[3], P. Fockens[1], E. Dekker[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Social Medicine, [3]Dept of Biostatistics and Clinical Epidemiology Academic Medical Centre, Amsterdam, The Netherlands

09.10 Pathology of cancers diagnosed in participants that tested negative in the first round of a FOBT based screening pilot (p.182)

K.S. Boparai[1,4], M.J. Denters[1], P.M. Bossuyt[3], P. Fockens[1], C.J.M. van Noesel[4], E. Dekker[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Social Medicine, [3]Dept of Clinical Epidemiology and Biostatistics, [4]Dept of PathologyAcademic Medical Center, Amsterdam, The Netherlands

09.20 Sensitivity and specificity of FIT in an average risk screening population (p.183)

T.R. de Wijkerslooth[1], E.M. Stoop[2], P.M. Bossuyt[3], G.A. Meijer[4], M. van Ballegooijen[5], R.A. Kraaijenhagen[6], P. Fockens[1], M.E. van Leerdam[2], E. Dekker[1], E.J. Kuipers[2], [1]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [3]Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, [4]Pathology, VU Medical Center, Amsterdam, [5]Public Health, Erasmus Medical Center, Rotterdam, [6]NDDO Institute for Prevention and Early Diagnostics (NIPED), Amsterdam, [7]Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

09.30 A randomized controlled trial comparing participation and diagnostic yield in colonoscopy and CT-colonography for population based colorectal cancer screening (p.184)

E.M. Stoop[1], M. C. de Haan[2], T.R. de Wijkerslooth[3], P. M. Bossuyt[4], M. van Ballegooijen[5], Y. Nio[2], M.J. van de Vijver[6], K. Biermann[7], M. Thomeer[9], M. E. van Leerdam[1], P. Fockens[3], J. Stoker[2], E. J. Kuipers[1,8], E. Dekker[3], [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [2]Dept of Radiology, Academic Medical Center, Amsterdam, [3]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [4]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, [5]Dept of Public health, Erasmus University Medical Center, Rotterdam, [6]Dept of Pathology, Academic Medical Center, Amsterdam, [7]Dept of Pathology, Erasmus University Medical Center, Rotterdam, [8]Dept of Internal Medicine, Erasmus University Medical Center, Rotterdam, [9]Dept of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands

09.40 Perceived burden and time investment of colorectal cancer screening by colonoscopy or CT-colonography: a randomized controlled trial (p.185)

T.R. de Wijkerslooth[1], L. van Dam[2], M.C. de Haan[3], E.M. Stoop[2], P.M. Bossuyt[4], M. Thomeer[5], M.L. Essink-Bot[6], M.E. van Leerdam[2], P. Fockens[1], E.J. Kuipers[2,7], M. van Ballegooijen[8], J. Stoker[3], E.W. Steyerberg[8] and E. Dekker[1], [1]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [3]Radiology, Academic Medical Center, Amsterdam, [4]Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, [5]Radiology, Erasmus Medical Center, Rotterdam, [6]Social Medicine, Academic Medical Center, Amsterdam, [7]Internal Medicine, Erasmus Medical Center, Rotterdam, [8]Public Health, Erasmus Medical Center, Rotterdam, The Netherlands.

09.50 Anticipating on implementation of colorectal cancer screening in The Netherlands: endoscopic demand versus capacity (p.186)

S.T. van Turenhout[1], J.S. Terhaar sive Droste[1], G.A. Meijer[2], and C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Pathology, VU University Medical Center, Amsterdam, The Netherlands

10.00 Evaluation of a quality assurance program for endoscopy services in The Netherlands (p.187)

J. Sint Nicolaas[1], V. de Jonge[1], F. ter Borg[2], J.T. Brouwer[3], D.L. Cahen[4], F.J.G.M. Kubben[5], W. Lesterhuis[6], W. Moolenaar[7], R.J.Th. Ouwendijk[8], M.J.F. Stolk[9], T.J. Tang[10], A.J.P. van Tilburg[11], R. Valori[12], M.E. van Leerdam[1], E.J. Kuipers[1,13], Depts of Gastroenterology and Hepatology of [1]Erasmus MC University Medical Center, Rotterdam, [2]Deventer Hospital, Deventer, [3]Reinier de Graaf Hospital Group, Delft, [4]Amstelland Hospital, Amstelveen, [5]Maasstad Hospital, Rotterdam, [6]Albert Schweitzer Hospital, Dordrecht, [7]Medical Center Alkmaar, Alkmaar, [8]Ikazia Hospital, Rotterdam, [9]Sint Antonius Hospital, Nieuwegein, [10]IJsselland Hospital, Capelle aan den IJssel, [11]Sint Franciscus Gasthuis, Rotterdam, [12]Gloucestershire Royal Hospital, Gloucester, United Kingdom, and [13]Dept of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

10.10 Factors affecting miss rate of polyps during colonoscopy: results from a prospective, multicenter back-to-back colonoscopy study (p.188)
A.M. Leufkens[1], M.G.H. van Oijen[1], F.P. Vleggaar[1], P.D. Siersema[1], for the TERRACE Study group, [1]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands

10.20 The valuation of the increase in quality of life and health-adjusted life expectancy as a result of colorectal cancer screening in future decades, a population-based study (p.189)
C.M. den Hoed[1], K. Isendoorn[2], W. Klinkhamer[2], A. Gupta[2], E.J. Kuipers[1,3], Depts of [1]Gastroenterology and Hepatology and [3]Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands and [2]Gupta Strategists, Ophemert, The Netherlands

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 Endoscopy and pH-impedance in children with GERD (p.190)
R.J. van der Pol[1], L. Peeters[1], C.M. Loots[1], Y. Vandenplas[2], M.A. Benninga[1], M.P. van Wijk[1], [1]Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital AMC, Amsterdam, The Netherlands, [2]Dept of Pediatric Gastroenterology and Nutrition, Academisch Ziekenhuis, Vrije Universiteit Brussel, Brussels, Belgium

11.10 Reproducibility of the histological diagnosis of celiac disease (p.191)
A. Mubarak[1], P.G.J. Nikkels[2], R.H.J. Houwen[1], F.J.W. ten Kate[2], Depts of [1]Pediatric Gastroenterology and [2]Pathology, University Medical Center Utrecht, The Netherlands

11.20 Antibodies against deamidated gliadin peptides outperform anti-endomysium and tissue transglutaminase antibodies in children <2 years (p.192)
A. Mubarak[1] , F.H.J. Gmelig-Meyling[2], V.M. Wolters[1], F.J.W. ten Kate[3], R.H.J. Houwen[1], Depts of Paediatric [1]Gastroenterology, [2]Immunology and [3]Pathology, University Medical Center Utrecht, The Netherlands

11.30 Prevalence and predictive factors of non-alcoholic fatty liver disease in severely obese adolescents. Assessment using Magnetic Resonance Spectroscopy (p.193)
B.Koot[1], J. van Werven[3], A. Nederveen[3], O. vd Baan-Slootweg[4], P. L. Jansen[2], J. Stoker[3], M. Benninga[1], [1]Dept Pediatric Gastroenterology, Academic Medical Centre, Amsterdam, [2]Dept Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, [3]Dept Radiology, Academic Medical Centre, Amsterdam, [4]Obesity Centre Heideheuvel, Hilversum, The Netherlands

11.40 Cognitive Behavior Therapy for children with Functional Abdominal Pain: preliminary results of a randomized controlled trial (p.194)
S.M.C. van der Veek[1], H.H.F. Derkx[2], E. de Haan[1], M.A. Benninga[2], & F. Boer[1], [1]Academisch Medisch Centrum Amsterdam, afdeling Kinder- en Jeugdpsychiatrie, [2]Emma kinderziekenhuis AMC, The Netherlands

11.50 Ursodeoxycholic acid use is associated with fat malabsorption and compromised growth in children with cystic fibrosis and mild liver disease (p.195)
H.P.J. van der Doef[1], A.M.V. Evelein[1], J.W. Woestenenk[1], H.G.M. Arets[1], R.H.J. Houwen[1], [1]C.F. Center Utrecht, University Medical Center Utrecht, The Netherlands

12.00 Lunch in de expositiehal

Sectie Experimentele Gastroenterologie — Baroniezaal

08.00 Ledenvergadering *(tot 08.30 uur)*

DEGH-Meeting — Baroniezaal

Voorzitters: J. McKeating en J.P.H. Drenth

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

Theme Liver disease and therapeutic options

08.30 Viral load reduction in chronic hepatitis B infectionameliorates the interaction of natural killer cells with dendritic cells: a key step in achieving anti-viral immunity? (p.196)
E.T.T.L. Tjwa, G.W. van Oord, P.J. Biesta, H.L.A. Janssen and A.M. Woltman, Dept of Gastroenterology and Hepatology, Erasmus Medical Centre Rotterdam, The Netherlands

08.42 In vivo immunosuppressive effects of intravenous immunoglobulin on innate and adaptive immune cells involved in allograft rejection (p.197)
A.S.W. Tjon[1], T. Tha-In[1], H.J. Metselaar[1], L.J.W. van der Laan[2], Z.M.A.Groothuismink[1], S. Mancham[1], M. van Hagen[3], J. Kwekkeboom[1], [1]Dept of Hepatology and Gastroenterology, [2]Dept of Surgery and [3]Dept of Internal Medicine and Immunology, Erasmus University Medical Center, Rotterdam, The Netherlands

08.54 Human hepatoma cell line HepaRG based bioartificial liver therapy increases survival time in rats with acute liver failure (p.198)
G.A.A. Nibourg[1,2], T.V. van der Hoeven[1,2], M.A. Maas[1], M.T. Ackermans[3], R.P.J. Oude Elferink[2], R.A.F.M. Chamuleau[2], R. Hoekstra[1,2], T.M. van Gulik[1], [1]Surgical Laboratory, [2]Tytgat Institute for Liver and Intestinal Research, [3]Dept of clinical chemistry, Laboratory of Endocrinology, Academic Medical Center (AMC), Amsterdam, The Netherlands

09.06 Pharmacological inhibition of human Multidrug Resistance-associated Proteins (MRPs) reverses liver fibrosis in vitro (p.199)
A. Rehman, B. Mikuš, M.H. Tiebosch, R. Modderman, H. Moshage,K.N. Faber, University Medical Center Groningen, University of Groningen, The Netherlands

09.18 Chronic prednisolone treatment leads to dyslipidemia in mice carrying a dimerization-defective glucocorticoid receptor (p.200)
A.J. Laskewitz[1], A. Rauch[2], A. Grefhorst[1], F. Kuipers[1,3], J.P. Tuckerman[2], A.K. Groen[1], [1]Dept of Pediatrics and [3] Laboratory Medicine, Center for Liver Digestive and Metabolic Diseases, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2] Tissue-specific hormone action, Leibniz Institute for Age Research, Fritz Lipmann Institute (FLI), Germany Jonge[1], J. Kwekkeboom[2], H.L.A. Janssen[2], H.J. Metselaar[2], H.W. Tilanus[1], G. Kazemier[1], L.J.W. van der Laan[1], Depts of [1]Surgery and [2]Gastroenterology & Hepatology Erasmus MC - University Medical Center, Rotterdam, The Netherlands

09.30 Hepatocyte-derived MicroRNAs in Human Serum are Sensitive Markers for Hepatic Injury in Liver Transplantation (p.201)
W.R.R. Farid[1], Q. Pan[2], A.J.P. van der Meer[2], P.E. de Ruiter[1], V. Ramakrishnaiah[1], J. de Jonge[1], J. Kwekkeboom[2], H.L.A. Janssen[2], H.J. Metselaar[2], H.W. Tilanus[1], G. Kazemier[1] and L.J.W. van der Laan[1], Departments of [1]Surgery and [2]Gastroenterology & Hepatology Erasmus MC - University Medical Center, Rotterdam, The Netherlands

09.42 **Invited Speaker: Prof. dr. Jane McKeating**
'The ins and outs of hepatitis C virus'

10.15 **Uitreiking Young Hepatologist 2010 prijzen**

10.30 Koffie/thee expositiehal

DEGH-Meeting **Baroniezaal**

Voorzitters: G. Bouma en L. Dieleman

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

Theme **Diet, Lifestyle and disease**

11.00 FcaRI expressing neutrophils induce severe colitis through binding of IgA-opsonized bacteria (p.202)

L.P.E. van der Steen[1], J. E. Bakema[1], C. W. Tuk[1], R.M. Korthouwer[1], S.H. Ganzevles[1], G. Bouma[2], M. van Egmond[1,3], [1]Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, [2]Dept of Gastroenterology, VU University Medical Center, Amsterdam, [3]Dept of Surgery, VU University Medical Center, Amsterdam, The Netherlands

11.12 A preoperative protein free diet protects against hepatic ischemia and reperfusion injury (p.203)

T.M van Ginhoven[1], T. Saat[1], M. Verweij[1], J.N.M. IJzermans[1], R.W.F. de Bruin[1], [1]Dept of Surgery Erasmus MC – University Medical Center, Rotterdam, The Netherlands

11.24 Smoking is an environmental factor that modulates innate immune functions associated with Crohn's disease (p.204)

A. Regeling, E.M.J. van der Logt, M. Geuken, T. Blokzijl, K. N. Faber, G. Dijkstra, Dept of Gastro-enterology and Hepatology, Center for Liver, Digestive and Metabolic Diseases, University Medical Center Groningen, Groningen, The Netherlands

11.36 Autophagy Regulates Immune Responses through Destabilization of the Immunological Synapse (p.205)

M.E. Wildenberg[1], A.C.W. Vos[1], S.C.S. Wolfkamp[2] , M. Duijvestein[1], A.P. Verhaar[1], A.A. te Velde[2], G.R. van den Brink[1,2], D.W. Hommes[1], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [2]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

11.48 Dietary non-digestible oligosaccharide-induced epithelial galectin-9 secretion correlates with protection against allergic symptoms (p.206)

S. de Kivit[1], E. Saeland[2], A.D. Kraneveld[1], H.J.G. van de Kant[1], B. Schouten[1,3], B.C.A.M. van Esch[1,3], J. Knol[3], A.B. Sprikkelman[4], L.B. van der Aa[4], L.M.J. Knippels[1,3], Y. van Kooyk[2], J. Garssen[1,3], L.E.M. Willemsen[1], [1]Pharmacology, Utrecht Institute Pharmaceutical Sciences, Utrecht University, Utrecht, [2]Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, [3]Danone Research, Wageningen, [4]Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Amsterdam, The Netherlands

12.00 **Invited Speaker: Prof. dr. Leo Dieleman**
Probiotics and prebiotics in GI; quo vadis?

Postersessies DEGH **Meierij Foyer**

ZonMw

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, 4 posters per categorie, 7 minuten per poster. U vindt een overzicht vanaf pagina 54 in dit programma.

Richtlijnbijeenkomst **Brabantzaal**

Programma rond de herziene richtlijn oesophaguscarcinoom

Voorzitter: P.D. Siersema

13.30 Opening en Inleiding
P. D. Siersema, MDL-arts, UMC Utrecht

13.40 Neoadjuvante behandeling
Dr. A. van der Gaast, internist-oncoloog, Erasmus MC, Rotterdam

14.00 Chirurgische en niet-chirurgische behandeling
Dr. B.P.L. Wijnhoven, chirurg, Erasmus MC, Rotterdam

14.20 Spreiding en concentratie van behandeling
Dr. G.A.P. Nieuwenhuijzen, chirurg, Catharina Ziekenhuis, Eindhoven

14.40 Behandeling niet-resectabel/recidief oesofaguscarcinoom
Prof. dr. P.D. Siersema, MDL-arts, UMC Utrecht

14.50 Discussie

15.00 Einde programma

Voorzitters: C.C. Paulusma en S.W.C. van Mil

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

Theme **Bile acids and cholestasis**

13.30 Activation of bile salt nuclear receptor FXR is repressed by pro- inflammatory cytokines activating NF-κB signaling in the intestine (p.207)

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

13.42 Involvement of G-protein coupled receptors in bile acid-induced apoptosis in primary rat hepatocyte (p.208)

G. Karimian[1], M. Buist-Homan[1], M. Schmidt[2], U.J.F. Tietge[3], K.N. Faber[1], H. Moshage[1], [1]Dept Gastroenterology and Hepatology, [2]Dept Molecular Pharmacology and [3]Dept Pediatrics, University Medical Center Groningen, University of Groningen, The Netherlands

13.54 Vitamin A deficiency strongly aggravates liver damage during obstructive cholestasis, acute vitamin A therapy is the cure (p.209)

M.O. Hoeke, M. Hoekstra, J. Heegsma, V.W. Bloks, H. Moshage, K.N. Faber, Dept of Gastroenterology and Hepatology, Dept of Pediatrics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

14.06 Essential fatty acid deficiency induces intestinal cholesterol excretion in mice (p.210)

M.Y.M. van der Wulp[1, 2], S. Lukovac[2], E.H.H.M. Rings[1, 2], A.K. Groen[1,2], H.J. Verkade[1, 2], [1]Top Institute Food and Nutrition, Wageningen, [2]Pediatric Gastroenterology, Dept of Pediatrics. Graduate School of Medical Sciences. Center for Liver, Digestive, and Metabolic Diseases, University Medical Center Groningen, University of Groningen, The Netherlands

14.18 Phosphorylation of FXR-S228 is necessary for transactivation of bile salt homeostasis genes but not transrepression of inflammatory signalling via NF-κB (p.211)

R.M. Gadaleta, E.C.L. Willemsen, A. Veenstra, A.B. Brenkman, S.W.C. van Mil, Dept of Metabolic and Endocrine Diseases, University Medical Centre Utrecht and The Netherlands Metabolomics Centre, The Netherlands

14.30 Targeting specific Fxr isoforms, the role in the bile acid biosynthetic pathway (p.212)

M. Boesjes[1], J. Hageman[1], V.W. Bloks[1], H. Havinga[1], F. Kuipers[1,2], A.K. Groen[1,2], Laboratory of [1]Pediatrics and [2]Laboratory Medicine, Centre for Liver, Digestive and Metabolic Diseases, University Medical Center Groningen, The Netherlands

14.42 Autotaxin is a Novel Diagnostic Marker for Intrahepatic Cholestasis of Pregnancy (p.213)

A.E. Kremer[1], P.H. Dixon[2], C. Ris-Stalpers[3], V. Geenes[2], J. Chambers[2], J.A. van der Post[3], C. Williamson[2], U. Beuers[1], R.P.J. Oude Elferink[1], [1]Tytgat Institute for Liver and Intestinal Research and Dept of Hepatology & Gastroenterology, Academic Medical Center, University of Amsterdam, [2]Aternal and Fetal Disease Group, Institute of Reproductive and Developmental Biology, Imperial College London, London, United Kingdom, [3]Dept of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands

14.54 Uitreiking prijzen beste presentaties en beste posters

15.15 Closing

Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie — Parkzaal

Voorzitters: A.A.M. Masclee en C.J.J. Mulder

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

13.30 Real-time PCR for simultaneous detection and identification of Brachyspira species reveals the presence of a novel Brachyspira species in human spirochaetosis (p.214)

L.J. Westerman[1], H.V. Stel[2], M.E.I. Schipper[3], L.J. Bakker[4], C.H.E. Boel[1], J.H.M. van den Brande[5], P.D. Siersema[6], and J.G. Kusters[1], Depts of [1]Medical Microbiology, [3]Pathology and [6]Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, The Netherlands, [4]Central Laboratory for Bacteriology and Serology, Depts of [2]Pathology and [5]Internal Medicine, Tergooiziekenhuizen, Blaricum and Hilversum, The Netherlands

13.40 Clinicians need support in determining familial colorectal cancer risk: results of a national survey (p.215)

N. Dekker[1,4], W.A.G. van Zelst-Stams[1], F.M. Nagengast[2], J.H.W. de Wilt[3], R.P.M.G. Hermens[4], N. Hoogerbrugge[1,5], [1]Dept of Human Genetics, Radboud University Nijmegen Medical Centre, [2]Dept of Gastroenterology, Radboud University Nijmegen Medical Centre, [3]Dept of Surgery, Radboud University Nijmegen Medical Centre, [4]Scientific Institute for Quality of Healthcare, Radboud University Nijmegen Medical Centre, [5]Dept of Medical Oncology, Radboud University Nijmegen Medical Centre, The Netherlands

13.50 The lack of evidence for treatment of uncomplicated diverticulitis (p.216)

Ç.Ünlü[1,2], L. Daniels[1], B.C. Vrouenraets[2], M.A. Boermeester[1], [1]Surgery Dept, AMC, Amsterdam, [2]Surgery Dept, SLAZ, Amsterdam, The Netherlands

14.00 Long-term outcome of treatment with temperature-controlled radio-frequency energy (SECCA) in patients with fecal incontinence: sustained improvement after 3 and 5 years (p.217)

T.J. Lam[1], M.M. Meurs-Szojda[1,2], C.J.J. Mulder[1], R.J.F. Felt-Bersma[1], [1]Dept of Gastro-enterology and Hepatology, VU University Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, Medical Center Alkmaar, Alkmaar, The Netherlands

14.10 Gastrointestinal ischemia is an important trigger for athletes with exercise induced abdominal complaints (p.218)

R.W.F. ter Steege[1], R.H. Geelkerken[2], A.B. Huisman[3], J.J. Kolkman[4], [1]Dept of Gastroenterology, University Medical Centre Groningen, [2]Dept of vascular surgery, Medical Spectrum Twente, Enschede, [3]Dept of radiology, Medical Spectrum Twente, Enschede, [4]Dept of gastroenterology, Medical Spectrum Twente, Enschede, The Netherlands

14.20 Clinical effect of vasodilating agents in patients diagnosed with non- occlusive mesenteric ischemia (p.219)

A. Sa[1] , L.M.G. Moons[1] , P.B.F. Mensink[1] , E.V. Rouwet[3] , D. Van Noord[1] , T.C. Leertouwer[2], H.J.M. Verhagen[3], E.J. Kuipers[1,4], [1]Depts of Gastroenterology and Hepatology, [2]Intervention Radiology, [3]Vascular Surgery, [4]Internal Medicine, Erasmus MC - University Medical Center, Rotterdam, The Netherlands

14.30 Chronic Gastrointestinal Ischemia due to Atherosclerotic Narrowing is related to Classical Risk Factors for Cardiovascular Disease (p.220)

A. Sana[1], D. v. Noord[1], S. Kooij[2], K. v. Dijk[2], B. Bravenboer[3], A.G. Lieverse[4], E.J.G. Sijbrands[2], J.G. Langendonk[2], P. Mensink[1], Depts of [1]Gastroenterology and Hepatology, [2]Internal Medicine, Erasmus Medical Centre, Rotterdam, [3]Dept of Internal Medicine, Catharina Ziekenhuis, Eindhoven, [4]Dept of Internal Medicine, Maxima Medisch Centrum, Eindhoven, The Netherlands

14.40 Epidemiology of Autoimmune hepatitis in The Netherlands: A nationwide study (p.221)

N.M.F. van Gerven[1], B.J. Verwer[1], B van Hoek[8], J.T. Brouwer[4], M. Pronk[8], M. Coenraad[10], H.R. van Buuren[9], R.A. de Man[9], K.J. van Erpecum[2], J. Drenth[3], U. Beuers[6], J. den Ouden[7], G.H. Koek[5], C.J.J. Mulder[1], C.M.J. van Nieuwkerk[1], G Bouma[1], [1]VUmc, Amsterdam, [2]UMC, Utrecht, [3]UMC St Radboud, Nijmegen, [4]Reinier de Graaf gasthuis, Delft, [5]AZM, Maastricht, [6]AMC, Amsterdam, [7]Sint Fransiscus Gasthuis, Rotterdam, [8]LUMC, Leiden, [9]Erasmus MC, Rotterdam, [10]UMCG, Groningen, The Netherlands

14.50 Percutaneous Radiofrequent Lesioning of the Splanchnic Nerves in Patients with Chronic Pancreatitis. An explorative study in 11 Patients (p.222)

B.P.M. Verhaegh[1], M. van Kleef[2], M. Puylaert[3], J. van Zundert[2,3], A.G.H. Kessels[4], A.A.M. Masclee[1], Y.C.A. Keulemans[1], [1]Dept of Gastroenterology, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Dept of Anaesthesiology and Pain Management, Maastricht University Medical Center, Maastricht, The Netherlands, [3]Dept of Anaesthesiology, Oost Limburg Hospital, Genk, Belgium, [4]Dept of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, The Netherlands

Vrijdag 18 maart 2011

15.00 Gadolinium-EOB-DTPA enhanced MRI in differentiating focal nodular hyperplasia from hepatocellular adenoma (p.223)

M. Bieze[2], J.W. van den Esschert[2], C. Yung Nio1, J.B. Reitsma3, T.M. van Gulik2, Saffire S.K.S. Phoa1 1Department of Radiology [2]Department of Surgery, [3]Department of Clinical Epidemiology Academic Medical Center Amsterdam The Netherlands*

15.10 Interobserver agreement among radiologists for pancreatic cysts using MRI (p.224)

K. de Jong[1], C.Y. Nio[2], B. Mearadji[2], S.S. Phoa[2], M.R. Engelbrecht[2], M.G. Dijkgraaf[3], M.J. Bruno[4], P. Fockens[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, [2]Dept of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, [3]Dept of Biostatistics and Clinical Epidemiology, Academic Medical Center, University of Amsterdam, Amsterdam, [4]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

15.20 Indication for CDKN2A mutation analysis in familial pancreatic cancer-families without melanomas (p.225)

F. Harinck[1], I. Kluijt[2], T.A.M. van Os[3], N. van der Stoep[4], R. Oldenburg[5], A. Wagner[5], C.M. Aalfs[3], R.H. Sijmons[6], J-W. Poley[1], E.J. Kuipers[1], P. Fockens[7], M.J. Bruno[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, [2]Familial Cancer Clinic, The Netherlands Cancer Institute Amsterdam, [3]Dept of Clinical Genetics, Academic Medical Center, University of Amsterdam, [4]Center for Human and Clinical Genetics, Leiden University Medical Center, Leiden, [5]Dept of Clinical Genetics, Erasmus MC, University Medical Center, Rotterdam, [6]Dept of Clinical Genetics, University Medical Center Groningen, [7]Dept of gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

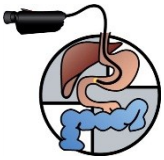
15.30 Einde programma

13.00	**Symposium Body composition, body function and energy expenditure** Chair: Dr. G. Ligthart – Melis, dietitian VUMC Dr. G. Wanten, gastroenterologist UMCN
13.00	Introduction and goals of symposium (platform research dietitians and nurse practioners) Dr. M.A.E. van Bokhorst – de van der Schueren
13.10	Do's and Don'ts in clinical research concerning body composition Dr. Carrie Earthman, Director of the Didactic Program in Dietetics, Department of Food Science and Nutrition, University of Minnesota. Visiting Associate Professor VUmc 2010/2011
13.50	Discussion
14.00	Short presentations of research dietitians on their studies in relation to bodycomposition, bodyfunction and energy expenditure *(7 minutes presentation / 3 minutes discussion)*
14.00	Lenny van Venrooij, AMC *The use of BIS and DXA in screening nutritional status in preoperative cardio surgical patients*
14.10	Kirsten Berk, EMC *The effectiveness of a Very Low Calorie Diet in patients with diabetes type 2 and overweight on weight, waist circumference, cardiovascular risk and glycaemic control*
14.20	Esther van den Hogen, MUMC *Handgrip strength in clinical practice*

Vrijdag 18 maart 2011

14.30	Sandra Beijer, MUMC *The effect of APT on nutritional status including weight, triceps skin fold, upper arm circumference and muscle strength*
14.50	Harriët Jager, UMCG *Changes in body composition and grip strength during head and neck cancer treatment*
15.00	Elles van der Louw, EMC *Evaluation of growth and energy need in children on a ketogenic diet*
15.10	Cora Jonkers, secretary NESPEN *What have we learned today, where do we want to go?*

V & VN - MDL **Diezezaal**



OCHTENDPROGRAMMA

10.15	Opening door de voorzitter
10.20	Gastro-intestinale bloedingen anno 2011 *Dr. René Van der Hulst, MDL-arts, Kennemer Gasthuis*
10.40	Ileal brake en eetgedrag *Dr. Jeroen Maljaars, AIOS Maag Darm Leverziekten, LUMC*
11.00	Filmpje
11.05	CT Colografie als alternatief voor coloscopie? *Mevr. Margriet de Haan, arts onderzoeker radiologie, AMC*
11.25	ATP meting in flexibele endoscopen, nuttig? *Lisette Kempenaar en Carlien de Jong, verpleegkundigen endoscopie afdeling LUMC*
11.50	Algemene Ledenvergadering
12.30	Lunchbuffet in de Kempenhal

MIDDAGPROGRAMMA

14.10	Inflammatory Bowel Disease, ontwikkelingen vanuit verpleegkundig perspectief *Maria de Jong, Verpleegkundig Specialist MDL, AMC Amsterdam*
14.30	"Met z'n 12-en voor scopie" . *Hester te Velde en Pauline Plaisier, MDL-verpleegkundigen Diakonessenhuis Utrecht/Zeist*
14.50	Onderzoek kwaliteit van leven en IBD *Bernadette Franke, arts assistent i.o., MST, Enschede*
15.10	Afsluiting voorzitter

ZonMw

Theme 1. Metabolisme - chair: K.N. Faber

Time *Poster* *Title*

12:45 **1** Factors secreted by liver-derived mesenchymal stem cells promote liver regeneration after partial hepatectomy

S.M.G. Fouraschen[1], J. de Jonge[1], Q. Pan[2], G. Kazemier[1], J. Kwekkeboom[2], H.J. Metselaar[2], H.W. Tilanus[1] and L.J.W. van der Laan[1], [1]Dept of Surgery and [2]Gastroenterology & Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

2 Plasma citrulline as a marker for ineffective fat absorption during methotrexate-induced gastrointestinal mucositis in a rat model

M. Fijlstra[1,2], W.J.E. Tissing[2], H.J. Verkade[1], F. Stellaard[1], W.A. Kamps[2], and E.H.H.M. Rings[1], Pediatric Gastroenterology[1] and Pediatric Oncology[2], Dept of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, The Netherlands

3 Disruption of endoplasmic reticulum homeostasis in human intestine in response to ischemia/reperfusion: novel insight from genome-wide transcript profiling

K. Lenaerts[1], J. Grootjans[1], M. Manca[2], B. Boonen[1], J.P. Derikx[1], R.M. van Dam[1], E.A. Biessen[2], C.H. Dejong[1], W.A. Buurman[1], [1]Dept of Surgery, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Centre, Maastricht, The Netherlands, [2]Dept of Pathology, CARIM School for Cardiovascular Diseases, Maastricht University Medical Centre, Maastricht, The Netherlands

4 Immunohistochemical study evaluating the vagal innervation of intestinal resident macrophages

C. Cailotto[1], P. Gomez, J. Pedro[2], J. van der Vliet[1], G. Matteoli[2], G.E. Boeckxstaens[1,2], [1]Tytgat Institute for Liver and Intestinal Research, Academic medical center (AMC), Amsterdam, The Netherlands, [2]Dept of Gastroenterology, University Hospital Leuven, Catholic University of Leuven, Leuven, Belgium

Theme 2. Cell biology - chair: C.C. Paulusma

Poster *Title*

9 Spontaneous tumorigenic transformation of mesenchymal stem cells caution therapeutic application

Q. Pan1, S.M.G. Fouraschen2, J. de Jonge[2], G. Kazemier[2], J. Kwekkeboom[1], H.J. Metselaar[1], H.W. Tilanus2, H.L.A. Janssen1, L.J.W. van der Laan2, Depts of [1]Gastroenterology & Hepatology and [2]Surgery, Erasmus MC-University Medical Center Rotterdam, The Netherlands

10 Fatty hepatocytes are not more susceptible to bile acid-induced apoptosis: alteration in mitochondrial permeability transition pore

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

11 The intracellular ABC-transporter PMP70 is required for the characteristic alpha-smooth muscle actin network in activated hepatic stellate cells

J. Woudenberg, A. -ur-Rehman, F.A.J. van den Heuvel, B. Mikuš, M.H. Tiebosch, K.P. Rembacz, H. Moshage, K.N. Faber, Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

12 Mitochondrial Manganese-superoxide dismutase prevents activation of stellate cells

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Theme 3. IBD – chair: A.A. te Velde

Poster Title

17 Copy number variations contribute to the genetic risk for coeliac disease

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18 A functional variant of the Farnesoid X Receptor (FXR) predisposes to ileocolonic localization of Crohn's disease

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19 Socs3 promoter hypermethylation status in ulcerative colitis related colorectal cancer

Y. Li[1], C. de Haar[1], E. J. Kuipers[1], C. J. van der Woude[1], [1]Gastroenterology and Hepatology Dept, Erasmus Medical Center, Rotterdam, The Netherlands

20 Pretreatment with interferon-gamma enhances the therapeutic activity of mesenchymal stromal cells in animal models of colitis

M. Duijvestein[1], M.E. Wildenberg[1], M.M. Welling[2], A.C.W. Vos[1], S. Hennink[1], T. Bosse[3], E.S.M. de Jonge-Muller[1], H. Roelofs[4], H.W. Verspaget[1], W.E. Fibbe[4], A.A. te Velde[5], G.R. van den Brink[1,6], D.W. Hommes[1], [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, [2]Dept of Radiology, Division of Nuclear Medicine, Leiden University Medical Center, Leiden, [3]Dept of Pathology, Leiden University Medical Center, Leiden, [4]Dept of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, [5]Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, [6]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

21 Activation of endoplasmic reticulum stress response and ABCG2 protein down regulation in active inflammatory bowel disease

J. J. Deuring[1], C. de Haar[1], C. L. Koelewijn[1], E.J. Kuipers[1], M. P. Peppelenbosch[1], C. J. van der Woude[1], Erasmus MC University Medical Center Rotterdam, [1]Dept Gastroenterology and Hepatology, The Netherlands

Theme 4. Cancer – chair: J.P.H. Drenth

Poster Title

26 The potential role of microRNA-145 via targeting Bone Morphogenetic Protein4 and its signal transduction pathway in the development of Barrett's esophagus

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27 Polymorphisms in the GATA-binding sites of the Vitamin D receptor gene affect its transcription in the esophagus, and are associated with a reduced risk for esophageal disease

A. van de Winkel[1], A.G. Uitterlinden[2], A.M. Rygiel[3], L.M.G. Moons[1], P.P. Arp[2], J.B.J. van Meurs[2], K.K. Krishnadath[3], E.J. Kuipers[1,2], L.J.W. van der Laan[4], [1]Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [2]Internal Medicine, Erasmus Medical Center, Rotterdam, [3]Center for Experimental Molecular Medicine, Academic Medical Center, Amsterdam, [4]Surgery, Erasmus Medical Center, Rotterdam, The Netherlands

28 Improving Lynch Syndrome Diagnostics by Multiplex SNaPshot Assays for the Detection of Mismatch Repair Gene LOH in MSI-H tumors

C.H.M. Leenen[1], W.R.R. Geurts-Giele[2], H.J. Dubbink[2], E.J. Kuipers[1,3], M.E. van Leerdam[1], A. Wagner4, W.N.M. Dinjens[2], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Pathology, Josephine Nefkens Institute, [3]Dept of Internal Medicine, [4]Dept of Clinical Genetics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

29 Cell surfaceproteomics identifies prion protein as a candidate biomarker for colorectaladenoma-to-carcinoma progression

M. de Wit[1], C.R. Jimenez[2], B. Carvalho [1], J.A.M. Belien[1], P.M. Delis- van Diemen[1], S. Mongera[1], S. Piersma[2], G.A. Meijer[1], R.J.A. Fijneman[1], [1]Pathology, Tumor Profiling Unit, [2]Medical Oncology, OncoProteomics Lab, VU University Medical Center Amsterdam, The Netherlands

Theme 5. Immunology – chair: G. Bouma

Poster Title

35 Human plasmacytoid dendritic cells induce CD8+CD38+CTLA-4+LAG-3+ regulatory T cells that suppress alloreactive memory T cells in a CTLA-4 dependent fashion

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

36 The interaction between Hepatitis B virus and Kupffer cells leads to immune activation

A. Boltjes[1], M.L. Op den Brouw[1], G.W. van Oord[1], H.L.A. Janssen[1], A.M. Woltman[1] , [1]Dept of Gastro-enterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

37 Ectopic Protein Kinase B (PKB/c-Akt) activity augments human plasmacytoid dendritic cell development and function, a therapeutic strategy to improve immunity?

L. van de Laar[1], A. van den Bosch[1], R.S. Binda[1], M. Buitenhuis[2], H.L.A. Janssen[1], P.J. Coffer[3], A.M. Woltman[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, [2]Dept of Immunology and [3]Dept of Cell Biology, UMC Utrecht, The Netherlands

38 NK cells can generate locally from early precursors in the adult human liver

V. Moroso[1], F. Famili[1], H.J. Metselaar[1], T. Cupedo[2], J. Kwekkeboom[1] , Depts of [1]Gastroenterology and Hepatology, [2]Hematology, Erasmus MC, Rotterdam, The Netherlands

Theme 1. Bile metabolism and transport– chair: J.P.H. Drenth

Time *Poster* *Title*

12.45 **39** Autotaxin – a Novel Therapeutic Target for Severe Pruritus of Cholestasis?

A.E. Kremer[1], P. Leckie[2], E.M.M. Kuiper[3], F.G. Schaap[1], T. Mettang4, K.S. Reiners5, U. Raap6, H.R. van Buuren[3], K.J. van Erpecum7, N.A. Davies[2], A. Engert5, P.L.M. Jansen[1], R. Jalan[2], R.P.J. Oude Elferink[1], U. Beuers[1] , [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, The Netherlands, [2]Institute of Hepatology, University College London, United Kingdom, [3]Dept of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [4]Dept of Nephrology, German Clinic for Diagnostics, Wiesbaden, Germany, [5]Laboratory of Immunotherapy, Dept of Internal Medicine, University Clinic Cologne, Cologne, Germany, [6]Dept of Dermatology and Allergy, Hannover Medical School, Hannover, Germany, [7]Dept of Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands

40 Human bile contains high levels of the endocrine factor FGF19. Potential role of FGF19 in the entero-hepatobiliary system

S.J.L.B. Zweers[1], K.A.C. Booij[2], M. Komuta[3], T. Roskams[3], D.J. Gouma[2], P.L.M. Jansen[1,4], F.G. Schaap[1] , [1]Tytgat Institute for Intestinal and Liver Research, Academic Medical Center, Amsterdam, The Netherlands, Depts of [2]Surgery and [4]Hepatology and Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands, [3]Morphology and Molecular Pathology, University Hospital Gasthuisberg, Leuven, Belgium

41 Plant sterol supplementation increases transintestinal cholesterol excretion in mice via Abcg5

G. Brufau[1], F. Kuipers[1,2], Y. Lin[3], E. Trautwein[3], A.K. Groen[1,2], Center for Liver, Digestive and Metabolic Diseases, Depts of [1]Pediatrics and [2]Laboratory Medicine, University Medical Center Groningen, University of Groningen, [3]Unilever Food and Health Research Institute, Unilever R & D, Vlaardingen, The Netherlands

42 FRET-based Sensors for Dynamic intracellular Bile Salt detection

L.M. van der Velden[1], M.V. Golynskiy[2], S.W.C. van Mil[1], L.W.J. Klomp[1], M. Merkx[2] and S.F.J. van de Graaf[1] , [1]Dept of Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, Utrecht, The Netherlands, [2]Laboratory of Chemical Biology, Dept of Biomedical Engineering, Eindhoven University of Technology, The Netherlands

Theme 2. Metabolism – chair: S.W.C. van Mil

Poster *Title*

5 Timing of meal ingestion determines gastric emptying of a test drink

D. Keszthelyi[1], D. Knol[2], FJ. Troost[1], S. Ludidi[1], R. Sleijpen[1], M. van Avesaat[1], M. Gribnau[2], M. Foltz[2], G. Duchateau[2] and A.A.M. Masclee[1], [1]Division of Gastroenterology-Hepatology, Dept of Internal Medicine, Maastricht University Medical Centre+, Maastricht, [2]Unilever Research and Development, Vlaardingen, The Netherlands

6 An oral bolus of glucose is not effectively absorbed during methotrexate-induced gastrointestinal mucositis in a rat model

M. Fijlstra[1,2], E.H.H.M.Rings[1], H.J. Verkade[1], T.H. van Dijk[1], W.A. Kamps[2], W.J.E. Tissing[2], [1]Pediatric Gastroenterology and [2]Pediatric Oncology, Dept of Pediatrics, Beatrix Children's Hospital, University Medical Center Groningen, The Netherlands

7 The effect of acute tryptophan depletion on systemic and intestinal serotonin metabolism in healthy humans

D. Keszthelyi[1,2], FJ. Troost[1,2], H. van Eijk[3], DM. Jonkers[1,2], WA. Buurman[3], J. Dekker[1], A.A.M. Masclee[1,2], [1]Top Institute Food and Nutrition, Wageningen, [2]Division of Gastroenterology-Hepatology, Dept of Internal Medicine, Maastricht University Medical Centre, [3]Dept of Surgery, Maastricht University Medical Centre, The Netherlands

8 The role of secretory leukoprotease inhibitor in regulating anti-microbial responses in the gastro-intestinal tract

C.L. Menckeberg[1], Y. Simons-Oosterhuis[1], D.J. Lindenbergh-Kortleve[1], J.C. Escher[2], G. Kraal[3] and J.N. Samsom[1] , [1]Laboratory of Pediatrics, division gastroenterology and nutrition, Erasmus Medical Center, Rotterdam, [2]Dept of Pediatrics – Sophia Children's Hospital, Erasmus Medical Center Rotterdam, [3]Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

Theme 3. Cell biology - chair: R. van Tol

Poster Title

13 Activated hepatic stellate cells do not express heme-oxygenase-1 in vitro and in vivo

M.H. Tiebosch, M. Buist-Homan, S. Dunning, A.T.M.G. Tiebosch[1], K.N. Faber, H. Moshage , Dept Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, and [1]Dept Pathology, Martini Hospital, Groningen, The Netherlands

14 Molecular mechanisms of resistance to bile-acid induced apoptotic cell death in cholestatic hepatocytes: a role for the mitochondrial permeability transition pore

E.M. Verhaag, G. Karimian, M. Buist-Homan, K.N. Faber and H. Moshage, Dept Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, The Netherlands

15 Muramyl dipeptide enhances responses of intestinal epithelial cells to bacterial TLR ligands

I.H. Hiemstra[1], G. Bouma[2], G. Kraal[1], and J.M.M. den Haan[1], [1]Molecular Cell Biology and Immunology, VU University Medical Center, Van der Boechorststraat 7, Amsterdam, [2]Dept of gastroenterology, VU University Medical Center, Amsterdam, The Netherlands

16 Reduced expression of LKB1 in colon cancer cells increases cell migration, and survival during metabolic stress

S.E. Korsse[1], R. Smits[1], E.J. Kuipers[1], M.E. van Leerdam[1], W. van Veelen[1], [1]Dept of Gastroenterology and Hepatology, Erasmus-MC University Medical Center, Rotterdam, The Netherlands

Theme 4. IBD – chair: G. Bouma

Poster *Title*

22 Towards a mouse model for celiac disease

A.E. Kozijn1, M.F. du Pré[1], M.N.D. ter Borg[1], L.A. van Berkel[1], D. Lindenbergh-Korleve[1], L. Torp Jensen[2], Y. Kooy-Winkelaar[3], F. Koning[3], L. Boon4, E.E.S. Nieuwenhuis[1], L.M. Sollid5, L.A. Fugger[6], J.N. Samsom[1], [1]Laboratory of Pediatric Gastroenterology, Erasmus Medical Centre, Sophia Children's Hospital, Rotterdam, The Netherlands, [2]Clinical Institute, Aarhus University Hospital, Skejby Sygehus, Denmark, [3]Dept of Blood Transfusion and Immunohematology, Leiden University Medical Center, Leiden, The Netherlands, [4]Bioceros B.V., Utrecht, The Netherlands, [5]Centre for Immune Regulation, Institute of Immunology, University of Oslo and Oslo University Hospital, Rikshospitalet, Oslo, Norway, [6]Dept of Clinical Neurology and MRC Human Immunology Unit, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom

23 In inflammatory bowel disease peripheral blood neutrophils have increased basal migratory activity associated with enhanced CXCR1 and CXCR2 expression

S. A. Overbeek[1], P. J. Koelink[1], P. A. Henricks[1], H. W. Verspaget[2], P. de Kruijf[3], M. J. Smit[3], S. C. Wolfkamp[4], A. A. te Velde[4], G. Folkerts[1] and A. D. Kraneveld[1], [1]Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, [2]Dept of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, [3]Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, VU University Amsterdam, Amsterdam, [4]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

24 The development of Th17 responses towards gut antigens during colitis requires both intestinal inflammation and TLR stimulation

M.E. Morgan[1], B. Zheng[1], H. van de Kant[1], L. Hazen[1], M. van Roest[1], G. Folkerts[1], A.D. Kraneveld[1], [1]Dept of Pharmacology, Utrecht University, Utrecht, The Netherlands

25 Increased IL-21, but not IL-17 production in the small intestine is characteristic for pediatric celiac disease

M.A. van Leeuwen[1], D.J. Lindenbergh-Kortleve[1], M.F. du Pré[1], R.R. de Krijger[2], J.C. Escher[1], J.N.I. Samsom[1] , [1]Laboratory of Pediatric Gastroenterology, Erasmus Medical Center, Rotterdam, [2]Dept of Pathology, Erasmus Medical Center, Rotterdam, The Netherlands

Theme 5. Cancer – chair: E.H.H.M. Rings

Poster *Title*

30 MMP9 is a prognostic biomarker for metastatic colorectal cancer

J.A.C.M. Goos[1,2], R.J.A. Fijneman[1], A.C. Hiemstra[1], A.A. Geldof[2], G.A. Meijer[1], O.S. Hoekstra[2] on behalf of the DeCoDe PET group, Depts of [1]Pathology and [2]Nuclear Medicine & PET Research, Amsterdam, The Netherlands

31 MicroRNAs located on 13q and 20q are differentially expressed between normal mucosa, adenomas and carcinomas of the large intestine

L.M. Timmer[1], J.S. Bolijn[1], B. Carvalho[1], C.J.J. Mulder[2], E. Cuppen[3], G.A. Meijer[1], B. Diosdado[1], [1]Dept of Pathology, VU University medical center Amsterdam, Amsterdam, [2]Dept of Gastroenterology and Hepatology, VU University medical center Amsterdam, Amsterdam, [3]Hubrecht Institute and University medical center Utrecht, Developmental Biology and Stem Cell Research, Utrecht, The Netherlands

32 The role of NF-κB in the expression of Barrett's specific markers in an esophageal squamous epithelial cell line upon exposure to bile salts at low pH

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

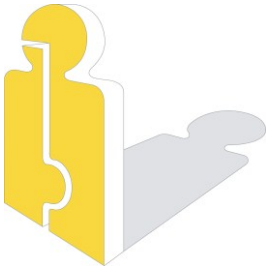
33 A possible role for Toll-Like Receptor 4 activation in Barrett's esophagus in the development of esophageal adenocarcinoma

R.E. Verbeek[1], P.D. Siersema[1], F.J. ten Kate[2], K. Fluiter[3], F.P. Vleggaar[1], J.W.P.M. van Baal[1] , [1]Dept of Gastroenterology and Hepatology, [2]Dept of Pathology, University Medical Center Utrecht, [3]Dept of Neurogenetics, Academic Medical Center, University of Amsterdam, The Netherlands

34 Statins reduce the risk on colorectal cancer in relation to SMAD4 expression

R. J. Jacobs[1], L.L. Kodach[1], N. L. Weil[1], P.W. Voorneveld[1], H. Morreau[2], G. R. van den Brink[1,3], D. W. Hommes[1], J. C. Hardwick[1], [1]Gastroenterology and Hepatology, LUMC, Leiden, [2]Pathology, LUMC, Leiden, [3]Tytgat Institute for Liver and Intestinal Research, AMC, Amsterdam, The Netherlands

Abstracts

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Chirurgie

Trademark and generic acid suppressive drugs more than 10 years after the endoscopical diagnosis of reflux oesophagitis

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Reflux oesophagitis needs maintenance therapy with acid suppressive drugs. Since generic preparations (gen) became available, clinicians made the observation that these drugs are probably less effective. Most studies on the efficacy of acid suppressive therapy report on short term follow-up after treatment with trademark (™) medication. Little data exist on the long term follow-up of patients with reflux oesophagitis. Data on comparison between these ™ and gen are not available. A study was done in order to determine complaints in correlation with the use of acid suppressive therapy more than 10 years after diagnosis. All 672 patients with endoscopically diagnosed reflux oesophagitis between 1998 and 2000 were reviewed to identify patients suitable for this investigation. A total of 262 patients were excluded because they met pre-defined exclusion criteria (ie. chronic cardiopulmonary disease, or treatment of cancer), leaving a study population of 410 subjects. All patients received a questionnaire regarding their use of acid suppressive therapy, drug dosage, prescriber, compliance and patient satisfaction. In addition, use of ™ or gen was assessed. Presence of reflux complaints was assessed via a validated questionnaire, and a symptom score was calculated using a 5-point Likert scale. A total of 208 patients returned the questionnaire (51%), 161 (78%) of them used acid suppressive therapy. Of the patients still on acid suppressive therapy 72% (116 patients, group 1) had reflux complaints, while the remaining 45 patients (28%, group 2) were in complete clinical remission. There was no difference in gender, age or severity of the initially diagnosed reflux oesophagitis between both groups. An equal number of patients in both groups received the prescription from their general practitioner. Patients in group 1 were significantly less compliant and satisfied compared to patients from group 2, 73% vs. 96% and 83% vs. 100% ($p<0,001$) respectively. An equal number of patients in both groups used ™ or gen (p=ns). Presence of reflux complaints as well as symptom score (although rather low) showed no differrence between users of ™ or gen. The majority of patients always uses the prescribed dosage.
It is concluded that more than 10 years after the diagnosis of reflux oesophagitis 22% of patients stopped using acid suppressive therapy. From the patients still on medication only a minority (28%) is in complete clinical remission associated with significantly higher patient satisfaction and compliance to therapy as compared to their symptomatic counterparts. There appears to be no difference in effect and usage of ™ versus gen preparations.

Complaints in patients with reflux oesophagitis more than 10 years after the diagnosis.

S.M.L.A. Loffeld, G.M.H.E. Dackus, R.J.L.F. Loffeld, Medical students University of Maastricht, Dept of Internal Medicine Zaans Medisch Centrum, Zaandam, The Netherlands

Treatment of reflux oesophagitis with acid suppressive therapy is effective. However, data on very long term follow-up are lacking. A study was done in patients in order to assess complaints more than 10 years after the endoscopic diagnosis.All patients diagnosed in the years 1998, 1999 and 2000 were studied. Exclusion criteria were chronic cardio-pulmonary disease, active treatment for any cancer, immigrants, Alzheimers, mental disability, and psychiatric illnesses. All patients received a questionnaire by mail. The questionnaire comprised four different, validated lists of questions. A general questionnaire consisted of 20 questions on reflux complaints. Severity as well as frequency was scored on a five and six point Likert scale respectively (scores ranged from 0-40 and 0-60). The GerdQ list, a symptom activity index (SAI), and the gastrointestinal symptom rating scale (GSRS) were used as well.In a period of three years 672 patients were diagnosed with reflux oesophagitis. After exclusions the study population comprised of 410 patients. Of these 208 questionnaires (51%) were available for evaluation.Complaints were reported by 130 patients (63%). The majority of these, 115 (88%), use acid suppressive therapy. Only 78 patients were in clinical remission, with or without therapy. The respondents with complaints were divided into two groups. Group 1: all patients with reflux complaints and using acid suppressive therapy. Group 2: all patients with complaints without medication. Patients in group 1 were significantly older at time of the endoscopic diagnosis compared with patients of group 2. Patients in group 1 had significantly more often a hiatal hernia ($p<0.001$). There was no difference in overall symptom or frequency score per patient between both groups, mean 5.97 versus 6.8 and 13.4 versus 13.8 respectively. However, heartburn, nausea, acid regurgitation, epigastric pain, dysphagia, and nocturnal complaints showed a significant higher prevalence in patients of group 2. Scores for specific complaints were significantly lower in group 2. There was no difference between the GERD-Q, SAI and GSRS.
It is concluded that despite effective therapy only a 37% of patients is in complete remission. However, although not in remission, the symptom score per patient is rather low. Patients without medication have more often reflux complaints but lower severity scores, being a possible reason for not taking medication. Hence it is to be expected that these patients regarded their complaints very mild not necessitating therapy. Patients who still had complaints and used medication had significantly more often a hiatal hernia seen during the initial endoscopy.

Risk factors for prevalent adenocarcinomas in patients with high-grade dysplasia in Barrett's esophagus: a Dutch population-based study

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The risk of esophageal adenocarcinoma (EAC) is increased in patients with Barrett's esophagus (BE), especially in patients with high-grade dysplasia (HGD). Interestingly, there is already a high prevalence of occult EAC at the time of HGD diagnosis. It is however unknown which patients are at an increased risk of having prevalent EAC in the presence of HGD in BE. The aim of this study was to identify independent risk factors for prevalent EAC in a large nationwide population-based cohort of patients with HGD in BE in the Netherlands. All patients with a diagnosis of HGD in BE between 1999 and 2008 in the Netherlands were identified in a nationwide histopathological registry (PALGA). Patients with HGD and follow-up data after a diagnosis of HGD were included. All pathology reports related to the esophagus were evaluated. An EAC was defined as prevalent when it was detected within 6 months following an initial HGD diagnosis. Patients who had at least 2 different sets of biopsies from BE in the database prior to a HGD diagnosis were assumed to have participated in a surveillance program. Cox proportional hazards regression analysis was performed to identify predictors for the presence of prevalent EAC at the moment of HGD diagnosis in BE. In total, 699 patients with HGD in BE were included. Prevalent EAC was found in 177 (25%) patients with HGD. Multivariate Cox proportional hazards regression analysis showed that the risk of prevalent EAC was increased when patients were between 65 and 75 years compared to a younger age (Hazard ratio (HR) 1.42, 95% CI 1.01-1.98), patients were not participating in a surveillance program prior to initial HGD diagnosis compared to patients undergoing surveillance (HR 1.53, 95% CI 1.09-1.14), a diagnosis was made in a general hospital compared to a university hospital (HR 1.85, 95% CI 1.14-3.01) and histologic follow-up was performed in case of HGD compared to endoscopic treatment (HR 2.60, 95% CI 1.75-3.85). The presence of unifocal compared to multifocal HGD (HR 0.33, 95% CI 0.20-0.56) reduced the risk of detecting prevalent EAC.
Conclusion: In this large nationwide HGD cohort, prevalent EAC is already present in at least a quarter of patients, particular when aged between 65 and 75 years, not participating in a surveillance program prior to a HGD diagnosis, HGD was diagnosed in a general hospital, HGD is endoscopically followed-up and not (endoscopically) treated, and HGD in BE is multifocally present. Based on this, we strongly recommend endoscopic treatment over histologic follow-up in patients with HGD in BE, the former preferably performed in centers with expertise in this field.

Inter- and intra observer variability in pH-impedance measurements between10 experts in pediatric gastroesophageal reflux and automated analysis

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The detection of gastroesophageal reflux (GER)on pH-impedance (pH-MII) tracings is based on pattern recognition. Criteria for the detection of bolus GER have been defined and automated analysis is available. Most investigators however prefer manual analysis of pH-MII tracings to ensure correct marking of GER episodes. This may introduce the potential for inter- and intra investigator variability. This study was designed to determine inter investigator variability in pH-MII interpretation between 10 experts in pH-MII measurements and pediatric gastroesophageal reflux, the accuracy of automated analysis and intra investigator variability in 3 investigators with different levels of experience. Methods: Ten pediatric 24-hr pH-MII tracings without markers from automated analysis or events were selected and analyzed by 10 investigators and by automated analysis. Investigators were asked to analyze the tracings the same way as they would analyze a pH-MII tracing in their hospital. Liquid and mixed GER episodes were included for analysis. Reflux episodes scored by ≥1 observer were included and compared between all observers for the presence of GER. A GER event was scored positive for an observer when the point of nadir impedance in the most distal channel was included in the marked area. Analysis was performed for all tracings combined. Cohen's kappa was calculated to assess inter and intraobserver agreement. Results A total of 1242 GER events were scored by ≥1 observer, of those 490(42%) were scored by ≥6 observers and 377(31%) were scored by 1 observer only. The median number of total GER events scored per observer was 518 (range 249-922), automated analysis detected a total of 653 GER events. Automated analysis missed 32 (6.5%) GER events that were scored by ≥6 observers and detected 37 (5.6%) events not scored by any other observer. Mean Cohen's kappa between all observer pairs was 0.46 (fair agreement). Intra observer kappa was 0.85, 0.71 and 0.49 for the observers with 0.5, 3 and 8 years of experience respectively.
Discussion. The inter and intra observer variability in the analysis of pH-MII amongst experts in pediatric GER is large. All observers state that a retrograde pattern is the most important factor to determine retrograde bolus flow. However we conclude that retrograde pattern recognition is subjective as only 42% of all GER events were recognized by a majority of the observers. Surprisingly intraobserver agreement was highest in the person with the least experience. These results support the use of automated analysis in terms of reliability and reproducibility compared to manual analysis.

Screening for dysplasia in idiopathic achalasia using Lugol staining

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A potential long-term complication of achalasia is the development of esophageal squamous cell carcinoma (SCC) which evolves through a series of progressively dysplastic changes. The stage of the disease at the time of detection determines the prognosis. Spraying of Lugol's dye stains esophageal epithelium brownish but leaves dysplastic areas unstained, and has a sensitivity of 96% for the detection of dysplastic areas in esophageal squamous epithelium. The aim of this study is to evaluate the presence of dysplasia in patients with idiopathic achalasia using lugol dye endoscopy. A cohort of 125 patients with achalasia (M82 F43 Age 50.4yr, range 20-87) underwent 3-annually upper endoscopy with lugol dye staining. Suspected regions for dysplasia at routine endoscopy and unstained lesions after lugol staining were biopsied. Patients with high grade dysplasia (HGD) were treated, patients with low grade dysplasia (LGD) had yearly follow-up with Lugol and patients without dysplasia were screened 3 years later. At the time of first endoscopy, patients were 9.2 ± 0.9 yrs after diagnosis of achalasia. Median time of endoscopic follow-up was 32 months (IQR 0-43) during which a median of 2 endoscopies were performed per patient. Ninety-five patients are still in follow up. 71 suspicious lesions were identified in 57 routine endoscopies (n= 35 patients) compared to 103 lesions in 76 endoscopies (n=43 patients) after Lugol staining. Biopsies taken from these lesions were positive for LGD in 13 cases (13 identified by Lugol staining, 8 by routine endoscopy) and positive for SCC in 2 cases (2 identified by Lugol staining, 2 by routine endoscopy), corresponding to a specificity for detection of dysplasia/SCC of (15/103) 15% and (10/71) 14% resp. Dysplasia/SCC was detected 23.5 yrs (median, IQR 22-29yr) after achalasia was diagnosed and mainly occurred >20 years after diagnosis (0-10 yrs (n=68): 1 low grade dysplasia (LGD); 10-20 yrs (n=21): no lesions; > 20 years (n=35): 3 LGD, 2 SCC, with a prevalence of 15% in this subgroup.) One patient with SCC underwent curative surgery; the other patient had lymph node metastasis and was treated with palliative radiotherapy. The 4 patients with LGD underwent annual Lugol endoscopy and did not progress to high grade dysplasia or SCC. LGD was confirmed in 9 of the 16 follow-up endoscopies.
Conclusion: Dysplastic changes are mainly detected in patients with longstanding achalasia (>20 years), with a prevalence of 15%. Lugol staining improves the detection of dysplasia/SCC compared to routine endoscopy. Based on these findings, we propose to screen patients with achalasia from 10 years after diagnosis onwards using Lugol staining.

Adherence to gastroprotective agents and the risk of upper gastrointestinal complications in coxib users

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Background: Little is known about the upper gastrointestinal (UGI) protective effect of gastroprotective agents (GPAs) in COX-2-specific inhibitors (coxib)-users.Objectives: To study the association between GPA adherence and UGI complications among coxib-users.Methods: We used primary care data from the United Kingdom's (UK) General Practice Research Database , the Dutch (NL) Integrated Primary Care Information database, and the Italian (IT) Health Search/Thales Database. A case-control study was conducted within a cohort of coxib+GPA users aged ≥ 50 yrs. Episodes of coxib use were defined as a period of coxib use with gaps between subsequent prescriptions that were no longer than 100% of the duration of the previous coxib prescription. Patients could have more than one episode of coxib use during follow-up, but only if at least a 180-days NSAID-free period was present prior to the start of each episode. Cases with UGI complications (UGI bleeding and diagnosed symptomatic UGI ulcers) during or within 60 days after coxib use were matched to controls on age, gender, database, and calendar time. Adherence to GPAs was calculated over the most recent episode of coxib use prior to the index date as the proportion of coxib treatment days covered (PDC) by a GPA prescription. Adherence was expressed as a continuous variable as well as categorical (low (PDC<20%) / moderate (PDC 20-80%) / high adherence (PDC>80%)). Adjusted odds ratios (OR) with 95% confidence intervals (95%CI) were calculated using conditional logistic regression.Results: 98,940 coxib episodes were counted in the coxib user cohort (UK: 52,698; NL: 7,201, IT: 39,041). In 16,442 (16.6%) of the eligible coxib episodes a GPA was prescribed (UK: 21.2%; NL: 13.4%, IT: 11.0%). Of the GPA users, 7.2% had low adherence (PDC<20%), 33.1% had moderate adherence (PDC 20-80%), and 59.7% had high adherence (PDC>80%). Overall, mean pooled adherence (PDC) to GPA was 0.76±0.30 (UK: 0.79±0.29; NL: 0.85±0.27; IT: 0.66±0.30). Only 18% used coxibs >90 days. In those patients, mean adherence dropped to 0.65 ± 0.34. Within the coxib+GPA users, we identified 74 cases with an UGI complication (30 UGI bleedings and 44 (un)complicated UGI ulcers). Among low adherers, the risk was 1.97 (95%CI 0.84-4.60) for all UGI complications, compared with high adherers. For every 10% decrease in adherence, the risk of all UGI complications increased by 9% (OR: 1.09, 95%CI: 1.00-1.18).
Conclusions: The risk of UGI complications increased by 9% in all coxib users ≥ 50 years for every 10% decrease in adherence of GPAs. Patients benefit from GPAs in addition to coxibs to lower their increased risk of UGI complications.

Gastric acid suppressive therapy and community-acquired pneumonia, etiology and outcome

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Background. Community acquired pneumonia (CAP) is an infection of the pulmonary parenchyma that can be caused by various microbial pathogens. Co-morbidity and medication are related to specific pathogens. Patients on gastric acid suppressive therapy have an increased risk to develop CAP. We aimed to assess whether there are specific pathogens independently associated with gastric acid suppressive therapy and its impact on infection severity. Methods. From December 2007 to January 2010, all subjects consulting the emergency care unit of a general hospital in the south of the Netherlands with a suspected CAP were prospectively registered. Each patient underwent chest radiography. Sputum, urine, nose swabs and blood samples were obtained for microbial culture, antigen detection and polymerase chain reaction techniques, respectively. To study the severity of CAP upon presentation, the validated CURB-65 score was calculated. Furthermore, we assessed hospital or intensive care admission, length of hospitalization and in-hospital mortality. We evaluated the association between use of acid suppressive therapy and microbial aetiology of CAP and severity of illness with logistic regression analysis. Results. The final cohort comprised 463 patients with CAP, defined as presence of infiltrate on chest radiography and/ or microbial aetiology. Overall 136 patients (29%) used acid suppressive therapy, mainly proton pump inhibitors (97%). Patients with acid suppressive therapy more frequently had an infection with Streptococcus pneumoniae (28% vs. 14%) and Haemophilus influenzae (10% vs. 6%), and less frequently with Coxiella burnetii (8% vs. 19%) or H1N1 influenza A virus (2% vs. 7%) in comparison to those without acid suppressive therapy. After adjustment for base differences, the risk of proton pump inhibitor users being infected with S. pneumonia was 2.18 times (95%Confidence Interval(CI): 1.2-3.6) higher compared to those not on acid suppressive therapy. Patients using more than one defined daily dose of a PPI had a 1.48-fold increased risk of a S. pneumoniae infection compared with patients using the defined daily dose (95%CI:1.1-2.0). No risk between PPI use and any other microbial pathogen was found. Patients with acid suppressive therapy had on average higher CURB-65 scores, longer hospital stay and subsequently a case fatality rate of 11% vs. 4% compared to those not using acid suppressive therapy. Conclusions. Proton pump inhibitor therapy predisposes with community acquired S. pneumoniae pneumonia, and was associated with higher morbidity.

Functional dyspepsia patients have lower mucosal cholecystokinin concentrations in response to duodenal lipid

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Introduction: Cholecystokinin (CCK)-1 receptor antagonism has been shown to relieve gastrointestinal symptoms induced by duodenal lipid load and gastric distension, demonstrating a role for CCK in postprandial symptom generation. Excessive release of CCK and/or hypersensitivity to CCK may explain the exaggerated response to duodenal lipid in functional dyspepsia (FD) patients. Thus far, only plasma CCK response has been determined in these patients; however, CCK acts in a paracrine manner, making mucosal levels in the duodenum relevant to measure. Presuming an excessive CCK release in FD, elevated levels of apolipoprotein A-IV (apoA-IV), a signaling protein released from enterocytes upon lipid absorption stimulating release of CCK, may also be found in FD. Aim: To investigate whether excessive fat-induced release of CCK at the level of the duodenum is involved in symptom generation in FD.Methods: Sixteen symptomatic FD patients and 10 healthy volunteers (HV) matched for age, gender and BMI (all normal weight) were included. All subjects underwent duodenal perfusions with Intralipid 20%, 2 kcal/min, for 60 min. Symptoms were scored and blood samples collected every 15 min. Fifteen minutes after discontinuation of the lipid infusion, duodenal biopsies were taken endoscopically. Plasma and mucosal protein levels of CCK were determined by a specific radioimmunoassay. Mucosal mRNA and protein expression of apoA-IV were quantified by real-time PCR and an established enzyme -linked immunosorbent assay, respectively. Results: Duodenal lipid infusion caused an increase in upper abdominal discomfort and nausea in FD patients but not in HV ($P=0.001$ and 0.033 relative to baseline, respectively). The mean (SD) mucosal CCK level in FD was 3.52 ± 1.11 pmol/mg protein and in HV 5.34 ± 0.79 pmol/mg protein, which was significantly different ($P<0.0001$). Fasting plasma CCK levels and the stimulation of plasma CCK by duodenal lipid infusion were comparable in FD patients and HV. No significant differences in mucosal apoA-IV mRNA and protein expression between the two groups were found.
Conclusion: The lower duodenal CCK concentration suggests excessive release of CCK in FD patients in response to duodenal lipid. This finding increases insight into the mechanism by which fatty foods induce and exacerbate symptoms in FD patients. Our data do not demonstrate involvement of apoA-IV, therefore the underlying cause of elevated peripheral CCK release in FD patients warrants further investigation.

The quality of prediction scores in gastrointestinal bleeding: a systematic review and quantitative appraisal

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Acute upper and lower gastrointestinal bleeding (GIB) is a common indication for hospital admission. It also accounts for a 15% mortality rate and even higher rebleeding rates. In order to facilitate risk stratification and clinical triage, algorithms for predicting outcome in GIB have been developed, such as the Rockall and Blatchford score. Recent international consensus guidelines on the management of patients with GIB recommend stratifying patients in low- and high-risk groups for rebleeding and mortality based on prognostic scales. However, whether currently available prediction scores have been established by employing high methodological quality standards has been questioned. We evaluated the quality of all published prediction scores in GIB by performing a systematic review and quantitative appraisal. An extensive literature search was performed until October 2010 using the PubMed database. The following medical subject headings (MeSH) or keywords were used: "gastrointestinal hemorrhage", "prognosis" and "risk factors". All studies reporting the development of a prediction score in GIB were included. Subsequently, a quantitative and quality evaluation of these scores was performed by assessing the prediction scores on methodological standards (score range 0-29; >25 was regarded high quality) by two independent reviewers. A total of 372 studies were identified, of which 15 were eligible for inclusion (upper GIB: n=13, lower GIB: n=1 and upper and lower GIB: n=1). These studies were subject to different outcomes: mortality (n=2), rebleeding (n=3), therapeutic failure (n=1), intervention required (n=1), or a combination (n=8). The mean overall quality rating was 16.9 (SD 4.1, range 9-23). None of the prediction scores was of high quality, not even the frequently used Rockall (23) and Blatchford (23) score. Moreover, the quality of different scores did not improve over the years. Major methodological shortcomings were the absence of validation or absence of impact analyses. Internal and external validation was performed in 4 (27%) and 7 (47%) studies, respectively, whereas in 4 (27%) studies no validation was performed at all. Furthermore, only 5/15 (30%) of the scores was 'easy to use' and 5 (30%) reported some kind of action based on the results.
Conclusion: None of the identified prediction scores was of an undisputed methodological quality, which was due to factors that potentially could have been remedied. This emphasizes the need for new high quality prediction scores on the outcome of GIB.

Risk factors for metachronous advanced colorectal neoplasia in a cohort of adenoma patients: advanced morphology and multiplicity

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Surveillance of adenoma patients aims to prevent colorectal cancer (CRC) by removing recurrent adenomas. Adenoma removal and subsequent surveillance can reduce CRC incidence by 76-90%. Colonoscopy is however scarce, expensive and potentially harmful. To ensure efficient use of resources, surveillance colonoscopy should be targeted at patients who will benefit most from the procedure. Current surveillance guidelines use advanced morphology or multiplicity as criteria for surveillance interval. The aim of this study was to assess the relative risks of advanced and multiple (≥3) adenomas, separately and combined, on metachronous advanced colorectal neoplasia in a representative cohort of adenoma patients. We collected prospective data on adenoma patients from 10 hospitals throughout the Netherlands, using a nationwide histopathology registry to select newly diagnosed adenoma patients from 1988 to 2002. Patients with CRC history or CRC at index colonoscopy, hereditary cancer syndromes or IBD were excluded. Electronic medical records were reviewed until December 1, 2008 for follow-up. Index colonoscopy was defined as colonoscopy with first adenoma diagnosis. Presence of advanced (≥10 mm, a villous histology or high-grade dysplasia) or multiple (≥3) adenomas and the combination at index colonoscopy were considered as potential risk factors for metachronous advanced colorectal neoplasia (advanced adenoma or CRC) at first follow-up endoscopy. To assess hazard ratios (HR) for the relative risk we performed a Cox-regression analysis, adjusted for age and gender. 3,041 adenoma patients (55% male, mean age 61 yrs (range 40 – 88)) were analyzed, of whom 1,351 (44%) patients had advanced adenomas (AA) at index endoscopy, and 161 (6%) ≥3 non-advanced adenomas (NAA). Median interval to first surveillance endoscopy was 21 months (interquartile range: 12-39). At follow-up, 182 patients had advanced colorectal neoplasia, including 26 CRC cases. Relative risks for metachronous advanced colorectal neoplasia were HR 2.9 (2.0–4.1) for 1-2 AA, HR 3.1 (1.7–5.7) for ≥3 NAA, and HR 6.4 (4.1–10.0) for ≥3 AA compared to a HR 1.0 for 1-2 NAA (reference category).
Conclusions: Advanced and multiple (≥3) adenomas at index colonoscopy are equally important risk factors for metachronous advanced colorectal neoplasia, resulting in a 3-fold increased risk of developing advanced colorectal neoplasia during follow-up. However, having both risk factors results in a 6-fold increased risk. The results suggest that advanced morphology and multiplicity should be used to tailor surveillance guidelines with a separate recommendation for adenoma patients that have both these risk factors.

Detection of proximal serrated polyps is dependent on quality of bowel prep and the endoscopist

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Colonic serrated polyps (SPs) were traditionally thought to be benign with little likelihood to progress to colorectal cancer. However recent studies have shown that SPs may progress to CRC and proximal location is associated with synchronous advanced neoplasia. SPs are easily missed during colonoscopy because of the flat morphology and ambiguous color. Aim of this study was to compare detection of proximal SPs in patients with adequate or inadequate bowel preparation. Secondary outcome was to compare detection of proximal SPs among endoscopists. All average risk individuals who participated in the Dutch primary screening colonoscopy program for CRC and underwent a complete colonoscopy were included. Colonoscopies were done by experienced colonoscopists (≥ 1000 colonoscopies) and all detected polyps were immediately removed. Proximal colon location was defined as proximal to the splenic flexure. Bowel prep quality was assessed by the validated Ottawa bowel preparation score and classified into 2 groups: adequate (0-7) and inadequate (8-14). Proximal SP detection was defined as the proportion of patients with at least one SP in the proximal colon. SPs included hyperplastic polyps, sessile serrated adenomas and traditional serrated adenomas. To compare proximal SP detection among endoscopists only those endoscopists were included with ≥ 100 colonoscopies within the study period. Odds ratios were calculated relative to the endoscopist with the highest proximal SP detection, adjusted for bowel prep. In total, 1283 subjects (male 51%, median age 60 yrs) underwent a complete screening colonoscopy. A total of 1523 polyps were detected, of which 666 (44%) were adenomas and 638 (42%) were SPs including 192 proximal SPs. At least one proximal SP was detected in 142 patients (12%). Bowel preparation was assessed as “adequate” in 954 patients (75%) and as “inadequate” in 327 patients (25%). The proportion of patients with ≥ 1 SP was significantly higher in patients with adequate bowel prep compared to patients with inadequate bowel prep (13% vs. 8%; p=0.03, OR 1.60 (95% CI: 1.03 to 2.48)). In total, 4 endoscopists performed ≥ 100 colonoscopies within the study period. Odds for proximal SP detection for endoscopists relative to the endoscopist with the highest detection and adjusted for bowel prep were 0.25 (95% CI 0.15 to 0.42; p<0.001), 0.67 (95% CI 0.40 to 1.12; p=0.12) and 0.71 (95% CI 0.40 to 1.27; p=0.24).
Conclusions: Detection of proximal SPs is dependent on the quality of the bowel prep and the endoscopist. To avoid undetected neoplasia and reduce the risk of interval cancers additional attention and training should be directed towards detection of SPs.

Influence of body mass index on outcome in advanced colorectal cancer patients receiving chemotherapy with or without targeted therapy

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IntroductionObesity is associated with an increased risk of development and recurrence of colorectal cancer. However, the role of obesity in advanced colorectal cancer (ACC) patients is unknown. We investigated the effect of body mass index (BMI) on overall survival (OS) in ACC patients receiving systemic treatment in two large phase III studies (CAIRO and CAIRO2).Patients and MethodsTreatment data were obtained and analyzed from 796 ACC patients who were treated with chemotherapy in the CAIRO study, and in 730 ACC patients who were treated with chemotherapy plus targeted therapy in the CAIRO2 study. Base height and weight were used to assign patients to one of the following BMI categories: I (<18.5 kg/m^2), II (18.5-24.9 kg/m^2), III (25.0-29.9 kg/m^2) and IV (≥30.0 kg/m^2). ResultsIn 796 patients of the CAIRO study a high BMI was associated with better median OS (8.0, 14.9, 18.4, and 19.5 months for BMI categories I, II, III, and IV, respectively; p=0.001), and was an independent prognostic factor for OS in a multivariate analysis. BMI was not associated with OS in 730 patients who participated in the CAIRO2 study, although a trend was observed (median OS 16.6, 17.8, 21.0, and 21.4 months for BMI categories I, II, III and IV, respectively; p =0.8068).
Conclusions:These results show that BMI is an independent prognostic factor for survival in patients receiving chemotherapy, but not in patients receiving chemotherapy and targeted therapy. The possible decreased efficacy of bevacizumab in obese patients may explain this discrepant result. The role of BMI in patients receiving targeted therapy should be further tested.

Microsatellite instability screening in young colorectal cancer patients in the Mid-Netherlands in the period 1999-2008

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Background: In 1997, the Bethesda Guidelines were published, recommending microsatellite instability (MSI) testing for colorectal cancer (CRC) in patients younger than 45 years. In 2004, these guidelines were revised and MSI testing was recommended in patients younger than 50 years. Adherence to these guidelines could further improve the identification of families with Lynch syndrome.AIM: To evaluate adherence to screening guidelines for Lynch syndrome in young patients and to identify factors associated with adherence. Methods: All patients diagnosed with CRC in the Mid-Netherlands (1 university and 6 general hospitals) younger than 45 years at diagnosis from 1999 to 2004 and younger than 50 years from 2005 to 2008 were included. Data from the Comprehensive Cancer Center and the National Pathological Archive (PALGA) were combined. Subsequently, MSI testing results were collected from PALGA and all hospitals that conducted MSI testing in these periods.Results: A total of 341 patients were identified and eligible for analysis. From 1999 to 2004, MSI testing was performed in 43/125 (34%) patients younger than 45 years. From 2005 to 2008, 89/216 (41%) patients younger than 50 years were tested. We found older age at diagnosis ($p<0.05$), male gender (OR 1.60, 95%CI 1.03-2.48), stage IV CRC (OR 2.12, 95%CI 1.19-3.77) and no primary surgery (OR 2.72, 95%CI 1.08-6.86) to be associated with non-adherence. Adherence did not improve over time ($p=0.21$). Moreover, adherence was not significantly associated with proximal tumor localization, poor differentiation grade, mucinous histology, tumor size or number of evaluated and tumor positive lymph nodes.
Conclusion: Although recommended in guidelines, younger patients with CRC were in two-thirds of cases not tested for MSI. After publication of the revised Bethesda guidelines, adherence did not improve. Based on this, we have started a teaching program in the Mid-Netherlands to improve awareness on the risk of familial forms of CRC.

Risk factors for the combined adenoma-serrated phenotype: a population-based study

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It has been shown that colorectal adenomas (ADs) and serrated polyps (SPs) frequently occur together, and with aging and screening this phenotype is expected to increase in prevalence. Our goal was to determine risk factors associated with the combined adenoma-serrated phenotype in a large population-based study. Methods: Between February 2008 and July 2009 all consecutive patients undergoing elective colonoscopy at a single academic center were asked to complete a questionnaire including the following items: smoking, alcohol intake, use of medication (i.e. aspirin, NSAID), body mass index (BMI) and presence of diabetes mellitus. Clinical and histopathological data were recorded. SPs were defined as hyperplastic polyps or serrated adenomas. Combined adenoma-serrated phenotype was defined as presence of at least one AD and one SP. Multiple logistic regression analyses were performed to identify independent risk factors for synchronous presence of ADs and SPs. Results: A total of 3897 patients underwent colonoscopy during the study period, of which 306 patients were excluded (<18 years of age, n=15; hereditary colorectal cancer syndrome, n=32; or second colonoscopy, n=259). Of the remaining patients, 2015 (56%) completed the questionnaire and 1836 patients (51%, mean age 60 years, 47% men) agreed to participate into this study. Responders were significantly older than non-responders (60 versus 57 years, p<.001). Out of the 1836 patients, 400 (22%) had ADs only, 149 (8%) had SPs only, 139 (7%) had synchronous ADs and SPs, while 1148 (63%) had no polyps at the time of endoscopy. Multiple logistic regression analysis showed that age ≥55 years (OR 5.6, 95% CI 3.2 – 9.9, p<.001), male gender (OR 2.3, 95% CI 1.5 – 3.5, p<.001), current smoking (OR 4.7, 95% CI 2.7 – 7.9, p<.001) and BMI ≥30 (OR 1.9, 95% CI 1.1 – 3.3, p=0.02) were independent predictors for the combined adenoma-serrated phenotype. Daily aspirin use was protective (OR 0.6, 95% CI 0.4 – 0.9, p=0.046), while alcohol intake (OR 1.2, 95% CI 0.8 – 1.7, p=0.50), frequent NSAID use (OR 0.6, 95% CI 0.3 – 1.3, p=0.21) and diabetes mellitus (OR 1.2, 95% CI 0.7 – 2.3, p=0.49) did not appear to have any effect.
Conclusion: Current smoking is associated with an increased risk of having synchronous adenomas and serrated polyps, especially in older males. These data are of importance as they may provide the basis for developing risk-stratification algorithms and assist us in targeting the appropriate surveillance intervals.

Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) for colorectal polyp and cancer detection: a prospective feasibility study

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Screening for colorectal adenomas is an effective way to reduce colorectal cancer (CRC) mortality. Currently available screening methods have several disadvantages. In contrast, diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) is non-invasive, does not require bowel preparation and is free of radiation exposure. Previous studies have indicated the potential utility of DWIBS for the detection of CRC, but provided The aim of our study was to prospectively evaluate the feasibility of DWIBS for CRC screening using subsequent colonoscopy as reference. In 27 patients scheduled to undergo colonoscopy for symptoms suggestive of a neoplastic colorectal lesion, first a DWIBS-scan was performed which was followed by colonoscopy. DWIBS scans were evaluated by reviewers who were blinded to the colonoscopy result. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of DWIBS, compared to colonoscopy as gold standard, were calculated on a per patient basis for all polyps, polyps ≥6mm, polyps ≥10mm and colorectal cancers (CRCs). Mean age was 65 (range 50-83) years and 41% (11/27) were males. Sensitivity and specificity for detecting polyps with DWIBS was 50% and 76%, respectively, and for CRC 100% and 75%, respectively. This resulted in a NPV of 84% for polyps and 100% for CRC, and a PPV of 38% for polyps and 33% for CRC. If the advice to perform a colonoscopy after DWIBS would have been followed consequently all three CRCs would have been detected and 8 of 11 (73%) clinically relevant lesions (polyps ≥6mm and/or adenomatous lesions).No complications or adverse events were seen due to DWIBS. Conclusion: Based on the high NPV of for detecting (adenomatous) polyps and CRC, DWIBS seems a promising non-invasive method for CRC screening. Further studies in larger and other patient populations are however required.

Can an individual risk profile for CRC be used as triage test in CRC screening

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Colorectal cancer (CRC) is one of the leading causes of cancer related death. Detecting cancer or one of its precursors at an early stage may reduce cancer morbidity. Due to its non-invasive character, triaging for colonoscopy with FOBT is an attractive method. However, FOBT has a less than perfect specificity and sensitivity. Risk stratification, based on established risk factors, could increase the sensitivity of FOBT-based screening. This way, the diagnostic yield from screening could be increased with a similar number of colonoscopies. We explored the use of a risk prediction model in CRC screening. We collected data in the Colonoscopy or Colonography for Screening (COCOS) study,a multicenter screening trial conducted in Amsterdam and Rotterdam, between June 2009 and October 2010. For this study 5,924 randomly selected, asymptomatic men and women between 50 and 75 years of age were invited to undergo colonoscopy. Participants were identified with advanced neoplasia. Participants were asked for one sample FIT (OC-sensor) and to complete a risk questionnaire prior to colonoscopy. Based on the questionnaire data, we developed a multivariable risk model with the following factors: total calcium intake, family history, age and FIT result. We evaluated goodness-of-fit, calibration and discrimination, and compared it to a model based on primary screening with FIT. Calibration refers to the agreement between calculated risk and observed outcomes. Discrimination expresses how well the risk model distinguishes between cases and non-cases. 1,236 invitees participated in the study, of which 1,022 (83%) completed the questionnaire. FIT results and colonoscopy outcome were known for 787 (77%)of the participants who completed the questionnaires, of which 67 had advanced neoplasia (8.5%); 5 (7.5%) had CRC and 62 (92.5%) advanced adenoma. The risk based model significantly increased the goodness-of-fit compared to the primary FIT screening model (p=0.0006). Discrimination improved with the risk-based model (AUC: from 0.630 to 0.745), but the gain was not statistically significant (p=0.06). Calibration was good (Hosmer-Lemershow test; p=0.90). With a FIT strategy and using a cut off of 50 ng/ml, 74 of the 787 (9.4%) participants would have been referred for colonoscopy, including 22 persons with advanced neoplasia (29%). If, hypothetically, the 74 participants with the highest calculated risk had been referred for colonoscopy, this group would have included 21 (27%) persons with advanced neoplasia. Risk based stratification can increase the accuracy of FOBT in triage for colonoscopy in CRC screening, but the actual gains in the yield of screening are probably modest.

The incidence and prediction of carcinomatosis peritonei in patients with a T4 colorectal carcinoma

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Cytoreductive surgery combined with hyperthermic intra-peritoneal chemotherapy (HIPEC) can improve the outcome of patients with carcinomatosis peritonei (CP) following T4 colorectal cancer. Data on the incidence of CP in this patient group are scarce. The aim of this study was to investigate the incidence of CP in patients undergoing resection for a T4 colorectal cancer at the time of the primary resection or during follow-up. We also evaluated which patient- or tumor characteristics predict the occurrence of CP. We retrospectively analyzed all patients undergoing primary resection for a T4 colorectal cancer during the period 2000-2007 in a large non-university teaching hospital. Patients were identified from the hospital electronic pathology database. The following data were collected: the occurrence of synchronous CP or metachronous (occurring later than 3 months after the primary resection) CP, patient demographics, mortality during follow up vice versa.The predictive value for the development of CP of several predefined patient- and tumor characteristics was evaluated using univariate and multivariate logistic regression analyses.A total of 873 consecutive patients underwent primary resection for colorectal cancer during the study period: 200/873 patients (23%) had a T4 carcinoma. CP was diagnosed in 71/200 patients (40%). This was synchronous CP in 45/200 patients (23%) and metachronous CP in 26/200 patients (13%). Metachronous CP was diagnosed at a mean of 5.4 months (range 3-47 months) after primary resection, with a median follow up of 21 months. In univariate logistic regression the following factors were associated with metachronous or synchronous CP: age (odds ratio [OR] 0.97; 95%-confidence interval [CI] 0.95-1.00; p=0.08), peroperative tumor perforation (OR 0.59; 95%-CI 0.33-1.08; p=0.09), the number of positive lymph nodes (OR 1.79; 95%-CI 1.23-2.61; p=0.002) and adjuvant chemotherapy (OR 1.66; 95%-CI 0.92-3.02; p=0.09).In multivariate analysis, the only factor significantly associated with CP was the number of positive lymph nodes (OR 1.88; 95%-CI 1.23-2.64; p=0.003).
Conclusion: A significant proportion of patients undergoing resection for a T4 colorectal cancer develops synchronous or metachronous CP. The lymph node status is the major prognostic factor. This information may be used to screen patients for CP or even select patients for a preventive HIPEC procedure in the future.

Rage signaling promotes intestinal tumorigenesis

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Introduction: In recent years it has become evident that activation of the innate immune system plays an important role in cancer development. Toll-like Receptors (TLR) are pattern recognition receptors that act as the gate keepers of the innate immune system. It has previously been shown that mice lacking TLR-4 or the intracellular mediator of TLR signaling MyD88 are protected from intestinal tumorigenesis. The receptor for advanced glycolysation endproducts (Rage) is a pattern recognition receptor that activates the innate immune system in response to HMGB1, a protein released by necrotic cells. Such activation by necrotic cells may be particularly relevant in the context of tumor development. Moreover it has previously been shown that Rage and its ligands are upregulated in human colon carcinomas. Therefore we investigated the role of Rage signaling in a model of sporadic intestinal adenoma development in the mouse. Methods: Rage knockout ($Rage^{-/-}$) mice were crossed with Apc^{min} mice to homozygosity (n=15). In addition, a Green Fluorescent Protein (GFP) reporter gene was used, which is expressed upon Rage deletion. $Rage^{wt}/Apc^{min}$ mice were used as controls. At 17 weeks of age, mice were sacrificed. The number and size of the polyps in the intestine were analyzed. Rage expression was analyzed by immunostaining for GFP. As well immunohistochemistry for neutrophils, macrophages, T cells and mast cells was performed. These immune cells were counted and analyzed. Further apoptosis and proliferation in polyps was assessed. Results: $Rage^{-/-}$ animals exhibited a marked reduction in the number of polyps compared to control animals (111.3 ± 51.65 vs 46.86 ± 27.58, $p<0.001$). The size of the polyps did not differ. Immunostaining for GFP showed increased Rage expression in tumor epithelium. Analysis of tumor associated immune cells showed a 14-fold increase in the number of mast cells in polyps of $Rage^{-/-}$ versus control animals (75.31 vs 5.25 cells per vision field $p<0.05$). In contrast, there was no difference in the number of infiltrating neutrophils, macrophages or T cells. Number of caspase positive cells per polyp was increased in $Rage^{-/-}$ animals (34.3 ± 21.8 vs 11.8 ± 6.0 $p<0.05$). There was no significant difference in the number of proliferating cells (7.92 ± 4.36 vs 9.98 ± 5.39).
Conclusion: Our results suggest that Rage signaling plays an important role in the initiation of spontaneous intestinal tumorigenesis. Rather than leading to diminished infiltration of immune cells, absence of Rage signaling results in a considerable recruitment of mast cells.

Non-canonical Bone Morphogenetic Protein signaling induces Epithelial to Mesenchymal Transition in SMAD4 deficient colorectal cancer

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Introduction:Epithelial–mesenchymal transition (EMT) is essential for organogenesis and is induced during carcinoma progression allowing cancer cells to invade and metastasize. In patients with colorectal cancer (CRC) negative expression of SMAD4, the main component of canonical SMAD-dependent Transforming Growth Factor (TGF)-β and Bone Morphogenetic Protein (BMP) signaling, has been correlated with poor survival. It is believed that SMAD4-negative cancers metastasize due to loss of function of the canonical tumor-supressor arm of the BMP and TGF-β pathways, but the role of non-canonical pathways in this process is poorly understood and underscored.
Methods:In this study we have for the first time extensively characterized non-canonical BMP signaling and investigated its role in EMT induction in the context of SMAD4 deficiency. HCT116 SMAD4-/- and SW480 (SMAD4-mutant) cells were transfected with a plasmid encoding BMPR2 to overactivate non-canonical BMP signaling. Kinome array was performed to generate a comprehensive description of non-canonical BMP signaling employing a peptide array containing 1176 spatially addressed mammalian kinase consensus substrates and these results were validated with immunoblotting and luciferase assay. The induction of EMT was analyzed by phase contrast microscopy, immunofluorescence, qRT-PCR and immunoblotting. Migration and invasion was evaluated by wound healing and invasion through matrigel. Results: Induction of non-canonical BMP signaling results in the activation of well known cell migration pathways Rac-MKK-p38MAPK, Rac-MKK-JNK, RHO-Rock and RAS-B-RAF-ERK. Moreover, AKT and WNT pathways, responsible for survival and proliferation of cancer cells, are significantly upregulated. Activation of the non-canonical BMP signaling induces changes in cell morphology and gene expression consistent with EMT. On BMPR2 transfection, SW480 and HCT116 SMAD4-deficient cells, but not parental HCT116 SMAD4-proficient cells, respond with inhibition of E-cadherin expression, upregulation of Vimentin expression, activation of transcription factors responsible for EMT (ZEB1, SNAIL1, SLUG and SIP1) and an increase in migration and invasion.
Conclusion:Non-canonical BMP pathway activation in SMAD4-negative cancer cells results in an activation of a signaling network potentiating migration and increasing survival of cancer cells, facilitating invasion and metastasis. Our data suggest that non-canonical BMP signaling contributes to the poor survival of patients with SMAD4-negative CRC. Inhibitors of non-canonical BMP signaling can be a new promising therapeutic option for patients with SMAD4-negative CRC.

ER-stress is sufficient for intestinal stem cell differentiation

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Introduction. The intestinal epithelium is constantly renewed from a pool of stem cells at the base of the crypt. Stem cell fate and cycling is dependent on Wnt signaling but the factors that mediate exit from the cell cycle and induce differentiation are poorly defined. Differentiation leads to an increased production of specialized proteins which need to be folded in the endoplasmatic reticulum (ER) by dedicated chaperones such as GRP78. Recruitment to the nascent proteins shifts GRP78 away from its binding sites on three distinct ER transmembrane receptors, PERK, IRE1α and ATF6. In their GRP78 unbound state the receptors 'sense' ER-stress and mediate the unfolded protein response (UPR). ATF6 and IRE1α increase protein processing capacity whereas PERK phosphorylates eIF2α which attenuates protein translation. Here we examine a potential role for the UPR in intestinal stem cell differentiation. Methods. Components of the UPR were localized in the intestine by immunohistochemistry and in situ hybridization. The UPR was examined in colon cancer cell lines. ER stress was induced in vitro with either thapsigargin or subtilase cytotoxin (SubAb) which cleaves and inactivates GRP78 or in vivo with thapsigargin or in Cyp1a1Cre-Grp78fl/fl-stopfl/fl-LacZ mice in which ER stress can be induced in the intestinal epithelium upon injections with β-naphtoflavone and recombined cells are marked by expression of LacZ. Results. Major components of the UPR in vivo are expressed in a gradient with increasing expression from the transit amplifying cells to the crypt-villus junction. Expression was undetectable in the intestinal stem cells. Treatment of mice with the ER-stress inducing agent thapsigargin abrogated Wnt signaling in the intestinal epithelium and depleted the crypts from proliferating cells. Next we induced ER-stress genetically by conditional deletion of Grp78 in the intestinal epithelium in mice. Recombination was highly efficient with >95% LacZ positive crypts at 1 day after recombination. We found that stem cells were lost at 24 hours after recombination in these mice with subsequent loss of proliferating cells. In the next three days the epithelium is almost entirely repopulated by small foci of LacZ negative (wildtype) Olfm4$^+$ and BrdU$^+$ epithelial cells. Induction of ER-stressin vitro similarly resulted in complete inhibition of Wnt signaling, loss of expression of stem cell markers and a G1 cell cycle arrest. Knockdown of PERK partially rescued the effect of ER-stress on the Wnt pathway and expression of stem cell markers.
Conclusion. Our data show that ER stress is sufficient for intestinal stem cell differentiation. This link between ER stress and stem cell differentiation may not only play a role in cell cycle exit and differentiation but also help to protect the fitness of stem cell pool by forcing stem cells with abnormalities in protein synthesis to undergo differentiation.

Intestinalization of esophageal squamous cells depends on a synergistic collaborative interaction between the BMP4/PSMAD pathway and CDX-2

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In Barrett's esophagus (BE) the multi-layered stratified squamous epithelium has changed into a single layered intestinal type of columnar mucosa. The biological processes inducing this intestinal type of metaplasia are still poorly understood. The homeobox gene CDX-2, a nuclear transcription factor for intestine specific genes, is highly expressed in BE, but its precise role in the process of metaplasia is unclear. Previously, we found that Bone Morphogenetic Protein4 (BMP4) is highly upregulated in BE, and its activation, via phosphorylation of receptor SMADs, induced expression of columnar type of genes in human keratinocytes. This suggested that the BMP4/PSMAD pathway is an early event in driving squamous cells towards a columnar phenotype. Here, we report that the induction of the specific intestinal columnar phenotype as associated with BE is induced through a direct cooperative interaction of CDX-2 and the BMP4 downstream target PSMAD 1,5,8. In a CDX-2 transfected human squamous cell (HET1A) expression of the CDX-2 target genes, such as Mucin-2 (MUC2) and Villin 1 (VIL1), were found to be dependent on activation of the BMP4/PSMAD pathway. Co-immuno-precipitation indicated that PSMAD and CDX-2 collaborate through direct interaction. Evidence that both PSMAD and CDX-2 engage the CDX-2 promoter binding region of the MUC2 gene and are involved in transcriptional regulation of MUC2 was obtained from Chromatin immunoprecipitation (ChIP) and Re-ChIP experiments. These results were confirmed by performing ChIP experiments on human BE biopsies specimens. Conversely, inhibition of translocation of PSMAD to the nucleus by silencing of SMAD4 with siRNA in columnar Barrett cells (CP-A and CP-B) resulted in downregulation of MUC2. By Q-PCR we demonstrated that expression of a large panel of intestine specific genes depends on this BMP4 mediated PSMAD – CDX-2 collaboration. Further evidence of the phenotypical changes that take place on ultrastructural level was obtained by electron microscopy (EM), which showed the appearance of typical intestinal type of cellular organelles, such as micro-villi and tight junctions in the CDX-2 transfected, BMP4 exposed squamous cells. In summary, the induction of an intestinal columnar phenotype as seen in BE is through a direct cooperative interaction of two known developmental key players namely the BMP4/PSMAD pathway, and the nuclear transcription factor CDX-2. This observation opens novel avenues for developing molecular strategies to treat intestinal metaplasia and prevent development of the highly malignant EAC.

Local administration of bone marrow-derived mesenchymal stromal cells induces normal liver regeneration in liver fibrosis

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Background and Aim. Chronic exposure of the liver to injuring circumstances results in the secretion of multiple mediators that activate diverse cell types, resulting in hepatic fibrogenesis. Key features are accumulation of fibrogenic cells, i.e., fibroblasts and myofibroblasts, accompanied by a progressive deposition of extracellular matrix. We assessed whether sustained reversal of the fibrosis-cirrhosis-cancer sequence in the liver can be obtained by induction of normal (non-fibrotic) liver regeneration through partial hepatectomy and concomitant treatment with bone marrow-derived mesenchymal stromal cells (MSCs). Methods. Liver fibrosis was established in mice by chronic administration of CCL_4 for 6 weeks and then a partial (approximately 65%) hepatectomy was performed. Perioperatively $1x10^6$ bone marrow-derived MSCs were administered, either intravenously (i.v.) through the tail vene or locally in the capsule of one of the 2 remaining fibrotic liver lobes. After 8 days the mice were sacrificed and the completely regenerated livers removed. Results. Histochemical analyses, by routine histology and Sirius red staining of the collagen deposition, revealed that in the liver lobes of control animals (n=7) no fibrotic septa or lobuli were present. In the hepatectomized liver parts (n=89) of the CCL_4-treated animals the fibrotic septa/lobuli formation was 66±3 %. In the CCL_4-treated control group (n=13) fibrotic septa/lobuli in both regenerated lobes was 15±4 % and 18±5 %. Intravenous administration of MSCs (n=8) had resulted in a significantly ($P<0.05$) increased fibrotic septa/lobuli formation, i.e., 28±6 % and 33±6 % of the regenerated lobes. Remarkably, local administration of MSCs in the capsule (n=7) resulted in a significantly ($P<0.05$) decreased fibrosis of the septa/lobuli to 8±2 % of that liver lobe. In the counterpart liver lobe, which received no local MSCs, the fibrosis formation was 22±8 %, comparable to the CCL_4 controls and somewhat but not significantly lower than in the MSCs-i.v. group.
Conclusions. Local administration of MSCs to liver lobes resulted in an almost normal regenerated liver, but not in the in situ liver counterpart, whereas intravenous administration of MSCs significantly increased fibrosis in the regenerated livers. These observations indicate that the route of MSC administration determines the effect on the fibrotic process in the liver.

Adverse effects of mTOR inhibition on liver regeneration and autophagy

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Current immunosuppressive strategies in the first period after liver transplantation (LTx) mostly involve treatment with steroids in combination with calcineurin-inhibitors or IL-2 receptor antagonists. A combination with the mTOR inhibitor rapamycin, although effective, is rarely used, especially after small-for-size LTx, since rapamycin is known to delay regeneration. The exact role of mTOR in liver regeneration however is to be defined. In rodents, it is known that IL-6 and HGF play an important role in stimulating hepatocyte proliferation and it is suggested that mTOR is involved in their downstream signal transduction. The aim of this study is to investigate the role of mTOR in IL-6 and HGF stimulated liver regeneration.C57BL/6 mice were subjected to a 70% partial hepatectomy (PH) and treated every 24 hours, starting at time of PH, with a combination of rapamycin and the steroid dexamethasone (rapa-dex) or with PBS. In the rapa-dex group, part of the animals was additionally treated with IL-6 and HGF. Animals were sacrificed 2 or 3 days after PH and liver and body weight, hepatocyte proliferation (BrdU), gene expression and effects on autophagy were determined.Treatment with rapa-dex caused a lower liver weight at day 3 compared to controls (53% vs 76% of pre-PH weight, p=0.04). This effect could be overcome if treatment was combined with IL-6/HGF (75%, p=0.02). The percentage of BrdU-positive hepatocytes was drastically reduced at day 2 by rapa-dex versus PBS treatment (2% vs 12%, p=0.0002) but was not restored by IL-6/HGF treatment. This effect was not seen in mice treated with dex alone, suggesting rapa causes the reduction in proliferation. Hepatic gene expression showed a signi-ficantly increased expression of TNF-a (7.6-fold) and IL-6 (3.9-fold) in the rapa-dex group versus controls. Furthermore, a decreased expression of Cyclin D1 (2.4-fold) and PCNA (6.4-fold) was seen. Combined treatment with IL-6/HGF significantly upregulated Cyclin D1 (3.6-fold) and PCNA (1.7-fold) expression and downregulated TGF-b expression (2.6-fold) versus rapa-dex treatment alone. Hepatic LC3-II and total LC3 levels were increased after rapa-dex treatment, indicating an increase in autophagy, which was reversed by additional treatment with IL-6/HGF.
Conclusions: This study shows that mTOR plays an important role in liver regeneration. mTOR inhibition impaired liver weight gain, hepatocyte proliferation and hepatic gene expression and furthermore upregulated autophagy. Exogenous IL-6 and HGF can, at least in part, overcome the adverse effects of rapamycin on liver regeneration and autophagy.

Quality of life after surgery for colon cancer in patients with Lynch syndrome; partial versus (sub)total colectomy

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Lynch syndrome (LS) is an autosomal dominant disorder caused by mutations in MMR-genes. Mutation carriers have a 60 to 85% lifetime risk of developing colorectal cancer (CRC). Most patients participate in intensive colonoscopic surveillance programs. If CRC is detected while under surveillance, generally, subtotal colectomy is recommended to reduce the risk of metachronous CRC as compared to partial colectomy. As the risk of CRC under intensive surveillance diminishes, recommendations for surgery should be reconsidered if a difference in quality of life (QoL) after both types of procedures exists. Aim of this study was to investigate the QoL and functional outcome in LS patients after partial (PC) and subtotal colectomy (STC).A nationwide cross-sectional study in the Netherlands was performed with two QoL questionnaires (SF-36 and EORTC QLQ CR-38) and a questionnaire about functional outcome (COREFO). Questionnaires were sent to 193 LS patients who underwent surgery for CRC. The response rate was 71%. 137 patients were included (64 patients in PC group and 73 patients in the STC group). None of the scales of the SF-36 showed a significant difference between both groups. The EORTC QLQ CR-38 presented more problems with defecation after STC (p= 0.01). Analysis of the COREFO revealed that after STC patients have a significant higher stool frequency compared to PC patients (p= <0.01). Conclusions Although stool frequency is higher after subtotal colectomy compared to partial colectomy, general QoL does not differ between both types of surgery in patients with LS. Therefore, subtotal colectomy is still the treatment of choice in young patients (e.g. < 60 years) with CRC, detected under surveillance. Patients should be informed about possible differences in functional outcome.

Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicenter randomized trial (Stent-in 2 study)

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Background: Colonic stenting as a bridge to elective surgery is an alternative for emergency surgery in patients with acute malignant colonic obstruction. We conducted a multi-centered randomized trial comparing colonic stenting with emergency surgery in patients with acute obstructive left-sided colorectal cancer. Methods: Twenty-eight Dutch hospitals participated. Eligible patients presented with obstructive symptoms existing less than one week and imaging compatible with left-sided colorectal cancer. After informed consent patients were randomized to either endoscopic stent placement or emergency surgery. The primary outcome was global health status during six months follow-up. Secondary outcomes were mortality, morbidity, other quality of life dimensions, and stoma rates. Analysis was done by intention-to-treat. Results: Between March 2007 and September 2009, 98 patients with acute left-sided malignant colonic obstruction were randomly assigned to stent placement (n=47) or emergency surgery (n=51). The study was terminated early, following advice of the Data Safety Monitoring Committee, because of a trend in absolute risk increase of morbidity in the colonic stenting arm. At final analysis no differences between emergency surgery and colonic stenting were observed regarding global health status (-4.7, p=0.36), 30 days mortality (Chi2=0.02, p=0.89), overall mortality (Chi2=0.04, p=0.84), morbidity (Chi2=0.64, p=0.43) and stoma rates at latest follow-up (Chi2=0.87, p=0.35). The only differences observed were a lower stoma rate directly after initial intervention (Chi2=5.8, p=0.016) and more frequently reported stoma-related problems (-12, p=0.046) in the colonic stenting group. Conclusion: Colonic stenting as bridge to surgery has no decisive clinical advantages to emergency surgery in colorectal cancer patients with acute left-sided colonic obstruction.

Outcomes of patients undergoing repeated cytoreductive surgery and peri-operative chemotherapy for recurrent colorectal cancer peritoneal carcinomatosis

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Cytoreductive surgery and peri-operative intraperitoneal chemotherapy is the only curative option for patients with peritoneal carcinomatosis for colorectal cancer. Unfortunately, a proportion of patients shows recurrence after this intensive combined treatment. The outcomes of patients undergoing a second procedure for recurrent peritoneal carcinomatosis were examined in this study. The study included all patients undergoing a second procedure with curative intent for recurrent colorectal cancer peritoneal carcinomatosis in two tertiary referral centres in Australia and the Netherlands. Data on patient characteristics, details of surgical procedures, perioperative course and follow-up were retrieved from the medical charts. Morbidity and mortality, overall survival and disease-free survival were the primary outcomes. Ten patients (7 female) were included in this study. Mean age was 49 years at the time of the first procedure. The mean Peritoneal Cancer Index (PCI) was 11, and in 8 patients (80%) a complete resection was achieved. The median time to recurrence after the first combined procedure was 11 months (range: 4-28). During the second procedure, a mean PCI of 6.5 was found. At this time complete cytoreduction was performed in all patients. In two patients severe adverse events occurred during postoperative course. No death occurred within the first 30 days after surgery. Median survival (defined as time between the first cytoreductive procedure and death or last follow-up) was 34 months (95% confidence interval (CI) 29.8-38.2). However, 9 out of 10 patients showed systemic or local recurrence after the second procedure, and disease-free survival then was only 4 months (95% CI 2.1-5.9).
Conclusions: Although the results of this study show that performance of a repeat cytoreductive procedure for colorectal cancer peritoneal carcinomatosis is safe and feasible, the results in terms of overall and especially disease-free survival are disappointing.The results of this study suggest that redo procedures for colorectal cancer peritoneal carcinomatosis are not beneficial.

Neoadjuvant short course radiotherapy followed by transanal endoscopic micro-surgery six weeks later for T2N0 or T3N0 rectum carcinoma in frail elderly patients: a pilot study

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Total mesorectal excision (TME) with neoadjuvant radiotherapy, the standard treatment for rectum carcinoma, is associated with 27% serious complications (Dutch Surgical Colorectal Audit). Low local recurrence rates justify this for the average patient (TME trial: 5.6% in 5 years). Local resection has a lower complication rate but a higher local recurrence rate. Frail elderly patients may benefit from local resection because they are more vulnerable and less resilient. Transanal endoscopic microsurgery (TEM), a local resection technique, resects lesions whole, allowing for definitive histological confir-mation of radicality. Neoadjuvant radiotherapy may counter local recurrence and a strict follow up protocol may diagnose recurrence while still salvageable. This study describes the first results of short course neoadjuvant radiotherapy followed by a TEM procedure six weeks later in frail elderly for patients with T2-3 rectum carcinomas (yTEM). Patients with (endo-ultrasound) staged uT2-3N0 rectum carcinoma without dissemination, unfit for laparotomy, were offered yTEM as an alternative to conservative treatment. The surgeon and the anesthesiologist determined frailty and opted for yTEM with informed consent. Procedures were performed by two surgeons with extensive TEM experience (CH & EM). After histological confirmation of radical resection, strict follow up was advocated. 8 patients (5 male, 3 female) were treated by yTEM between 2007 and 2010. Their median age was 86 years (range 74-93). Except for an 86 year old, all patients had a history of cardiac disease. The 4 uT2 and 4 uT3 tumors at a median 6cm from the dentate (range 2-13) had no evidence for dissemination save one uN1 case. This patient was included after flatly refusing TME. Procedures were performed in median 52 minutes (range 25-155) without complications or conversions. The median tumor area was 17cm2 (range 11-25). All tumors were resected intact but one where an additional resection was performed for doubt of macroscopic radicality. Luckily, histology indicated this was a mere adenoma. The other tumors were staged 1 ypTis, 3 ypT1, 1 ypT2 and 2 ypT3. All resections were radical and full thickness. Only one serious postoperative complication occurred: a patient with extensive cardiac disease was treated for cardiac failure with diuretics. Patients have a median follow up of 8 months (range 3-35). One patient with severe Alzheimer was consciously withdrawn from follow up after 3 months and died two years later in a palliative setting, probably due to local recurrence and caecum blowout. No other local recurrence or metastasis was diagnosed. These initial results justify further study of yTEM.

Adherence to adjuvant treatment guidelines in high risk stage II colonic cancer patients

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Usually, patients with curatively resected colonic cancer without nodal tumor involvement do not receive adjuvant chemotherapy in the Netherlands. However, a subgroup of stage I-II colonic cancer patients are considered at high risk for recurrent disease and/or metastases based on 1) tumor obstruction or perforation at presentation 2) less than 10 lymph nodes (LNs) detected in the surgical specimen 3) T4 lesions and 4) lymphangio invasion at pathological examination. These patients, especially those having stage II disease, are regarded as comparable to stage III colon cancer and therefore adjuvant chemotherapy should be considered according to national guidelines. Two of those high risk factors are registered in the Eindhoven cancer registry, i.e. 1) less than 10 lymph nodes and 2) a T4 lesion. We analyzed data of stage II colonic cancer patients treated in 10 hospitals between 2000-2009. We describe the proportion of patients meeting high risk criteria (T4 or less than 10 LNs) and the proportion of these high risk patients receiving adjuvant chemotherapy. Inter-hospital variation in chemotherapy proportion in stage II was analyzed. Survival analyses for high risk patients with and without adjuvant chemotherapy were performed using Cox regression analysis. 1896 stage II colon cancer patients were analyzed; 191 patients showed a T4 lesion and 851 patients had less than 10 lymph nodes detected in the surgical specimen. In the less than 10 LNs group, only 24 % of patients aged <75 and 5% of patients aged >75 received adjuvant chemotherapy between 2006-2009. Overall survival did not differ significantly between patients who did and who did not receive adjuvant chemotherapy in this insufficient lymph node group in both age groups. In the T4 group, 45 % of patients aged <75 and only 10% of patients aged >75 received adjuvant chemotherapy between 2006-2009. However, in the younger T4 group overall survival differed significantly between patients who did and who did not receive adjuvant chemotherapy (patients aged <75 years). ($p=0.004$) Significant inter-hospital variation in the use of adjuvant treatment in the total stage II colonic cancer patients was observed, ranging from 3 to 35%. ($p<0.001$)

Despite easy, tangible criteria for high-risk stage II colonic cancer patients in the Netherlands, just a minority of the selected high risk patients received adjuvant chemotherapy. Inter hospital variability was observed. Therefore, adherence to national guidelines is less than expected and more attention should be given to the treatment schedule and definition of high risk N0 patients.

Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study

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Hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C can improve survival if used as an adjunct to cytoreductive surgery (CS) for treatment of peritoneal carcinomatosis (PC). It remains unclear if both hyperthermia and chemotherapy are essential for the reported survival benefit. Eighty WAG/Rij rats were inoculated intraperitoneally with the rat colon carcinoma cell CC-531. Animals were randomly assigned to one of the four treatment groups (n=20): CS only, CS followed by HIPEC (mitomycin 35 mg/m2 at 41°C), CS followed by intraperitoneal mitomycin perfusion at 37°C (IPEC) and CS followed by intraperitoneal sa perfusion at 41°C. Survival was the primary outcome with a maximum follow up of 126 days. Median survival was 62 days in rats treated with CS only and 57 days in rats treated with CS followed by hyperthermic sa perfusion. Rats receiving HIPEC had a median survival of 121 days (p=0.022 when compared to CS only). In the group treated with chemotherapy at 37oC, 13 out of 20 animals were still alive at the end of the experiment so median survival was not reached. (CS vs IPEC: p = 0.002, hazard ratio 0.36, 95% CI 0.19-0.69).
Conclusions: The effectiveness of intraoperative intraperitoneal perfusion after CS is highly dependent on the presence of chemotherapeutic agents in the perfusate but not on hyperthermia. The need to include hyperthermia in the adjuvant intraoperative treatment after CS for PC should be further investigated.

Colonoscopy after conservative treated diverticulitis: sense or non-sense?

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Traditionally, colonoscopy is advised after an episode of diverticulitis as it is thought to be related to colorectal malignancies. The aim of this study is to evaluate the benefit of a colonoscopy after a radiologically confirmed episode of diverticulitis. Records of all patients presenting at the Meander Medical Center for clinical suspicion of diverticulitis between 2007 and 2009 were retrieved from an in-hospital database. Patients with a radiologically confirmed diverticulitis and who subsequently underwent colonoscopy were included. This study assessed the frequency of significant findings at colonoscopy. Significant findings were defined as colorectal malignancies, dysplastic polyps or stenosis requiring surgery. Three hundred and five patients were radiologically confirmed with a diverticulitis by ultrasound, CT-scan or both. Two hundred and six (68%) patients received a colonoscopy. At colonoscopy there were 29 (14%) significant findings: eleven patients (5%) had a stenosis requiring surgery and 13 patients (6%) had dysplastic polyps. One patient (2%) was diagnosed with a low grade dysplastic tumor. No colorectal malignancies were found. There were no differences between patients with a radiologically confirmed diverticulitis who received a coloscopy and those that did not with regard to age and alarm symptoms for colorectal malignancies (anorexia, rectal bleeding, abnormalities at rectal examination).
Conclusion: A colonoscopy after an episode of diverticulitis does not seem to be useful to exclude malignancies in patients with a radiologically confirmed diverticulitis that has been treated by a conservative strategy. However, it might be of use to exclude other significant findings such as polyps or stenosis necessitating subsequent treatment or endoscopic follow-up.

Short-term outcomes of ligation anopexy in combination with transanal hemorrhoidal dearterilisation (THD) for the treatment of mucosal rectal prolapse and hemorrhoids

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Ligation anopexy is a new minimal invasive treatment for mucosal rectal prolapse and hemorrhoids. It can be performed in combination with transanal hemorrhoidal de-arterilisation (THD) for grade III and IV hemorrhoids. We studied the short term outcomes of patients who underwent THD in combination with anopexy because of grade III and IV hemorrhoids and mucosal rectal prolapse. We wanted to assess the results of this new procedure which eventually could reduce the need for conventional open hemor-rhoidectomy.Between February 2008 and October 2010, 68 patients were treated with THD in combination with ligation anopexy for grade III to IV hemorrhoids (and mucosal prolapse). All patients were previously treated with rubber band ligation. The procedure was performed in day care surgery under spinal anesthesia. All operations were performed by one surgeon. Outpatient follow-up occurred 8 weeks after the procedure. Another follow-up appointment was made if necessary.We studied 68 patients (60% men, mean age 48 years), including 49 (72%) patients with grade III and 19 (30%) patients with grade IV hemorrhoids. Besides prolapse, which was the indication for ligation anopexy, complaints consisted of blood loss 47%, pain 13%, swelling 6%, itching 2%, soiling 4% and other (6%). The median number of ligations placed was 2 (range 1-4).After a median follow-up period of 4.3 (range 0-39) months, 50 (77%) of the patients were free of symptoms, 15 (22%) had a 50 percent reduction of complaints and in none of the patients the treatment was not effective. The recurrence rate in patients with complete recovery of symptoms was 4%. One patient eventually underwent a third and fourth THD for recurrent complaints and one patient underwent open hemorrhoidectomy for persisting complaints in our follow-up period. There were 10 postoperative compli-cations, including 4 cases of severe anal pain, 2 anal blood loss, 1 urinary retention, 1 meningitis, 2 other. Rehospitalisation was necessary in 3 patients.
Conclusion: Short term results of THD combined with ligation anopexy show that it is an effective and safe therapy for hemorrhoids with mucosal prolapse. It may eventually reduce the need for conventional open hemorrhoidectomy.

Alternative specimen extraction techniques after laparoscopic emergency colectomy in Inflammatory Bowel Disease

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Omitting the extraction site incision potentially further decreases the abdominal wall trauma in laparoscopic surgery. The aim of this study was to report the results of alternative specimen extraction techniques after laparoscopic emergency colectomy in patients with Inflammatory Bowel Disease (IBD). Ten consecutive patients with IBD underwent (sub) acute emergency colectomy for refractory disease from October 2009 until December 2010. Specimen retrieval was done via the stoma site in three and transrectally in seven patients. Patient data were prospectively collected. In case of later completion proctectomy and pouch procedure, adhesions were systematically scored. In 4 patients the indication for a colectomy was therapy resistant ulcerative colitis, 3 patients had therapy resistant Crohn's disease, and 3 patients had undefined colitis of which one patient developed a toxic colitis. The alternative extraction of the colon specimen was feasible in all patients. Median operative time was 219 minutes (interquartile range (iqr) 197-232). The pain scores and morphine requirement in patients decreased quickly after surgery (visual analogue scale (VAS) pain score of 4.5 on postoperative days 1 and 2 and VAS score 3 on day 3, and morphine requirement of 60 mg, 49 mg and 0 mg on days 1, 2 and 3 after the operation, respectively). No infectious complications occurred. In 5 patients a completion proctectomy was done at a median time of 7 months (iqr 3.8-9.3) after colectomy. All patients showed absence of any adhesions in the pelvis. In 2 patients limited adhesions of the cut side of the mesentery was present. This study suggests that the transrectal and trans-stomal extraction techniques are feasible for retrieval of the colectomy specimen after laparoscopic subtotal colectomy with low postoperative morbidity and few intra-abdominal adhesions. The techniques seem to have the benefits of little postoperative pain, improved cosmesis, and a short recovery period. The foresights for these alternative extraction techniques are promising; however the techniques still need refinement and are only applicable in selected patients.

Ileocolic resection: a safe and durable option for limited Crohn's disease of the terminal ileum

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Aim of the present study was to assess the long-term results in patients who underwent an ileocolic resection for Crohn's disease. All patients who underwent primary ileocolic resection for Crohn's disease within the period 1998-2009 were included. Endpoints were postoperative complication rates, the clinical and surgical recurrences and time to re-resection. Clinical recurrence was defined as any intestinal recurrence requiring treatment, either at the outpatient department or admitted. In univariate and multivariate regression analyses, factors influencing complication rates and recurrence outcomes were investigated During the study period, 184 patients underwent an ileocolic resection. Median follow-up was 4.2 years (inter quartile range: 1.5 – 7.2). Laparoscopy was performed in 107 patients (58%), of whom 4 were converted to a laparotomy (3.7%). Direct postoperative complications occurred in 35 patients (19%), significantly more often in patients who had open surgery (23/77 (29.9%) vs. 12/107 (11.2%), OR 3.372 (95%CI: 1.555-7.310; p=0.002). Nine patients required a reoperation due to postoperative complications (4.9%). After adjustment for case mix (older age at time of diagnosis and at time of surgery and a temporary ileostomy after primary resection) the only factor remaining associated with a higher complication rate in multivariate analysis was open approach (OR 2.570 (95%CI: 1.118-5.911; p=0.026)). One hundred-and-twelve patients (61%) remained relapse free after resection. Of the 72 (39%) patients with recurrent disease, 59 could be treated in an outpatient setting. The remaining 26 patients (26/184: 14%) required a readmission and of those, 19 patients underwent a re-resection (19/184: 10.3%). Median time between the ileocolic resection and re-resection was 63.75 months (inter quartile range: 26.8 – 71.2). In multivariate analysis, the only factor significantly associated with relapse was an end-to-side anastomosis (OR 2.924 (1.294 - 6.606), p= 0.010). Smoking at time of surgery showed a trend to more relapses in this analysis (OR 2.176 (0.923 - 5.131), p=0.076).
Conclusions: Ileocolic resection is a safe and effective treatment option in patients with ileocecal Crohn's disease, leading to low recurrence and re-resection rates.

MRI features associated with acute appendicitis

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Due to the lack of ionizing radiation and the high intrinsic contrast resolution MRI is gaining ground in the diagnostic work-up of several acute abdominal conditions. Previous studies have shown a high accuracy of MRI in detecting acute appendicitis. The aim of this study was to identify MRI features associated with acute appendicitis. Radiological signs expected to be associated with acute appendicitis were recorded by sixteen readers (9 radiologists, 7 residents) in 82 abdominal MRI scans of patients with suspected appendicitis. An expert panel had assigned acute appendicitis as the final diagnosis in 36 of 82 patients based on histopathology and follow-up. All readers had been trained to appraise MRI examinations for appendicitis during 20 scans with direct feedback.

Associations between imaging features and acute appendicitis were evaluated with logistic regression analysis. Seven evaluated MRI features were significantly associated with acute appendicitis in multivariable analysis: thickened appendix (>6mm), peri-appendiceal fat infiltration, peri-appendiceal fluid, appendicolith, restricted diffusion of the appendiceal wall, the appendiceal lumen and of focal fluid collections. The probability of appendicitis was at least 89% if two of these MRI features were present, 91% if three MRI features were present. The combination of peri-appendiceal fat infiltration and presence of an appendicolith on MRI had the highest probability of appendicitis (99%; 95% CI 94% to 100%). In absence of any of these features appendicitis was present in 7% (95% CI 5% to 10%) of patients.

Conclusion – Presence of a thickened appendix (>6mm), peri-appendiceal fat infiltration, peri-appendiceal fluid, appendicolith, restricted diffusion of the appendiceal wall, the appendiceal lumen and focal fluid collections on MRI are associated with acute appendicitis.

Longitudinal health-related quality of life and self reported treatment preference of patients scheduled for pancreatoduodenectomy with or without preoperative biliary drainage

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Background/Aim: In patients suspected to have a pancreatic tumor the value of preoperative biliary drainage (PBD) to reduce overall treatment complications was investigated in a two-arm multicenter RCT (early surgery vs. PBD). In a parallel study we analyzed health-reported quality of life (HR-QoL) for both treatment arms, and we asked which arm patients would have preferred as treatment strategy if not for randomization. Methods: The RCT comprised 202 patients of whom 82 were recruited at the initiating trial centre, and who were asked to participate in the current study. Of 82 patients 73 (89%) self-completed the EORTC QLQ-C30, PAN-26 QoL and the treatment preference questionnaires prior to randomization, two weeks following PBD [PBD-group only], and three and six weeks after hospital discharge following surgery. Results: Mean age of the study cohort was 64 years (SD 9.8), 67% male. Of 73 patients 38 (52%) underwent early surgery and 35 (48%) PBD. Clinicopathological and operative characteristics were not significantly different between groups, and closely resembled the original trial cohort. Mean reported global health status (possible range 0-100) for the entire group was 49 (95%CI: 43-55) before randomization, 54 (95%CI: 43-64) two weeks following PBD, and 57 (95%CI: 51-32) and 61 (95%CI: 56-67) three respectively six weeks after hospital discharge. The within-group improvement over time was significant (P 0.002), but there was no between-group difference (P 0.16). For another 12 HR-QoL subdomains patients from both groups also improved equally over time. Only for the hepatic symptom domain (jaundice, pruritus) patients that underwent PBD improved slightly better (B -34; 95%CI -40 - -28), compared to early surgery patients (B -25; 95%CI -32 - -18) (P 0.04). Before randomization 81% preferred to undergo early surgery, 7% PBD, and 12% did not have a treatment preference, while after ending treatment 74% still preferred early surgery, 10% PBD, and 16% had no preference.
Conclusions: We observed a significant improvement over time for nearly all HR-QoL domains following surgery for a suspected pancreatic tumor, without significant differences between an early surgery or PBD strategy except for the hepatic domain. From the perspective of HR-QoL both treatment strategies can be considered equivalent. However, the large majority of patients consistently admits early surgery to be the preferred treatment strategy from their own perspective.

Locally advanced pancreatic and periampullary cancer – is palliative resection justified?

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After pancreatoduodenectomy (PD) for cancer in the pancreatic head area, a radical (R0) resection is the most important predictor of survival. A bypass procedure is generally accepted as palliative treatment for locally advanced disease. Currently, a non-radical (R1/R2) resection is more frequently advocated for these patients. The aim of the present study was to analyse perioperative outcomes and survival after non-radical PD and palliative bypass procedure (PBP) for locally advanced pancreatic and periampullary cancer.

In a prospective database of patients who underwent surgery for suspected pancreatic and periampullary cancer, we identified patients who had undergone non-radical PD (R1/R2-group) or PBP for locally advanced disease (in absence of metastasis, bypass-group). In these groups, we analysed demographics, perioperative outcomes and survival.

Between 1992 – 2009, 1182 explorations for suspected pancreatic or periampullary cancer were performed, resulting in 790 PDs and 382 PBPs. 192 PDs were non-radical (R1/R2-group), and 197 PBPs were performed because of locally advanced disease (bypass-group). Mean age in these two groups was 62.2 and 62.8 years, respectively. In the R1/R2-group, 48% of patients were male, versus 58% in the bypass-group (P=0.039). Overall morbidity rates were 50% (R1/R2-group) and 35% (bypass-group) (P=0.003). Hospital mortality rates were 1% (R1/R2-group) and 2.5% (bypass-group) (P=0.27). Median hospital stay was 15 days in the R1/R2-group, versus 10 days in the bypass-group (P<0.001). 5-Years follow-up was complete for 96% of patients. Estimated median survival times were 17.1 months (R1/R2-group) and 9.8 months (bypass-group), log-rank test, P<0.001.

Conclusions: Non-radical PD can be performed at an acceptable morbidity rate with low mortality. Survival after non-radical PD is better than after PBP for locally advanced disease. Despite a selection bias, these results support the idea that PD can be considered in selected patients with intraoperatively encountered locally advanced disease. If there is doubt about the local resectability, resection should be performed.

Preconditioning in patients undergoingesophagectomy: A randomized controlled pilot study

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Esophagectomy in combination with neoadjuvant therapy is considered to be the optimal curative treatment for esophageal cancer. However, this treatment is associated with high morbidity and mortality rates. Optimizing cardiopulmonal status preoperatively by inspiratory muscle training has already been shown to significantly reduce the incidence of postoperative pulmonary complications and duration of hospital stay in patients undergoing coronary bypass graft surgery. This pilot study examines whether preconditioning in patients suffering from esophageal cancer, who are scheduled for esophagectomy, is feasible and will lead to better postoperative outcomes. Patients were randomly assigned to intervention or control group. The intervention group received daily inspiratory muscle training at home, supervised physical therapy twice a week, nutritional support once a week and psychological support if necessary. The intervention took place in the period between chemoradiation therapy and surgery. The control group received care as usual. Main outcome measures are feasibility, progression in general muscle strength, inspiratory muscle strength, nutritional status and quality of life. Secondary outcome measures are postoperative outcomes. A total of 20 patients was included, 11 in the control and 9 in the intervention arm. Two controls and 1 intervention patient withdrew from the study soon after randomization. One control subject started his own training program, similar to our intervention. There was a significant improvement in maximal inspiratory pressure in the entire group (paired t-test, p: 0,050), differences between the groups were not significant.The intervention group seemed to show less postoperative pulmonary complications, shorter duration of hospital stay and improved knee extensor and elbow flexor strength, although not significant. Bodyweight significantly reduced in the entire group (paired t-test, p: 0,011), but not significantly between the groups. Analysis of the psychological intervention and quality of life is still in progress.
Conclusions: In our study we have found the organization of a preconditioning program to be feasible; patients were very eager to participate in the rehabilitation program and they noticed much improvement with regard to physical fitness. Although the results are mostly not significant, probably due to a low number of patients and available data, there seems to be a trend towards better outcomes in favour of the intervention group. We conclude that a large randomized trial is warranted.

Implementation of an enhanced recovery program in esophageal surgery

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A recent development in gastrointestinal surgery is the implementation of enhanced recovery after surgery (ERAS) programs. Evidence regarding the benefit of these programs in patients undergoing esophageal surgery is scarce. Therefore we investigated the feasibility and possible benefit of a perioperative enhanced recovery program in patients undergoing esophagectomy for malignant disease.
From January 2009 until March 2010 all esophageal cancer patients undergoing surgical resection who were treated according to the ERAS were included in this study. ERAS items included preoperative counselling, preoperative nutrition, early removal of nasogastric tube and early mobilization. Primary outcome parameters were overall hospital stay and the incidence of postoperative complications. Outcome measures in the ERAS cohort were compared to a cohort of patients who underwent surgical resection in the three years prior to implementation of the ERAS protocol.
A total of 89 esophageal cancer patients underwent surgical resection between January 2009 and March 2010. 72 patients were included in the ERAS protocol (ERAS + group) and compared to 296 patients who underwent an esophagectomy between 2005 and 2008 (ERAS – group). Patient characteristics were comparable with the exception of a history of cardiovascular disease and the number of patients who underwent neoadjuvant therapy (50% in ERAS + versus 36% in ERAS –, p=0.03 and 60% in ERAS + versus 22% in ERAS –, p<0.001 respectively). Overall hospital stay was 14 days in ERAS + versus 15 days in ERAS – (p0.04). There were no significant differences in the incidence of postoperative complications in both groups.
Conclusion:The implementation of an ERAS program in esophageal surgery resulted in a small but significant reduction of overall hospital stay, whereas overall morbidity was not affected.

Results of the introduction of a minimally invasive esophagectomyprogram in a tertiary referral center

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Conventional open esophagectomies are accompanied by a high rate of postoperative complications. Although not yet proven by randomized clinical trials, minimally invasive esophageal surgery appears to be apromising technique that could be associated with a lower morbidity rate. The objective of this study was to compare the results of minimally invasive esophagectomies to conventional open esophagectomies in a non-randomized patient series. Preoperative characteristics and the postoperative course of patients that underwent a transthoracic esophagectomy for esophageal carcinoma were registered in a prospectively monitored database. The results of patients that underwent a minimally invasive esophagectomy and a conventionalopen resection were compared. From October 2009 until November 2010 a total of 73 esophageal cancer patients underwent a transthoracic resection of whom 34 by means of a minimally invasive resection. Preoperative characteristics were comparable for both groups. There was a trend towards a shorter hospital stayin the minimally invasive group (10.5 versus 13.5 days, p=0.19). The overall complication rate was 63% in both groups; pulmonary complications were presentin 32% of patients in the open TTOCR group versus 31% in the MIE group.
Conclusion: The morbidity after a minimally invasive resection oran open transthoracic esophageal resection is comparable. Furthermore, there isa trend towards a shorter hospital stay after minimally invasive surgery. Therefore, minimally invasive esophagectomies appears to be a safe technique for patients with potentially curable esophageal carcinoma.

Low impact of staging EUS for determining surgical resectability of esophageal cancer

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Current Dutch guidelines recommend computed tomography (CT) of chest and abdomen, ultrasonography (US) of the neck and endoscopic ultrasonography (EUS) for staging of esophageal cancer. TNM (UICC 7th edition) stages T1-4a N0-3 M0 cancers are considered surgically resectable. While studies have shown that EUS has a high sensitivity and specificity for T and N staging, the impact of EUS findings after CT and US neck staging for final surgical decision making (resectable or irresectable) is largely unknown. We, therefore, assessed the additional value of staging EUS for determining resectability of esophageal cancer. From June 2006 - May 2010, consecutive patients in our center with esophageal cancer who underwent staging EUS, CT and US were retrospectively reviewed. Tumors were considered resectable when there was no evidence of distant metastases or tumor ingrowth in adjacent structures (except for pleura or diaphragm). Sensitivity, specificity, positive (PPV) and negative (NPV) predictive value of CT/US neck and CT/US neck+EUS for predicting surgical resectability were pre- and postoperatively calculated. In total, 211 patients (155 men; mean age of 64 ± 9.4 years) were included, of which 176 (83%) underwent all 3 staging investigations. EUS was incomplete in 17 patients due to an obstructing tumor and US neck was missing in 18 patients. Based on preoperative staging, 173 (82%) patients were considered resectable and 38 (18%) irresectable. Of the latter, 17 had biopsy-proven metastases, 9 had tumor progression during neoadjuvant therapy, 2 had biopsy-proven tracheal/bronchial ingrowth and 10 had ingrowth or metastases as shown by other investigations. Preoperative sensitivity, specificity, PPV and NPV of CT/US and CT/US+EUS for predicting surgical resectability were 88%, 76%, 94% and 58%, and 87%, 87%, 97% and 59%, respectively. Of all 173 initially resectable patients, 145 were operated, 14 received another treatment (endoscopic resection or chemo- and/or radiotherapy), 5 refused surgery, 7 were not operable due to co-morbidity and 2 had other reasons. Of the 145 operated patients, 5 (3.5%) patients were found to be irresectable during surgery. Postoperative sensitivity, specificity, PPV and NPV of CT/US and CT/US+EUS for predicting surgical resectability were 88%, 20%, 97%, and 6%, and 87%, 40%, 98% and 10%, respectively.
Conclusion: Although EUS adds to the specificity of esophageal cancer staging after CT of chest and abdomen and US of the neck have been performed, the overall added value seems limited. More studies are therefore needed to determine in what subgroup of patients with esophageal cancer EUS adds to the treatment decision.

High expression of the mammalian target of rapamycin is associated with poor survival in patients diagnosed with esophageal adenocarcinoma; is there a role for rapamycin targeted therapy?

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Protein kinase mammalian target of rapamycin (mTOR) is an important downstream effector of phosphatidylinositol 3-kinase (PI3K)/ Akt kinase signalling pathway. In cancer cells this pathway is frequently dysregulated resulting in increased cell proliferation, angiogenesis and tumor progression. Recently, in esophageal squamous cell carcinoma (ESCC) high phosphorylated mTOR (p-mTOR) expression was identified as an independent prognostic marker. However, in esophageal adenocarcinoma (EAC) p-mTOR expression has not been assessed before. Therefore, this study evaluated the prognostic value of p-mTOR using a phospho-specific p-mTOR antibody (Ser2448) in EAC. A tissue micro array (TMA) was constructed comprising tumor cores of 156 consecutive patients undergoing esophagectomy. Scoring criteria was based on p-mTOR staining intensity (range, negative (0) to strong (3+)), whereby cores staining <2+ were defined as low and cores staining ≥ 2+ as high p-mTOR. Prognostic significance of p-mTOR expression was examined by Kaplan–Meier and Cox proportional regression analysis (multivariate analysis) and correlations between clinical parameters and p-mTOR staining were evaluated using Fisher exact test.In total 149 (96%) patients were available for immunohistochemical evaluation. Furthermore, 141 cases whose follow up was complete and whose tumor cores were immunohistochemically assessable, were included for univariate and multivariate analysis. High expression was detected in 31 (21%) of 149 tumors, whereas 118 (79%) patients showed low p-mTOR expression. Expression was not correlated to any of the clinical or pathological variables. High expression was significantly associated with poor survival in univariate analysis (hazard ratio (HR) 1.823; 95% CI 1.095-3.036; p= 0.021) and was correlated with reduced disease free survival (DFS) (HR 1.588; 95% CI 0.960-2.629; p= 0.072). Median survival was 21 in the high expressing group and 34 months in the low p-mTOR group (p= 0.019). However, in multivariate analysis, including all clinical and pathological factors that were significant in univariate analysis, only T-stage (HR 3.198; 95% CI 1.082-9.454; p= 0.036), differentiation grade (HR 2.004; 95% CI 1.155-3.486; p= 0.014) and lymph node ratio (HR 3.329 95% CI 1.426-7.769; p= 0.005) were independent prognostic markers of poor survival.

In conclusion, high p-mTOR expression was detected in 21% of patients and was associated with poor prognosis. Therefore, patients with highly activated mTOR signaling pathways might benefit from targeted therapy such as rapamycin (analogues).

Assessment of hepatic function using hepatobiliary scintigraphy in patients with parenchymal liver disease

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Compromised livers (fibrosis, steatosis, cholestasis or severe inflammation) are considered to have an impaired function and the limit for safe liver resection is therefore set at a future remnant liver volume of 40% instead of 25%. A quantitative scoring system that takes into account multiple different liver diseases is however not commonly used to identify patients with a compromised liver and the specific effect of different liver diseases on liver function is unknown.The aim of this study was to assess the value of a quantitative scoring system for identifying compromised livers and to evaluate the specific effect of different liver diseases on liver function measured by ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS). In 111 patients, preoperative HBS was performed to measure liver function after which resection specimens or perioperative biopsies were scored by an experienced pathologist: Fibrosis (0= absent; 1= fibrous expansion of portal areas; 2= incomplete portoportale septa; 3= marked portoportale bridging; 4= cirrhosis) and steatosis (0= absent, 1= < 5% of hepatocytes, 2= 5–30%, 3= 30–60%, 4= >60%) were scored on a 5 point scale. Cholestasis and inflammation (both portal and lobular) were scored on a 4 point scale (0= absent; 1= mild, 2= moderate, 3= severe). A compromised liver was defined as: either fibrosis ≥ 3, steatosis ≥ 3, cholestasis ≥ 2 inflammation ≥ 2.5 (average score of portal and lobular inflammation) or a combination of mild-moderate diseases with a total score ≥ 4.5 with ≥ 3 for (fibrosis+steatosis+ cholestasis), with at least 2 for fibrosis or steatosis)Liver function was significantly impaired in compromised livers (n=54) vs. normal livers (7.07±1.70 %/min/m^2 vs. 8.19±1.53 %/min/m^2, P=0.0004). Liver function in fibrotic livers was 6.55±2.24 %/min/m^2 (n=16), in steatotic livers 7.35±1.13 %/min/m^2 (n=11) and cholestatic livers 6.99±1.83 %/min/m^2 (n=26). A combination of mild-moderate diseases was seen in 9 patients with an uptake function of 7.40±0.90 %/min/m^2.
Conclusion: A quantitative scoring system identifies patients with a compromised liver. Liver function was most impaired in patients with severe fibrosis or cholestasis.

Metastaticlymph nodes in hilar cholangiocarcinoma: does size matter?

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Aim: To evaluate the association between lymph node (LN) size and the presence of metastasis and to define specific size categories for optimal assessment of nodal status in patients with hilar cholangiocarcinoma (HCCA). Introduction: LN metastasis is one of the most significant independent prognostic factors in patients with HCCA. At this time, despite the well known lack of sensitivity and specificity, one of the most used clinical criteria for nodal metastases is LN size. Methods: Pathologic specimens of 147 patients who had undergone laparotomy for HCCA were assessed. The size (maximum diameter) of each single node was retrieved from the pathology report or measured from section on the glass slide by using a stereo microscope and a calibrated ruler integrated in the soft-ware. When a metastatic lesion was detected the proportion of the lesion in relation to the LN size was estimated. Results: Of 147 surgical specimens 645 LN were retrieved and measured. 106 Nodes showed evidence of metastasis. The proportion of positive nodes increased from 8% in nodes <5mm to 37% in nodes > 30 mm. Ten percent of LN smaller than 10 mm are positive, whereas only 23% of LN larger than 10 mm are metastastically involved. In 50% of positive LN the metastatic lesion accounts for 10% or less of the LN size.
Conclusion: The cut-off point of 10 mm for LN in HCCA patients as a predictor of nodal malignancy is strikingly inaccurate. No cut-off point could be determined for accurately predicting nodal involvement. Thus imaging studies should not rely on LN size when assessing nodal involvement

Improved liver regeneration and functional recovery after partial hepatectomy in fatty livers treated with omega-3 fatty acids in rats

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Hepatic steatosis is an important risk factor for postoperative morbidity and mortality after major hepatectomy. Omega3-fatty acids (FA) have shown to inhibit experimental steatosis. The aim of this study was to examine reduction of steatosis and the consequent effect on liver regeneration in an experimental steatosis model in rats. Liver steatosis was induced in rats by 3wk methione/choline-deficient diet (MCDD) followed by 2wk omega3-FA treatment. Regenerative and functional recovery following partial hepatectomy were measured by ^{99m}Tc-mebrofenin hepatobiliairy scintigraphy (HBS). Firstly, HBS measurements before, after steatosis induction and following 2wk daily oral omega3-FA (Omega3-group)or NaCl (saline-group) administration were performed and compared with control rats (N=6/group).Secondly, HBS was performed in Omega3, sa and control rats, 1, 2, 3 and 5 days after 70%-partial hepatectomy (N=7/group). Hepatocellular damage and proliferation (Ki-67 staining), anti-oxidative capacity and Kupffer cell activation (hepatic TNF-alpha) were assessed.Histologically severe (>66%) steatosis (saline-group) was reduced by Omega3-FA to mild (<33%) steatosis. HBS-uptake in the saline-group was >2.0 fold impaired, as compared to control, but improved significantly ($P<0.05$) following omega3-FA treatment. Posthepatectomy, hepatocellular damage (ASAT/ALAT) and bilirubin levels were decreased in Omega3-group at day 1, 2 and 3, as compared to the saline-group. HBS-uptake and regenerated liver mass were significantly improved as compared to saline-group at day 1 and 3 ($P<0.05$). Posthepatectomy proliferation peak response was delayed in sa rats until day 2, as compared to day 1 in Omega3 and control rats. Anti-oxidative capacity was significantly improved ($P<0.05$) by omega3-FA treatment, as compared to the sa group, before and 1, and 3 days post-hepatectomy. Kupffer cell activation was lowered in Omega3 rats before and 1 day posthepatectomy, as compared to saline-group.
In conclusion, omega3-FA treatment effectively reduced severe steatosis resulting in improved liver regeneration and functional recovery following partial hepatectomy.

Pancreatic neuroendocrine Tumors (PNETs): diagnostic and operative results

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Pancreatic neuroendocrine tumors (PNETs) are rare tumors with an incidence of 1-4 per million per year. PNETs can be asymptomatic or present with clinical syndromes depending on anatomical extension or hormonal hypersecretion. In this study we analysed the diagnostic and operative results of all PNET-patients treated at out hospital.A prospective database is available of all patients who underwent a pancreatic resection in our hospital since 1996. From this database all patients with a PNET were selected. Diagnostics and operative results were analysed. From 1996-2010 a total of 95 patients with a PNET were operated. Patients had a mean age of 45 years (range 19-78), 44 were male and 51 female. Hormonal overproduction was present in 28/95 patients (29%), 16 insulinoma's. 8 gastrinoma's, 2 vipoma's, 1 glucagonoma and 1 nesidioblastosis. Hormonal function tests were performed in 43/95 patients (45%), 52/95 patients (55%) were not tested for hormonal overproduction. Patients without clinical syndromes of hormonal overproduction who were tested preoperatively showed high calcitonine levels in 3/15 patients (20%) and high glucagon levels in 1 patient (7%). Octreotide scans were performed in 68/95 patients (72%) but in 25/68 patients (37%) there was no uptake in the tumor. In 3/68 patients (4%) the octreotide scan gave additional information to the CT-scan, one patient had multiple gastrinoma locations in the pancreatic head area, 2 patients had octreotide positive lymphnodes near the pancreatic head. In none of these selected patients the operative strategy was changed. Some 21 patients underwent an enucleation, 30 patients a pancreatic head resection (PPPD/PD), 21 patients underwent a corpus/tail resection, 12 patients underwent a corpus resection with a pancreato- jejunostomy on the pancreatic tail and 12 patients underwent other operations. The type of operation performed depended on anatomical considerations and diagnoses since most insulinoma's were enucleated. Complications occurred in 35/95 patients (37%), 14 patients had a pancreatic fistula, 5 patients had bleeding complications and 14 patients had other complications. Two patients (2%) died of postoperative complications.
Patients with PNETs can have hormonal overproduction, even in the absence of specific complaints. Octreotide scans are often negative in patients with resectable PNETs. In general, PNETs have a more indolent behaviour and therefore patients with PNETs have a better survival then patients with pancreatic adenocarcinoma. However the operation related morbidity and mortality are similar for PNETs and pancreatic adenocarcinoma.

Endoscopic closure of iatrogenic perforations of the gastrointestinal tract using the over-the-scope-clip: a prospective multicenter human trial

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Latrogenic perforations of the gastrointestinal tract are rare but severe complications of endoscopy with relatively high morbidity and even mortality. Surgical repair is usually indicated. Secure endoluminal repair of perforations would obviate the need for a surgical intervention. Aim was to evaluate safety and reliability of endoscopic closure of iatrogenic perforations of the gastrointestinal tract using the Over-the-Scope-Clip (OTSC; Ovesco).
We conducted a prospective international multicenter trial in which all consecutive patients from March 2009 with acute iatrogenic perforations were included. Closure was performed according to a standard operating procedure, which could be divided in 3 steps:1) Approximation of deep layers using a twin grasper; 2) Pulling the tissue into the OTSC-cap; 3) Releasing the clip. Primary endpoint was successful closure, determined as macroscopic adequate closure and no leakage on water soluble contrast X-ray within 24 hours without the need for an additional intervention. Secondary endpoints included closure, adverse events and additional interventions needed.Thirty-six patients (15 male) were included until May 2010. Five esophageal, 6 gastric, 12 duodenal and 13 colonic perforations were included. Eighteen patients (50%) suffered from a perforation after a therapeutic and 13 (36%) during a diagnostic endoscopy. In 5 cases there was another cause. In one patient with a duodenal perforation a deep esophageal laceration occurred while introducing the OTSC-cap and in two case adequate closure using the OTSC failed. All three perforations were closed surgically. Endoluminal closure was macroscopically successful in all 32 remaining patients in a median of 5:46 minutes (SD 4:19). In none of the patients there was leakage of soluble contrast on X-ray within 24 hours after closure. One patient in whom a colonic perforation appeared to be successfully closed, deteriorated within 24 hours and was referred for surgery which showed a detached clip at the perforation site. Within 24 hours after successful surgery the patient deceased of unknown cause. Overall endoluminal closure was successful in all remaining 32 patients, meaning a success rate of 89% (95%-CI: 75-96%)
Conclusions: This multicenter prospective human trial showed a successful immediate endoscopic closure rate using the OTSC, in 89% of acute iatrogenic perforations of the gastrointestinal tract. Consequently, surgery was avoided in 89% of cases as well.

Chemoprevention in Barrett's esophagus with non-steroidal anti-inflammatory drugs and statins: results of a large multicenter prospective cohort study

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Barrett's esophagus (BE) is a premalignant condition predisposing to the development of esophageal adenocarcinoma (EAC). Strategies to prevent EAC have focused on reversal of BE and detection of high grade dysplasia (HGD) or early EAC during surveillance. However, despite these strategies the incidence of BE and EAC has increased in Western countries. Recent data suggests that non-steroidal anti-inflammatory drugs (NSAIDs) and statins may reduce the risk of developing EAC. Therefore the aim of this study was to evaluate whether use of NSAIDs or statins is associated with a reduced risk of neoplastic progression in patients with BE. In this multicenter, prospective cohort study patients were included with BE of at least 2 cm. Information about medication use was collected from patient interviews and cross-checked with pharmacy records. Multiple pharmacies were contacted for each patient to obtain documentation of all medications that were handed out, including dose and time of prescription. Besides, patients filled out a questionnaire about the use of over-the-counter medication. Surveillance was performed according to the ACG guidelines and incident cases of HGD and EAC were identified during follow-up. Patients, who developed HGD or EAC within 9 months after inclusion, were excluded from this analysis. Cox regression analyses were performed to evaluate the association between NSAID or statin use and the risk of neoplastic progression in BE. In this study 570 patients (72% male; mean age 55.1 ± 12.3) were included and followed for a median duration of 7.9 (5.9-11.8) years. Thirty-eight patients developed HGD or EAC during a median follow-up period of 7.6 (4.7-13.0) years. Almost all patients (99%) used a PPI during follow-up. NSAIDs were prescribed in 400 patients (70%) for a relative short median duration of 0.5 (0.17-4.6) years. Statins were prescribed in 209 patients (37%) for a median duration of 5.3 (1.9-8.3) years. In 173 patients (30%) NSAIDs and statins were prescribed. NSAID use was associated with a significantly reduced risk of neoplastic progression (HR 0.51; 95%CI 0.26-1.00; p=0.048) after adjustment for age, gender, BE length, base histology and use of other medications. Statin use was associated with a significantly reduced risk of developing HGD or EAC as well (HR 0.36; 95%CI 0.17-0.77; p=0.009). Use of both NSAIDs and statins was associated with an additional reduction in the risk of neoplastic progression (HR 0.19; 95%CI 0.07-0.50; p=0.001). Conclusion: Use of NSAIDs or statins reduces the risk of neoplastic progression in patients with Barrett's esophagus. Use of NSAIDs and statins seems to have an additional protective effect.

Exosomes can mediate transmission of Hepatitis C Virus in the presence of neutralizing antibodies: relevance for Hepatitis C recurrence?

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Introduction: Management and treatment of recurrent hepatitis C virus (HCV) after liver transplantation remains a major clinical challenge. Unlike for HBV, treatment with neutralizing antibodies (nAbs) does not prevent HCV re-infection. The exact mechanism of this immune deviation remains largely unknown. Recent evidence suggests that small vesicles/exosomes can transfer mRNA and microRNA between cells. Therefore, the aim of our study is to investigate whether exosomes can shuttle HCV and contribute to the nAb-independent transmission of viral infection. Method: Huh7 cells harbouring JFH-1 derived infectious HCV virus and naive Huh7 cells were used. Exosomes were isolated by density gradient ultracentrifugation and analysed for HCV content by primary and secondary infectivity assays, real time RT-PCR, mass spectrometry and immunostaining electron-microscopy. Cellular uptake of labelled exosomes was visualized by real-time confocal microscopy Results: Purified exosomes from JFH-1 infected Huh7 cells, but not from naive Huh7 cells, contained HCV genomic RNA as detected by quantitative RT-PCR. Electron-microscopy showed the presence of virus-like particles within exosomes from HCV infected cells and was confirmed by immuno-gold staining. Mass Spectrometry analysis confirmed the presence of HCV viral proteins. Exosomes, labeled with rho-damine, are rapidly taken up by Huh7 cells (figure1). Moreover, exosomes can transfer HCV to naive Huh7 cells and establish a productive infection. Treatment with nAbs had a minor effect on exosomes-mediated infecion, whereas almost completely inhibited HCV infection by free viral particles.
Conclusion: Hepatocyte-derived exosomes can harbour and transfer HCV to naive cells and establish a productive infection. Exosome-mediated transfer of HCV is largely resistant to nAbs and therefore may represent an immune evasion strategy of the virus. This may shed new light on the ineffectiveness of prophylactic nAbs to prevent HCV recurrence.

High incidence of a second primary esophageal squamous cell carcinoma in patients with previous head-and-neck cancer: a nationwide population-based study

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Background: Esophageal cancer is among the ten most common malignancies in the world. The prognosis is often quite poor, with a 5-year survival of 10-15%, often due to the advanced state of disease at time of diagnosis.Previous studies have found that patients diagnosed with a cancer of the head-and-neck and lung, are at a higher risk for esophageal squamous cell carcinoma (ESCC). However, population-based data on the magnitude of this risk is scarce. AimTo assess the risk of developing a second primary ESCC among head-and-neck and lung cancer survivors in the Netherlands in order to determine the usefulness of a ESCC screening program in these patients. Methods:The population-based Netherlands Cancer Registry (NCR) provides unique incidence data on all malignant tumors diagnosed in the Netherlands. Through an annual linkage with the Dutch Municipality Register, complete information on vital status of each patient in the registry is ensured. All Dutch patients who developed a first primary cancer between 1989 and 2008 were included in our analysis (n: 1,391,490). We subsequently studied how many of these patients developed a second primary esophageal cancer. We calculated the Standardized Incidence Ratio (SIR) and the 95% CI, which was computed under Poisson regression. Results:In total, 5,619,927 person years at risk were obtained from the cohort. During a median of 3 years, ~ 10% of our cohort of first cancer patients (n: 135,725/1,391,490) developed a second primary cancer. Of them, 2,214 (1.6%) had a second esophageal cancer. Cancer patients had a 70% higher risk of developing any esophageal cancer (SIR: 1.7 (95% CI: 1.6-1.7)) and a twofold higher risk of developing ESCC (SIR: 2.2 (95% CI: 2.1-2.4)) as compared to the general population. The relative risk (SIR) of a second ESCC among lung cancer patients was 3.70 (95% CI: 3.0-4.5).A remarkably high relative risk of developing a second ESCC was observed among patients with a first head-and-neck cancer with a SIR of 19.3 (95% CI: 16.9-22.0) and 36.9 (95% CI: 29.8-45.4) for males and females respectively. Of the 9,584 female patients with a first head-and-neck cancer 92 developed a second ESCC with a Number Needed to Screen of 96.
Conclusions: This first nationwide, population-based study in the Western world on the incidence of ESCC in head-and-neck cancer survivors shows that these patients have a 22 times higher risk of developing ESCC. This observation is even more pronounced in female patients. These data suggest that head-and-neck cancer survivors may benefit from periodical screening for ESCC.

Reduction of rectal distensibility and external anal sphincter function after radiation therapy for localized prostate cancer

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Late anorectal toxicity is a frequent adverse event of external beam radiotherapy (EBRT) in patients treated for prostate carcinoma. To prevent troublesome symptoms like fecal incontinence and urgency, more insight into its pathophysiology is needed. We hypothesize that an increased stiffness of the rectal wall is one of the factors involved. Our goal is to compare anorectal mechanical parameters prior to prostate EBRT to measurements one year after radiotherapy, and to explore whether there are specific changes related to anorectal complaints.Thirty-two men (mean age 68 yrs; range 52 - 79 yrs), irradiated for localized prostate carcinoma between 2007 and 2009, underwent barostat measurements, anorectal manometry, and completed a questionnaire prior to and one year after radiotherapy. Rectal distensibility in response to isobaric distensions was the primary outcome measure. In addition we determined sensory thresholds, anal pressures and anorectal complaints.Maximal rectal capacity (227±14 ml vs. 277±15 ml; $p < 0.001$), area under the pressure-volume curve (3212±352 ml·mm Hg vs. 3969±413 ml·mm Hg; $p < 0.005$) and rectal compliance (15.7±1.2 ml/mm Hg vs. 17.6±0.9 ml/mm Hg; $p = 0.12$) were reduced after EBRT. No significant differences were found in sensory pressure thresholds. Sixteen of the 32 patients (50%) had one or more anorectal complaints (urgency n=10; increased frequency n=4; fecal incontinence n=1; loose or liquid stools n=10; painful bowel movements n=2; abdominopelvic cramps n=4). Patients with complaints of urgency, had a more reduced anal squeeze pressure (mean decrease 29±11 mm Hg vs. 1±7 mm Hg; $p < 0.05$) and maximum anal pressure (mean decrease 31±12 mm Hg vs. 2±8 mm Hg; $p < 0.05$) but no larger reduction in rectal capacity (mean decrease 57±22 ml vs. 63±14 ml; NS) compared to patients without any complaints.
Conclusions: There is a reduction of rectal distensibility in patients who got EBRT for prostate cancer. Thirty one percent of irradiated patients develop urgency which is related to a deterioration of external anal sphincter function.

Assessment of pain perception in irritable bowel syndrome: towards an optimal definition of rectal hypersensitivity

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Background: Visceral hypersensitivity is considered a hallmark of irritable bowel syndrome (IBS) and is present in up to 60% of IBS patients. A rectal barostat test is frequently used to investigate intestinal sensitivity in IBS. This test allows discrimination between IBS patients and healthy controls (HC) based on pain perception. However, there is no consensus regarding the procedure of testing visceral sensitivity and threshold or normal values. Aim of the present study was therefore to assess the optimal threshold and cut-off to detect altered visceral perception (hypersensitivity and allodynia) in IBS, by standardised rectal distensions. Methods: Barostat data of 126 IBS patients (38±1.3 years) according to Rome III criteria and 30 HC (37±3.1 years) were analysed for visceral pain perception. The rectal barostat procedure consisted of intermittent staircase distensions between 0-50 mmHg above MDP, with increments of 3 mmHg. Participants scored pain at 100mm visual analogue scales (VAS). Based on perception data in IBS and HC, area under receiver operating characteristic curve (AUC); sensitivity (SEN); specificity (SPE); positive predictive value (PPV) and positive likelihood ratio (LR+) were calculated. This resulted in a cut-off point (i.e. combination of pressure step and VAS-score for pain) for optimal discrimination between IBS and HC. VAS-scores above this cut-off optimum were defined as hypersensitive, VAS-scores below this cut-off optimum but above the cut-off for first sensation (VAS of 10mm) were defined as allodynic. Results: Diarrhoea-, constipation-predominant and mixed stool type were found in 50, 29 and 21% of IBS patients, respectively. Five pressure steps with corresponding cut-off values had AUC > 0.75. The cut-off that allowed optimal discrimination between IBS and HC was found to be 26mmHg with a VAS-score >20mm (i.e. pain threshold), based on sensitivity (0.64), specificity (0.90), AUC (0.77), PPV (0.96) and LR+ (6.3). Using this criterion, 63.5% of IBS patients and 10.0% of HC were hypersensitive, whereas allodynia percentages in these groups were 11.1% and 6.6%, respectively.
Conclusion: Threshold and cut-off values during rectal barostat procedure to a large extent determine hypersensitivity percentages amongst IBS patients. When using the barostat as a descriptive or diagnostic tool for IBS, international standardisation of the distension protocol is required. With this study, we have shown that 26mmHg at VAS>20mm is most optimal for the detection of visceral hypersensitivity in IBS patients, compared to healthy controls during rectal barostat.

The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients (MLDS-project MWO 05-42)

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Visceral hypersensitivity to distension is thought to play an important role in the pathophysiology of the irritable bowel syndrome (IBS). Cannabinoïds are known to decrease somatic pain perception, but their effect on visceral sensitivity in IBS remains unclear. Therefore, we evaluated the effect of the mixed CB1/CB2 receptor agonist delta-9-tetrahydrocannabinol (Δ^9-THC, dronabinol) on rectal sensitivity.

Ten IBS patients and twelve healthy volunteers (HV) underwent a barostat study to assess rectal sensitivity using an intermittent pressure-controlled distension protocol before and after sigmoid stimulation. Repetitive sigmoid stimulation is a validated method to increase visceral perception in IBS patients, consisting of a 10-min period of 30 sec stimuli (60 mmHg), separated by 30 sec of rest (5 mmHg). The effect of placebo and Δ^9-THC (5 and 10 mg in healthy volunteers and 10 mg in IBS patients) on rectal sensitivity was evaluated on respectively three and two separate days in a double blind, randomised, crossover fashion.

All participants (HV and IBS) reported central side effects during the highest dose of Δ^9-THC, most frequently increased awareness of the surrounding, light headedness and sleepiness, whereas no side effects where reported during placebo. Although blood pressure was not affected, heart rate increased in both HV and IBS, but was most pronounced in IBS patients. The cannabinoid agonist Δ^9-THC did not alter baseline rectal perception to distension compared to placebo in HV or IBS patients. Similarly, after sigmoid stimulation there were no significant differences between placebo and Δ^9-THC in sensory thresholds of discomfort.

In conclusion, these findings implythat Δ^9-THC does not modify visceral perception to rectal distention and argue against (centrally acting) CB agonists as tool to decrease visceral hypersensitivity in IBS patients.

The role of esophageal acid exposure on esophageal base impedance levels

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Introduction:Base esophageal impedance, which is the esophageal impedance between reflux or swallows, is determined by the conductivity of the surrounding esophageal wall and can be decreased in GERD patients. The aim of this study was to investigate base impedance levels in 1) GERD patients with and without pathological acid exposure and healthy volunteers and 2) patients with and without inhibition of gastric acid secretion. Methods:Ambulatory 24-h pH-impedance monitoring was performed in 1) 24 GERD patients with and 24 without pathological esophageal acid exposure after cessation of PPIs for 7 days as well as in 10 healthy controls and in 2) 20 patients with refractory GERD symptoms despite PPI, once on PPI and once after cessation of the PPI for 7 days. Base impedance level in the most distal and the most proximal impedance channel was assessed every two hours. Results:Mean acid exposure time (% of time withpH<4) in patients with physiological acid exposure (2.9) was not significantly different from controls (2.1). Median (IQR) distal base impedance (Ω) in patients with physiological acid exposure (2092 (1550-2561)) was significantly lower than in controls (2834 (2135-3285), $p<0.05$). In patients with pathological acid exposure, distal base impedance (781 (608-1134)) was significantly lower compared to patients with physiological acid exposure and controls (both $p<0.001$). In GERD patients, a negative correlation between acid exposure time and base impedance was observed ($r=-0.7$, $p<0.001$). In patients with GERD symptoms despite PPI the median acid exposure time on PPI (1.1) was not significantly different from healthy controls (1.8). Median distal base impedance in patients off PPI was significantly lower than on PPI (886 (715-1348) vs 1381(965-1975), $p<0.05$) and both measurements were significantly lower than in healthy controls ($p<0.05$ and $p<0.001$). Proximal base impedance did not differ significantly between the patients off PPI or on PPI (1814 (1375-2523) vs 1937 (1624-2525)), however, baselines in both measurements were significantly lower than in healthy controls (3671 (2822-3960), both $p<0.001$).
Conclusions: In GERD patients, distal esophageal base impedance shows a negative correlation with esophageal acid exposure time and distal base impedance is lower in patients than in controls. Base impedance is increased but not normalized by PPI treatment in patients with refractory GERD symptoms. These findings suggest that base impedance could be a non-invasive marker of reflux-induced changes to the esophageal mucosa.

Effect of Transoral Incisionless Fundoplication 2.0 on esophagogastric junction distensibility in GERD patients: a study using an endoscopic functional luminal imaging probe (EndoFLIP)

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Transoral incisionless fundoplication (TIF) is a new endoluminal procedure that has been developed and evaluated for the treatment of GERD. Measurement of esophagogastric junction (EGJ) distensibility with an endoscopic functional luminal imaging probe (EndoFLIP) has been demonstrated to be feasible and it has been suggested that EndoFLIP measurements may be useful in the course of surgical or endoluminal procedures. The aim of the present study was to assess the effect of TIF on EGJ distensibility with EndoFLIP in GERD patients and its persistency after 6 months. Nineteen patients with documented GERD and symptoms refractory to medication (12 men; mean age 42, range 21-64 yr) underwent a TIF procedure using the TIF 2.0 technique (EndoGastric Solutions, Redmond, WA, USA). Using the EndoFLIP device (Crospon Medical Devices, Galway, Ireland), EGJ distensibility was measured pre- and immediately post TIF 2.0 procedure. In 10 patients (6 men; mean age 41, range 24-60 yr) EndoFLIP measurement was repeated after six months. The EndoFLIP probe consists of an inflatable bag attached to a 2.5 mm catheter. The part of the catheter surrounded by the bag comprised 16 impedance planimetry segments. The catheter was positioned at the lower esophageal sphincter and the bag was distended to 20 and 30 mL. The narrowest cross sectional area (CSA: mm^2) following the narrowest diameter, with the corresponding intra-bag pressure (mmHg), was identified at each intra-bag volume. EGJ distensibility (ratio between CSA and intra-bag pressure) was assessed at each intra-bag volume. Immediately post procedure, the CSA did not decrease significantly at both intra-bag volumes (20 mL: 22±2 vs 18±1, p=0.07; 30 mL: 37±6 vs 32±5, p=0.41) but the corresponding intra-bag pressure increased significantly (20 mL: 15±1 vs 20±2, p=0.02; 30 mL: 18±2 vs 24±2, p=0.05). EGJ distensibility decreased significantly after treatment at both volumes (20 mL: 1.9±0.4 vs 1.0±0.1, p=0.03; 30 mL: 2.5±0.5 vs 1.5±0.2, p=0.03). After six months, the decrease in CSA (20 mL: 21±3 vs 16±1, p=0.17; 30 mL: 32±6 vs 28±4, p=0.69), the increase of intra-bag pressure (20 mL: 16±3 vs 24±3, p=0.09; 30 mL: 18±3 vs 26±3, p=0.11) and decrease in EGJ distensibility (20 mL: 2.2±0.7 vs 0.7±0.1, p=0.08; 30 mL: 2.3±0.6 vs 1.3±0.2, p=0.14) were comparable to the post-procedure measurement but did not reach statistical significance.
Conclusion: Transoral incisionless fundoplication 2.0 leads to a significant reduction of esophagogastric junction distensibility and this effect was persistent after six months. We anticipate that distensibility reduction may lead to a decrease in number of reflux episodes and in refluxate volume.

Impaired distensibility of the esophagogastric junction in patients with achalasia and persistent symptoms

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Esophageal emptying in patients with achalasia is impaired, leading to symptoms such as dysphagia and regurgitation. As previous studies have suggested that basal lower esophageal sphincter pressure (LESP) >10mmHg is a risk factor to develop recurrent symptoms, LESP is often used to decide if patients would benefit from further treatment. Patients with low basal LESP however report persistent symptoms and show impaired esophageal emptying on timed barium esophagram (TBE). As the resistance to flow at the esophagogastric junction (EGJ) largely determines emptying, we hypothesized that assessment of the distensibility of the EGJ would be better parameter to evaluate the effect of treatment in patients with achalasia. Patients with previously treated achalasia underwent EndoFLIP measurement, esophageal manometry and a TBE. EndoFLIP uses impedance planimetry with 16 electrodes to measure cross sectional areas at 4mm intervals inside a saline-filled bag, and contains two pressure side holes allowing assessment of EGJ distensibility. Esophageal stasis was determined using TBE after 5 minutes. Symptom scores were assessed using the Eckardt score. Patients were considered as a treatment success if the Eckardt score ≤3. Twenty-six patients (age 50±3.5yrs M13) were studied. Compared to successfully treated patients, patients with an Eckardt score >3 (n=9) had significantly more stasis after five minutes (3.7 ± 1.2 vs 1.0 ± 0.5 cm, $p<0.05$), a higher LESP (13.1±3.7 vs 4.3±1.2 mmHg, $p<0.05$) and a lower distensibility (1.7±0.44 vs 4.4±0.48 mm^2/mmHg, $p<0.01$). Patients with stasis on TBE (n=11) had a significantly lower distensibility compared to patients without stasis (n= 11) (2.4±0.4 vs 5.1±0.7mm^2/mmHg, $p<0.01$). In contrast, LESP was comparable (9.6±3.0mmHg vs 4.6±1.7mmHg, $p=0.15$). Furthermore, esophageal stasis correlates well with EGJ distensibility but not with LESP ($r=-0.70$, $p<0.01$ and $r=0.22$ $p=0.41$ resp). Using a ROC curve, an optimal test value for unsuccessful treatment of 2.8mm^2/mmHg was determined, which has a sensitivity and specificity of 89% and 75% resp. In the same line, 80% of patients with a distensibility > 2.8 mm^2/mmHg had complete emptying after 5 minutes. In contrast, 44% of unsuccessfully treated patients had a basal LESP of <10 mmHg.

Conclusion: EGJ distensibility is impaired in patients with recurrent symptoms. EGJ distensibility correlates well with esophageal emptying and recurrent symptoms, whereas LESP does not. Therefore, EGJ distensibility might be a better parameter to evaluate treatment in achalasia. However, whether an impaired EGJ distensibility is predictive of treatment failure remains to be studied.

Effect of stepwise gastric band adjustment on esophageal motility in obese patients

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Placement of an adjustable gastric band (allowing for postoperative adjustments of intraband volume) is an effective surgical treatment for obesity. However, some patients develop severe dysphagia, which may lead to esophageal complications and/or therapy failure. This study aimed to assess the effect of band placement and stepwise adjustment of the band on esophageal motility. Obese patients (BMI > 35 kg/m2) underwent high-resolution manometry (HRM) of the esophagus before and 6 weeks after gastric band placement. During the postoperative assessment (within 2 months after surgery) HRM was combined with simultaneous intraband pressure measurement at different filling volumes (range 0-8 ml, steps of 1 ml). In the manometric recordings percentage of peristaltic waves, peristaltic amplitude, distal contractile integral (DCI) and intrabolus pressure (IBP) were measured. Dysphagia for liquid and semi-solid food was scored by the patients using a visual analogue scale. In total, 15 patients (33% male, mean age 40.9 ± 10.2 years) had a mean preoperative weight of 128.8 ± 17 kg (BMI 42.0 ± 2.7 kg/m2). The percentage of normal swallows was 66% before and 56% after band placement (p=0.097). After band placement, DCI decreased from 1085.3 ± 1101.5 mmHg.cm.s to 507 ± 359.4 mmHg.cm.s (p=0.051). Stepwise gastric band filling was accompanied by an increase in DCI, IBP and intraband pressure: IBP increased from (mean) 4.3 mmHg at 1 ml to 31.1 mmHg at 8 ml; DCI increased from (mean) 766 mmHg.cm.s. at 1 ml to 7231 mmHg.cm.s at 8 ml; intrabrand pressure increased from (mean) -109.1 mmHg at 1 ml to 150.2 mmHg at 8 ml. On average, patients noticed dysphagia for semi-solid food at a mean volume of 6.5 + 1.7 ml, corresponding to an intraband pressure of 145.3 + 88.5 mmHg and an IBP of 24.4 + 17.4 mmHg. At that time, the DCI had increased to more than 5000 mmHg (criterion for hypertensive peristalsis) and the IBP was > 15 mmHg in 6/15 (40%) of the patients.
Conclusions: Band placement slightly impairs esophageal peristalsis. Stepwise filling of the band leads to a progressive increase in IBP and DCI, reaching pathological values in 40% of the patients at volumes >6 ml. This increase is associated with perception of impaired esophageal transit.

Azitromycin reduces the number of acid reflux episodes by changing the position of the gastric acid pocket

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The risk for acidic reflux is mainly determined by the position of the gastric acid pocket. In a recent study, treatment with Azitromycin (AZI) resulted in a reduction of acidic reflux events in patients after lung transplantation (Mertens et al, Dig Dis Sci, 2009, 972-9). The aim of this study was to examine whether AZI has similar effects on acidic reflux in patients with gastroesophageal reflux disease (GERD) and whether this reduction was associated with a change in the position of the gastric acid pocket. Twenty patients with GERD were included (13M 7F, age 55.8 yrs (45-67)), of whom 7 had a large hiatal hernia (>2cm) (L-hh) and 13 had a small or no hiatal hernia (S-hh). Patients were invited to undergo high resolution manometry (HRM) and pH-impedance on 2 separate study days. One week before each study day, acid suppressive therapy was stopped for 1 week and patients were randomized to AZI 250 mg/day or placebo (Plac) for 3 days in a cross-over manner. After a standardized meal (550 kcal), reflux episodes were detected using concurrent HRM and pH-impedance during 2 hours. The acid pocket was visualized using scintigraphy after i.v. injection of 350 MBq ^{99m}Tc-pertechnetate, and was classified as above, at the level or below the diaphragm for each reflux event using the position of the diaphragm on HRM and radionuclide markers on the catheter. AZI had no effect on the total number of reflux episodes compared to Plac (13.8±2.0 vs 14.0±1.7 resp). However, the number of acid reflux events (AZI 5.6±1.8 vs Plac 8.0±2.2, $p < 0.01$), as well as postprandial acid exposure (AZI 10.5±3.8% vs Plac 5.9±2.5%, $p < 0.014$) were significantly reduced by AZI compared to Plac. This effect resulted mainly from reduction of acid reflux episodes in S-hh patients (S-hh: AZI 1.7±0.5 vs Plac 3.7±1.0, P<0.05 l-HH: AZI 14±3.6 vs Plac 17±5.1 P=NS). Acid reflux occurred mainly when the acid pocket was located above (117 of 129 reflux episodes (91%)) or at the level (103 of 169 (62%)) of the diaphragm. Treatment with AZI was associated with a more distal position (sub-diaphragmatic) of the acid pocket compared to Plac in S-hh (subdiaphragmatic position: AZI 89 of 122 (73%) vs Plac 66 of 123 (54%) reflux episodes, P=0.002, Chi-square) but not in L-hh patients (AZI 14 of 120 (12%) vs Plac 17 of 120 (14%) P=0.86, Chi-square).
Conclusion: Relocation of the acid pocket to a more distal position by Azitromycin leads to a reduction in acid reflux episodes in patients with a S-hh. These data indicate that modulation of the acid pocket has an impact on the acidity of the refluxate, further confirming the importance of the position of the acid pocket in the pathogenesis of GERD.

Response of chronic constipation symptoms to prucalopride treatment and relationship with patient satisfaction

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Introduction/objectives: Prucalopride (PRU) is a selective 5-HT_4 agonist, effective and approved in EU for treatment of chronic constipation (CC) in females in whom laxatives do not provide adequate relief. Aims&Methods: The aim of this study was to assess the meaningfulness of changes in constipation symptoms and patient satisfaction after 4 weeks of treatment with placebo, PRU 2 mg or 4 mg. In addition, the relationships between changes in symptom scores and patient satisfaction were explored. Symptoms of CC were assessed in 1552 female subjects of 3 identical pivotal trials. Subjects were selected if treated for at least 21 days and with data at base (BL) and 4 weeks of treatment. Symptom severity was evaluated by the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire, a 12-item self-report instrument with abdominal (4 items), rectal (3 items) and stool (5 items) symptom subscales. Patient satisfaction with bowel habit and treatment was evaluated by the 5-item subscale of the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL). The meaningfulness of changes in the PAC-SYM items and patient satisfaction was assessed by the effect size (ES), i.e. mean change from BL divided by the standard deviation of the BL value. The relationship between changes after treatment with PRU in PAC-SYM items and patient satisfaction was evaluated using partial least squares path modeling (PLSPM).RESULTS: At BL the mean symptom severity score was “moderate” for abdominal symptoms, “severe” for stool symptoms, and “mild” for rectal symptoms. Treatment with PRU 2-4 mg resulted in a substantial relief of all symptoms with ES varying from moderate (ES: 0.5-0.8) to large (ES>0.8) and with the largest ES for the abdominal bloating and discomfort symptoms for both doses of PRU. Analysis of the 3 subscales showed that the ES of PRU were large (>0.8) for both the abdominal and stool symptoms. Comparison between placebo and PRU of the cumulative distributions of the changes from base showed that PRU provides a consistent benefit among patients. PRU treatment also resulted in large ES of patient satisfaction, with regularity of bowel movement frequency as the most responsive item. PLSPM showed that improvement in patient satisfaction can largely be attributed to relief of abdominal and stool related symptoms (r=0.6).
Conclusion: Prucalopride is highly effective in relief of abdominal and stool related symptoms. Relief of these symptoms is associated with a substantial improvement in patient satisfaction with bowel habit and treatment.

Best response distribution of 12-week treatment with prucalopride (Resolor) in patients with chronic constipation: combined results of three randomised, double-blind, placebo-controlled phase III trials

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Introduction/objectives: Treatment of severe chronic constipation (CC) is suboptimal. Prucalopride (PRU) is a selective high affinity 5-HT_4 receptor agonist, first representative of new chemical class (dihydro-benzofurancarboxamide compounds), developed for CC treatment. This study evaluates the combined efficacy results of PRU in 3 identical pivotal, randomised, placebo (PLA)-controlled trials. The objective of each trial was to compare the efficacy and safety of a 12-week once daily treatment of 2 mg or 4 mg PRU with PLA in CC. Aims & Methods: All 3 trials, 2 in US and one in Europe, Canada, Australia and South Africa, were of identical design with 3 parallel treatment groups: PLA, PRU 2 mg and PRU 4 mg. A 12-week treatment phase followed a 2-week run-in. For research purposes a most stringent primary endpoint was selected: the % of patients with an average of ≥ 3 spontaneous complete bowel movements (SCBM) per week over a 12-week treatment period (i.e. normalisation of bowel movements). Clinical benefit could also be present in patients who did not meet this criterion but satisfied other efficacy endpoints. Patients' best response was derived from (in order of importance): an average increase of ≥ 1 SCBM/week, an improvement of ≥ 1 point on a satisfaction scale (validated PAC-QOL 5-point subscale), an increase of ≥ 1 SBM or an increase of ≥ 1 BM. Results: A total of 1924 ITT patients were included; 89% female, average age 47 years, average duration of constipation 20 years. During the 2-week run-in 57% of the patients had no SCBM. In each individual trial the results for the primary and secondary endpoints were significantly better for both PRU groups compared to PLA.

	Placebo (N=645)			PRU 2mg (N=640)			PRU 4mg (N=639)		
	n	%	Cum %	n	%	Cum %	n	%	Cum %
≥3 SCBM/Week	73	11.3	11.3	151	23.6	23.6	158	24.7	24.7
Increase avg SCBM ≥1	82	12.7	24.0	115	18.0	41.6	124	19.4	44.1
Impr ≥1 Satisfaction	54	8.4	32.4	92	14.4	55.9	92	14.4	58.5
Increase avg SBM ≥1	106	16.4	48.8	109	17.0	73.0	103	16.1	74.6
Increase avg BM ≥1	64	9.9	58.8	31	4.8	77.8	35	5.5	80.1

Thus, in addition to the response on the primary endpoint almost 75% of patients had clinical benefit from treatment with PRU with at least an increase of ≥ 1 SBM.
Conclusion: In addition to primary response rates of about 24% with both 2 and 4 mg PRU, another 50% of patients had clinical benefit of at least an increase of ≥ 1 SBM per week.

Disclosure of Interest: V. Stanghellini Consultancy for: Movetis NV, L. Vandeplassche Other: Employee Movetis NV, R. Kerstens Other: Employee Movetis NV

Tissue damage and brain activation in postoperative ileus

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Postoperative ileus (POI) results from intestinal handling induced inflammation.We previously demonstrated that this inflammation is confined to the manipulated intestine,leading to activation of visceral afferents and brain stem nuclei such as the nucleus of the solitary tract (nTS) and the motor nucleus of the vagus nerve. Other groups however report a more generalized inflammation involving non-manipulated areas of the intestine. We hypothesized that differences in intensity of intestinal manipulation and accompanying tissue damage may explain this discrepancy, and therefore compared the degree of inflammation, tissue damage and brain activation after different methods of intestinal manipulation. Mice were subjected to laparotomy (L); gentle Manipulation using a device enabling the application of a constant pressure of 9 grams (gentleM); or more intense Manipulation by rolling compression of the intestine (intenseM). 1h later, tissue damage was assessed by determining plasma levels of Ileal fatty acid-binding protein (IL-FABP). 24h after surgery intestinal transit was determined and the inflammatory response was assessed by intestinal IL-6 production and the number of MPO-positive cells in the intestinal muscularis. In addition, the brainstem was collected to determine brain activation using c-Fos expression. Plasma IL-FABP levels were significantly elevated in mice subjected to more intense manipulation (intenseM: 286±80, gentleM: 2±1, L: <1 ng/ml, p=0.0005) at 1h. In line, intenseM resulted in a more pronounced delay in intestinal transit after 24h (geometric center: intenseM: 3.8±0.2, gentleM: 6.3±0.8, L: 8.9±0.7,p=0.0001).This was associated with increased neutrophil recruitment (intenseM: 114±18, gentleM: 94±17, L: 1±1 cells/mm2, p=0.0001) as well as increased IL-6 production (11.4±0.9 vs 7.5±0.4 vs 5.6±0.3 pg/mg protein,p<0.0001). The number of c-Fos positive neurons in the nTS&area postrema were significantly increased after intenseM 191±25&64±13, compared with gentleM 76±19&26±4 and L 31±4&16±3 (respectively p<0.0001&p=0.0014).
To conclude:1.More intense manipulation leads to tissue damage and increased inflammation resulting in more severe POI. 2.Intense handling of the intestine is associated with enhanced c-Fos expression in the area postrema. As activation of the area postrema indicates systemic release of mediators in the circulation, our data suggest that tissue damage following intestinal manipulation contributes to a more systemic inflammatory response also affecting non-handled intestine. Our data further stress the need of standardization of intestinal handling in animal models of POI.

Effect of probiotic treatment on visceral hypersensitivity in Irritable Bowel Syndrome

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Alterations in gut microbiota composition and visceral hypersensitivity have been proposed as pathophysiological factors in Irritable Bowel syndrome (IBS). Visceral hypersensitivity is a hallmark of IBS, present in up to 60% of IBS patients. Probiotics are considered to have therapeutic potential in IBS with respect to control of symptoms. Animal studies point to a beneficial effect of lactobacilli strains on visceral perception, but human data in IBS are lacking. In a larger study on the effect of a probiotic dairy product containing Lactobacillus casei strain Shirota (LcS) on IBS symptoms, we performed a side study to evaluate visceral perception in IBS patients. IBS patients between 18 and 65 years of age, fulfilling the Rome II criteria, were included in a randomized placebo controlled double blind trial. Probiotic and placebo product were provided by Yakult Europe, Almere, NL. Patients had to take 2 bottles daily for 8 weeks, containing at least 6.5 x 10^9 CFU living Lactobacillus casei Shirota per bottle (65 ml). Rectal perception was studied at week 0 (before intervention) and week 8 (at the end of intervention) using a barostat, with a phasic ascending pressure distension protocol. Perception of urge and pain was scored on a Visual Analogue Scale (0-100 mm). Dynamic compliance was calculated by dividing the highest change in volume during a pressure step by the change in pressure.Of the 80 patients included in the main study, 21 patients agreed to participate: 8 patients (5F; 40 ± 16 yrs) in the probiotic and 13 patients (7F; 43 ± 12 yrs) in the placebo group. Demographic data did not differ between treatment groups. Rectal compliance did not differ significantly before and after treatment for both treatment groups (probiotic week 0: 33 ± 29 ml/mmHg; probiotic week 8: 33 ± 22 ml/mmHg; placebo week 0: 25 ± 18 ml/mmHg; placebo week 8: 27 ± 21 ml/mmHg). In the probiotic group, perception of urge during the highest pressures (32-40 mmHg) did decrease significantly in week 8 compared to week 0 (from 65 ± 27 mm to 53 ± 23 mm respectively, $p < 0.05$), in contrast to the placebo group, where no difference in urge perception scores could be detected after treatment (55 ± 24 mm; 50 ± 22 mm respectively). Pain scores at higher pressures were not different between groups nor after probiotic or placebo compared to before treatment.
Conclusions: Treatment with LcS in IBS patients did not affect pain perception scores but beneficially and significantly influenced urge perception scores

HSPA6 and HSPA1B are smoke inducible genes that reside in Ulcerative Colitis susceptibility loci

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Introduction. Cigarette smoking has diametrically opposite effects on inflammatory bowel diseases, aggravating Crohn's Disease (CD) while ameliorating Ulcerative Colitis (UC). However, the mechanisms by which cigarette smoke modulate these diseases are poorly understood. Recent Genome Wide Association Studies have identified many susceptibility loci for UC, but the causative mutation or gene involved is not known yet. We hypothesize that cigarette smoke interacts with some of the UC-associated genes. Aim: To find genes associated with UC that are regulated by smoke. Materials & Methods: Jurkat (T-lymphocytes) and DLD-1 (colon epithelial cells) cells were exposed to Cigarette Smoke Extract (CSE), which was obtained by diffusing cigarette smoke through cell culture medium. The gene expression profiles of both CSE-treated and control cells were determined using Illumina microarray. Genes in proximity to UC-associated SNPs were retrieved from recent meta-analyses. The genes that were differentially expressed in CSE-exposed cells were compared to the UC-associated genes using the nuID dataset containing universal RNA-probe and gene ID's. Micoroarray data were confirmed by qPCR. ResultsThe microarray showed smoke induced expression of several Heat Shock Proteins (HSPs): HSPA1A, HSPA4L, DNAJB9, DNAJB4, DNAJB6, DNAJB4, DNAJA1, DNAJB1, HSPH1, HSPA1B and HSPA6 in DLD-1 cells (FDR < 1 %) and HSPA6, HSPH1, HSPA1B, DNAJB1 in Jurkat cells (FDR < 1 %). Furthermore, protein folding pathways, one of the HSP functions, are significantly influenced according to DAVID, Metacore, ErmineJ and GSEA databases.The mRNA of HSPA6 (Limma log2 fold change in DLD-1 20,3 and in Jurkat 9,1) and HSPA1B (Limma log2 fold change DLD-1 12,0 and Jurkat 12,9) was differentially expressed in both DLD-1 and Jurkat cells (microarray, FDR 1 < %). These fold changes were confirmed by qPCR. Interestingly, HSPA6 and HSPA1B are situated proximate to the UC-associated SNPs rs1801274 and rs9268853, respectively.
Conclusion. Our data show for the first time that Heat Shock Proteins may play a role in susceptibility to UC and that smoke-induced expression of specific HSPs may be responsible for the beneficial effects of smoke on UC.

Tissue factor-dependent chemokine production aggravates experimental colitis (MLDS project WO 06-02)

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Tissue factor (TF), a 47-kD transmembrane receptor, is traditionally known as the initiator of the blood coagulation cascade. However, TF is not only involved in thrombotic events associated with acute exacerbations of inflammatory bowel disease (IBD) but this coagulation factor also seems to exert an import role in the inflammatory process. Considering the pivotal role of the inflammatory response in IBD, we hypothesized that TF would play a detrimental role in IBD. To prove or refute this hypothesis, we assessed whether genetic ablation of TF expression would affect experimental colitis. To this end, wildtype and TF deficient (TFlow) mice were subjected to a state of the art DSS-induced experimental colitis model. To determine whether TF exerts its detrimental effects in a coagulation-(in)dependent manner, we also treated wildtype with the anticoagulant dalteparin before and during experimental colitis. Importantly, wildtype mice developed colitis as evident from weight loss, reduced length and increased weight of the colon, increased cytokine levels (both on the protein and mRNA level) and an increased disease score. Although the TFlow animals did develop colitis as well, it was clearly not as severe as in the wildtype animals. Most notably, TFlow mice had less oedema, lower neutrophil numbers at the site of inflammation, reduced inflammatory cytokine levels and diminished coagulation as compared to wildtype mice. The detrimental effects of TF were (largely) independent of its coagulant activity as dalteparin treatment did not limit experimental colitis. Instead we show that TF exerts its effect locally within the inflamed colon dependent on its signaling properties. Indeed, 'ex vivo' stimulation of small pieces of colon obtained from wildtype mice with FVIIa (i.e. TF ligand) significantly induced the production of the neutrophil chemoattractant KC in a dose dependent manner. Similar experiments using TFlow colons also showed increased KC production but this increase was dramatically reduced compared to wildtype colon.
Overall, our data show that TF plays a detrimental role in experimental colitis in a coagulation independent manner. Instead, TF-dependent signal transduction in colon epithelial cells leads to KC production thereby provoking neutrophil influx with subsequent inflammation and organ damage.

Formation of tertiary lymphoid tissue in dextran sulfate sodium induced colitis is partially dependant on LTa_1b_2-LTbR axis

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Patients with inflammatory bowel disease (IBD) suffer from chronic inflammation of the intestine, which may lead to the formation of lymphoid aggregates that closely resemble secondary lymphoid tissue. The formation of secondary lymphoid tissue is dependent on the lymphotoxin alpha1 beta2 - lymphotoxin beta receptor signaling axis. Hematopoietic lymphoid tissue inducer (LTi) cells express lymphotoxin alpha1 beta2 (LTa_1b_2) which binds to the lymphotoxin beta receptor (LTbR) expressed on stromal organizers cells, and leads to the induction of chemokines (CXCL13 and CCL21) and adhesion molecules (VCAM-1, ICAM and MAdCAM-1). These molecules serve to attract and retain additional hematopoietic cells leading to the formation of secondary lymphoid tissue. Here we show, using dextran sulfate sodium (DSS) induced colitis, that stromal cells in the acute inflammatory setting have the ability to upregulate LTbR expression along with CXCL13, CCL21, VCAM-1 and MAdCAM-1. In the more chronic setting tertiary lymphoid tissues were detected in inflamed colons and consisted of tightly clustered B cell follicles with distinct T cell areas. Surprisingly, these structures could also be found at the chronic phase of DSS colitis in $LTa^{-/-}$ mice, although the B cell areas were devoid of follicular dendritic cells (FDCs) and germinal centers (GCs). These results show that lamina propria stromal cells become activated upon damage to the epithelial barrier and function as organizer cells to locally form lymphoid tissue. This process is only partially dependent on the LTa_1b_2-LTbR axis and must involve alternate pathways.

Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease

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Previous studies have reported a chemopreventive effect of 5-aminosalicylic acid (ASA) therapy for colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD). This is supposed to be related to its anti-inflammatory and pro-apoptotic properties as well as its inhibitory effect on cell growth and survival. Thiopurines (azathioprine and 6-mercaptopurine) have also anti-inflammatory properties, but, in contrast, have been associated with an increased risk of developing malignant lymphoma and other malignancies. In the present study, the association between thiopurine and 5-ASA therapy and advanced neoplasia risk (high-grade dysplasia and colorectal cancer) was investigated in a large cohort of IBD patients in the Netherlands.Patients with IBD were identified in an anonymized computerized database of one of the Dutch health insurance companies, including 1.2 million policyholders. From this database, information regarding type of drugs and number of dosages provided to patients were collected between January, 2001 and December, 2009. Each IBD patient was linked to the Dutch nationwide pathology archive (PALGA) to verify the IBD diagnosis and to determine whether a patient had developed advanced neoplasia. Cox proportional hazard regression analysis was used to calculate the risk of advanced neoplasia in patients with and without thiopurine or 5-ASA use. A total of 2605 patients with a confirmed IBD diagnosis were included in this study. Of these, 981 patients (38%) used 5-ASA, 315 patients (12%) used thiopurines, 459 patients (18%) used both 5-ASA and thiopurines and 850 patients (33%) used none of these drugs. No statistically significant differences were found for type of IBD, gender, age, duration of IBD and extent of IBD between these groups. Thirty-one patients (1%) developed advanced neoplasia during 16,568 person years of follow-up. Of these, 12 patients (39%) had used 5-ASA, 2 (7%) thiopurines and 1 (3%) both drugs. Increasing age and disease involvement of more than 50% of the colon were associated with an increased risk of developing advanced neoplasia (adjusted hazard ratio (HR) 1.07, 95% confidence interval (CI) 1.04-1.11 and adjusted HR 5.88, 95% CI 2.00-17.3, respectively). Thiopurine use was associated with a significantly decreased risk of developing advanced neoplasia (adjusted HR 0.10, 95% CI 0.01-0.73). 5-ASA therapy had also a protective effect on developing advanced neoplasia, but this was not statistically significant (adjusted HR 0.51, 95% CI 0.20-1.26).
Conclusion: Thiopurine use protects colitis patients against the development of advanced neoplasia. The effect of 5-ASA appeared to be less pronounced.

Different Risk Factors for Colitis Associated Colorectal Cancer in Ulcerative Colitis and Crohn's Disease

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Background: Patients with inflammatory bowel disease (IBD) are at an increased risk of developing colorectal cancer (CRC). However, the risk might not the same for every patient. It is not exactly known which factors increase CRC risk in subgroups of IBD, i.e., ulcerative colitis (UC) and Crohn's disease (CD). This information could help in further refining surveillance strategies to prevent advanced neoplasia in high risk patients.Aim: To identify risk factors for IBD-associated CRC in UC and CD.Methods: We designed a retrospective case-control study. All IBD-associated CRC cases diagnosed between 1990 and 2006 in 7 tertiary referral centers in the Netherlands were selected via the nationwide pathology database (PALGA). This tool was also used to identify controls matched to our referral population in a 1:2 ratio. Follow-up started Jan. 1, 1990 for all cases and controls. We chose this fixed date to adjust for varying incidence IBD diagnosis dates. All patient variables at that time point were collected from patient charts. Disease duration until Jan. 1, 1990 was used as a variable in the multivariate analysis. Disease extent was measured as more or less than 50% colonic inflammation for both UC and CD. Hazard ratios (HR) were calculated for patient variables by multivariate Cox regression. The endpoints were CRC and end of follow-up (proctocolectomy, end of study or lost to follow-up).Results: In total, 118 IBD-associated CRCs were diagnosed since Jan. 1, 1990. We identified 206 controls. Mean follow up after January 1st 1990 was 4059 days. The risk of CRC in CD was only half of the risk in UC (HR 0.5; 95%CI 0.3-0.7). Risk factors for CRC in UC were disease extent (>50% of the colon) (HR 3.0; 95%CI 1.4-6.5), presence of pseudopolyps (HR 2.5; 95%CI 1.2-5.2) and colonic stenosis (HR 5.2; 95%CI 2.6-10.3), whereas 5-ASA use >3 months was protecting (HR 0.4; 95%CI 0.2-0.8). A risk factor for CRC in CD was disease extent >50% of the colon (HR 4.7; 95%CI 1.6-14.1), whereas 5-ASA use >3 months was protecting (HR 0.4; 95%CI 0.2-0.9). The co-presence of primary sclerosing cholangitis was also associated with an increased hazard ratio but this was not statistically significant (UC: HR 1.7; 95%CI 0.6-4.3, CD: HR 1.8; 95%CI 0.2-14.8).
Conclusion: Disease extent is an important risk factor for in both UC and CD for developing CRC, whereas 5-ASA medication is protective in both disorders. Pseudo-polyps and colonic stenosis are only associated with CRC development in patients with UC.

5-ASA inhibits Phospolipase D-dependent mammalian Target of Rapamycin signaling in colorectal cancer

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Mesalazine or 5-aminosalicylic acid (5-ASA) is a cornerstone in the induction and maintenance of remission of patients with ulcerative colitis. In addition to its anti- inflamematory activity it may also protect against the development of inflamemation-associated colorectal cancer. The molecular mechanism of the anti-inflammatory and anti-cancer actions of 5-ASA remain to be fully determined. Here we focus on mammalian Target of Rapamycin (mTOR), an important regulator of cell cycle progression, and examine the anti-proliferative effects of 5-ASA on colorectal cancer in vitro and in vivo and aim to dissect the signal transduction events that lead to 5-ASA mediated inhibition of proliferation in colorectal cancer cells. We examined the effect of 5-ASA on mTOR signaling in a panel of cancer cell lines originating from different tissues. Effects of 5-ASA on the pathways that control mTOR activity were studied in detail in two different colorectal cancer cell lines, using western blot, siRNA, a phospholipase D (PLD) activity assay and proliferation assays. The phosphorylation status of mTOR and its downstream target, ribosomal protein S6, was studied in colorectal cancer biopsies taken from patients before and after topical 5-ASA treatment.We found that treatment of colorectal cancer with 5-ASA inhibited mTOR signaling in vitro and in vivo. This effect seemed to be generic, as 5-ASA treatment also reduced mTOR signaling in several cancer cell lines originating from tissues other then colon. In colorectal cancer cells, 5-ASA did not affect any of the pathways known to control the tuberous sclerosis complex (TSC), a major regulator of mTOR activity, including the AMPK, PKB/Akt and MAPK pathways. Indeed the 5-ASA effect was independent of TSC-integrity as assessed by knockdown of TSC-component TSC2. Using inhibitors and knockdown experiments, we were able to show that in colorectal cancer cells both proliferation and mTOR activity depended on PLD, an enzyme that generates phosphatidic acid (PA). 5-ASA treatment inhibited both PLD-activity and proliferation, and these effects could be rescued with exogenous PA.
We conclude that 5-ASA interferes with proliferation of colorectal cancer cells via inhibition of PLD-dependent generation of PA and consequent loss of mTOR signaling.

Transcriptomic profiles in colon tissue from inflammatory bowel diseases patients in relation to N-nitroso compound exposure and colorectal cancer risk

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N-nitroso compounds (NOC) have been suggested to play a role in human cancer development but definitive evidence is still lacking. There is also evidence that intestinal inflammation stimulates endogenous NOC formation, which may explain the increased colorectal cancer (CRC) risk associated with inflammatory bowel disease (IBD). In this study we therefore investigated gene expression modifications induced in human colon tissue in relation to NOC exposure to gain insight in the relevance of these compounds in human CRC development. A non-randomized case-control study was performed with IBD patients diagnosed with ulcerative colitis (n = 37) and irritable bowel syndrome patients who served as controls without inflammation (n = 44). Strong transcriptomic differences were identified in colonic biopsies from IBD patients compared to controls that enhance the understanding of IBD pathophysiology. Fecal NOC levels were slightly but not significantly increased in IBD patients, suggesting that inflammation did not strongly stimulate NOC formation. By relating gene expression changes of all subjects to fecal NOC levels, we did, however, identify a NOC exposure-associated transcriptomic response that suggests that physiological NOC concentrations induce genotoxic responses and chromatin modifications in human colon tissue, both of which are linked to carcinogenicity. In a network analysis, chromatin modifications were linked to 11 significantly modulated histone genes, pointing towards a possible epigenetic mechanism that may be relevant in comprehending the molecular basis of NOC-induced carcinogenesis. We conclude that NOC exposure is associated with gene expression modifications in the colon that may increase CRC risk in humans.

Colorectal cancer surveillance in patients with longstanding ulcerative colitis and colonic Crohn's disease: actual practice does not match surveillance guidelines

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The incidence of colorectal cancer (CRC) in patients with longstanding ulcerative colitis (UC) and colonic Crohn's disease (CD) is increased. Therefore, various organizations of gastroenterologists have published surveillance guidelines for inflammatory bowel disease (IBD)-patients. Dutch surveillance guidelines recommend to start endoscopic surveillance 8-10 years after IBD-onset. Colonoscopy should be performed every three years during the first decade of surveillance, every two years during the second decade of surveillance and annually during the third (and subsequent) decade. During each colonoscopy 36 random biopsies should be taken. However, despite the available guidelines, daily practice and survey-studies suggest that most gastroenterologists do not follow the recommendations. The aim of this study was to analyze actual endoscopic surveillance practice in IBD-patients in a large teaching hospital. Information of various aspects of endoscopic surveillance (as mentioned above) was obtained by analyzing medical files of 345 adult IBD-patients (CD 174, UC 171) with a disease duration of at least 10 years. Furthermore, all patients were checked for colonic dysplasia and carcinomas, using a national pathology database (PALGA). In total 238 (69%) patients received at least one surveillance colonoscopy during a mean follow-up period of 16 years. Half of all patients received their first surveillance colonoscopy within 14 years after diagnosis. The median numbers of surveillance colonoscopies per patient were 1.0 (Inter Quartile Range (IQR) 0.0-2.0), 2.0 (IQR 1.0-2.9) and 1.8 (IQR 0.5-2.6) during respectively the first, second and third decade of the surveillance. The median number of random biopsies per surveillance colonoscopy was 10 (IQR 9-12). Factors associated with an earlier start of surveillance were UC, a more extensive disease location and the co-existence of primary sclerosing cholangitis (PSC). In total, only 8 (2.3%) cases of dysplasia (sporadic adenomas excluded) and 4 (1.2%) cases of CRC were identified. Conclusions: actual endoscopic surveillance practice in patients with ulcerative colitis and colonic Crohn's disease is not conform available guidelines. This may potentially lead to an increased mortality from colitis-associated CRC. However, the risk for developing colitis-associated CRC may be overestimated. Further research on the epidemiology of colitis-associated CRC and reevaluation of surveillance strategies is recommended to further improve IBD-patient care.

Osteoporosis in adult patients with inflammatory bowel disease is more related to classical than to disease-specific risk factors

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Patients with inflammatory bowel disease (IBD) are at increased risk of osteoporosis. Case finding of low bone mineral density (BMD) is hampered by the lack of knowledge concerning its risk factors in these patients. In 2008, a Dutch IBD-guide (IBDG) stated a high-risk profile of osteoporosis based on disease-specific risk factors. This study evaluates the prevalence of low BMD and its risk factors in a large sample of adult IBD patients. IBD outpatients were prospectively screened using the IBDG-criteria. Patients were classified as high-risk and DXA-scanning was advised if they met one or more of the stated IBDG-criteria: postmenopausal state, men >55 years, systemic corticosteroid treatment for at least 1 year and >7.5mg daily for at least 6 months, low-energy fracture or multiple fractures in the past, IBD since childhood, lactose/calcium deficient diet, or inflammation of the small intestines (in Crohn's disease). Furthermore, risk factors of osteoporosis in the general population were assessed according to WHO guidelines (i.e. vertebral fracture or corporal collapse in the past, decrease of body length or scoliosis, low body weight or weight <60 kilogram). Determinants were analyzed using Mann-Whitney U or unpaired T-test (continuous) and χ^2-test (categorical, [SPSS17.0, significance set at <0.05]). Independent risk factors of low BMD (osteopenia and osteoporosis) were assessed using a logistic regression model. Two-third (n=212) of the 316 included patients were classified as high-risk according to the IBDG. In the 189 patients in which DXA-scanning was performed, prevalence rates of osteoporosis and osteopenia were 10% and 43%. Based on univariate analyses, age (p<0.001), female gender (p=0.006), disease duration of IBD (p=0.003), decrease of body length or scoliosis (p=0.001), postmenopausal state (p=0.001), multiple fractures in the past (p=0.025), and low body mass index (p=0.003) were associated with low BMD. Independent risk factors for low BMD were: age (odds ratio [OR] 1.04 [95% confidence interval [CI]: 1.01-1.07]), female gender (OR 1.94 [95% CI]: 1.01-3.77), disease duration of IBD (OR 1.06 [95% CI]: 1.02-1.10), and body mass index (OR 0.88 [95% CI]: 0.81-0.96).
Conclusions: among high-risk patients, prevalence rates of osteoporosis and osteopenia are respectively 10% and 43%. By extrapolating these data to the total study population, general prevalence rates of osteoporosis (6%) and osteopenia (26%) are relatively low. Independent risk factors of low BMD are more related to classical risk factors (i.e. increase of age, female gender, and low body mass index) than to disease-specific risk factors.

Tolerability and safety of conventional thiopurines concomitantly with allopurinol in IBD-patients with a skewed thiopurine metabolism

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Background & Aim: Conventional therapeutic thiopurines, azathioprine (AZA) and 6-mercaptopurine (6-MP), are pivotal in inflammatory bowel disease (IBD) treatment, having a positive balance between efficacy and safety. Costs are relatively low. Unfortunately, up to 60% of IBD-patients discontinue thiopurine therapy, often due to gastrointestinal complaints and hepatoxicity, allegedly related to high 6-MMP levels. Addition of allopurinol to conventional thiopurines reduces enigmatically 6-MMP levels and, thus, appears to reduce adverse reactions. Material and methods: IBD-patients with a skewed thiopurine metabolism profile, arbitrarily defined as 6-MMP:6-TGN>7,5 were eligible. Treatment with full-dose conventional thiopurine had to be discontinued, due to inacceptable adverse reactions (AR), mainly hepatotoxicity, defined as ≥ grade 1 of the WHO-toxicity criteria. Subsequently, patients were treated with 100 mg allopurinol and low-dose (= 25-33% of common dose) AZA or 6-MP. All patients were stringently monitored at baseline, and at week 1, 2, 4, 6, 8, 12 (and every 12 weeks further on). Levels of 6-TGN and 6-MMP (during monotherapy) were compared with levels at 4 and 12 weeks (during combination therapy). The activity of thiopurine methyltransferase (TPMT) and xanthine oxidase (XO) were determined during monotherapy and 4 and 12 weeks after initiating combination therapy. Results: Of the 19 included patients (15 female; 16 CD and 3 UC), eleven patients were enrolled because of hepatoxicity and 8 patients due to other adverse reactions during thiopurine monotherapy. The median age at initiating allopurinol was 41 years (IQR 30-55 years) and the median duration of IBD was 2 years (IQR 1-10 years). At 4 weeks, levels of 6-TGN were increased (from 333 to 649 pmol/8x10*8 RBC; p<0,001) whereas 6-MMP-levels were decreased (from 12970 to 1217 pmol/8x10*8 RBC; p<0,001). These levels remained stable in the concurrent 8 weeks of combination therapy (p=0,2 [6-TGN]; p=0,1 [6-MMP]). Five patients (18%) had to discontinue combination therapy, all due to AR (4 weeks (IQR 1,5-7,0) median duration of combination treatment). Leukocytopenia occurred in one case, who inadvertently continued full-dose AZA. Hepatoxicity did not reoccur in 10 out of 11 patients (91%), as opposed to non-hepatotoxic AR, in which only 63% tolerates combination therapy.
Conclusion: The majority of IBD patients that fail to tolerate full dose conventional thiopurine treatment due to a skewed metabolism, can be safely and effectively treated with a low dose thiopurine in conjunction with allopurinol, inhibiting (by unexplained mechanism) TMPT-activity, besides xanthine oxidase.

Crohn's disease patients treated with adalimumab benefit from co-treatment with immunomodulators: results from a nationwide study in the Netherlands

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Concomitant use of immunomodulators (IM) in patients with Crohn's disease (CD) receiving infliximab (IFX) is associated with reduced disease activity and IFX dose escalation, probably because of reduced antibody formation against IFX. Less is known about antibody formation against adalimumab (ADA) and the effect of co-treatment with IM in ADA users. We aimed to determine whether concomitant IM use is associated with ADA treatment continuation in a nationwide 'real practice' cohort of CD patients.
Data was obtained from the 'ApotheekZorg' registry, responsible for the nationwide distribution of ADA in the Netherlands. All CD patients in the Netherlands treated with ADA between 2004 and 2010 were included in this study. Data on age, gender, hospital, dosing schedules, previous use of IFX, and concomitant use of IM (azathioprine/ 6-mercaptopurine and methotrexate) was analyzed. Treatment success was defined as ongoing prescription of ADA on July 1, 2010. Multivariate logistic regression analysis was performed to assess the association between concomitant IM use and ADA treatment success.
For a total of 2,860 CD patients, data was available (64% women, mean age 38 (SD 13) years). ADA was prescribed in university medical centers (n=1,043; 36%) and in general hospitals (n=1,818; 64%). Thirty-two percent (n=913) received thiopurines and 3% (n=95) methotrexate concomitantly, whereas 55% (n=1556) was previously treated with IFX. The induction dose was 160-80 mg per week in 1,650 (58%) patients, 80 mg in 722 (25%) patients and 40 mg in 442 (17%) patients. After a median use of 12 months, 2,129 (74%) patients were on 40 mg ADA and 19 (1%) on 80 mg every other week, and 581 (20%) on 40 mg per week. During follow-up, 771 (27%) patients discontinued treatment after a median use of 6 months. Co-treatment with either thiopurines (adjusted (adj.) odds ratio (OR) 0.35, 95%CI 0.28-0.43) or methotrexate (adj. OR 0.46, 95%CI 0.27-0.79), and male gender (adj. OR 0.69, 95%CI 0.57-0.83) were associated with a lower risk for discontinuation, whereas previous IFX treatment (adj. OR 1.38, 95%CI 1.56-1.64) and treatment in a academic setting (adj. OR 1.30, 95%CI 1.08-1.57) were associated with a higher risk for discontinuation. Patients receiving lower induction doses were not more prone to discontinuation of ADA than those receiving a higher induction dose (adj. OR 0.96, 95%CI 0.80-1.15).
In a real practice population of all ADA users in the Netherlands, 27 % discontinued therapy. Concomitant use of IM was independently associated with a decreased risk of discontinuation. Like in IFX, this effect could well be attributed to a reduced risk of antibody formation against ADA.

Quantitative comparison of the neutralizing capacity of therapeutic anti-TNF-a drugs and the cross-reactivity of anti-anti-TNF-a antibodies

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TNF-α blocking drugs, such as infliximab (IFX) and adalimumab (ADA), are highly effective in the treatment of Crohn's disease (CD) and rheumatoid arthritis (RA). There is no head to head comparison between these drugs. Furthermore many patients develop antibodies against these drugs, even when cotreated with immunosuppressives, which leads to loss of response and/or adverse infusion reactions. It is unclear whether the anti-anti-TNF-α antibodies neutralize the anti-TNF-α drug and whether they show cross-reactivity towards other available anti-TNF-α therapeutics. Here, we compared the TNF-α-neutralizing capacity of all available anti-TNF-α drugs, as well as the antigenic cross-reactivity of anti-anti-TNF-α antibodies. We developed a sensitive and quantitative TNF-α sensor assay using HeLa 8D8 cells that express the Green Fluorescence Protein (GFP) under control of an NF-κB response element. GFP expression was quantified by flow cytometry. All commercially available anti-TNF-a drugs and the F(ab)2 fragment of infliximab (IFX-Fab) (dose range 0-40 ng/ml) were tested for their TNF-α-neutralizing capacity. In addition, patient sera with specific anti-anti-TNF-α antibodies were tested for their potential to block the activity of anti-TNF-a drugs. TNF-α (1 ng) strongly induced GFP expression in Hela 8D8 cells. Higher concentrations of the first generation anti-TNF-α drugs IFX and ADA were required to neutralize TNF-α compared to etanercept (ETA), certolizumab and golimumab. Serum of 11 CD patients and 10 arthritis patients with established anti-IFX and anti-ADA antibody titers blocked the TNF-α-neutralizing properties of IFX and ADA, respectively, but did not show cross-reactivity. Serum of 3 patients with loss of response or non response to ETA did not show a blocking effect on TNF-α neutralizing properties of ETA, suggesting that the loss of response in these patients was not related to the formation of anti-ETA antibodies.
Conclusions: The second generation anti-TNF-a drugs show increased TNF-α neutralizing potential. Anti-IFX and anti-ADA antibodies do not show antigenic cross-reactivity. Patients with loss of response due to anti-anti-TNF-α antibody formation may still respond to other anti-TNF-α drugs.

Naturally-occurring autoantibodies against TNF-alpha are present in sera of inflammatory bowel disease patients and influence the response to adalimumab

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Naturally-occurring auto-antibodies against tumor necrosis factor alpha (TNF-alpha) are present in sera of patients with different infectious and chronic inflammatory conditions. It is unknown whether these auto-antibodies are also present in patients with inflammatory bowel disease (IBD). Their hypothetical presence might reflect a specific TNF-alpha driven disease phenotype that would in turn have impact on the response to the therapy with anti-TNF agents. First, the aim of this study was to determine whether naturally-occurring anti-TNF auto-antibodies are present in inflammatory bowel disease patients. Second, in case of their presence, the aim was to compare the levels of these antibodies between the responders and non-responders to treatment with adalimumab. Between May 2007 and December 2009, all consecutive anti-TNF treatment naïve IBD patients with active disease and indication for anti-TNF treatment were included. The sera from patients were collected prior to start therapy with adalimumab and anti-TNF auto-antibodies were determined by ELISA. The patients were prospectively followed and their clinical response to adalimumab was assessed at month 3 of the treatment. The differences in the levels of anti-TNF auto-antibodies between responders and non-responders were compared by t-test. In total, forty-four IBD patients were included, 19 males/25 females, mean age 36 yrs (range 18-63). The indication for anti-TNF treatment was luminal disease in 39 patients, fistulae in 2 patients, extra-intestinal manifestations in 2 patients and one patient had luminal and fistulizing disease. Anti-TNF auto-antibodies were detected in 32 (73%) patients, with the mean level of 0.8 µg/mL (+-SEM 0.2 µg/mL). Thirty-seven patients (84%) were responders as assessed at month 3 of the treatment. The mean level in responders to adalimumab was significantly higher compared to non-responders (1.3+-SEM 0.3 µg/mL vs. 0.4+-SEM 0.1 µg/mL; p=0.012). Conclusion: Naturally-occurring auto-antibodies to anti-TNF are present in IBD patients with active disease. There are quantitative differences in the levels of these auto-antibodies with regards to response to anti-TNF treatment with significantly higher levels in responders.

Tolerability of shortened infliximab infusion times in patients with inflammatory bowel diseases: a single center cohort study

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Introduction: Scheduled maintenance therapy with infliximab decreases the risk of infusion reactions. Many centers have accelerated infusion times to 1 h in selected patients who tolerate 5 mg/kg infliximab infusions. Aim: To compare the tolerability of 1-h and 2-h infliximab infusions in patients with IBD in a large single center cohort. The primary analysis concerned the proportion of 1-h infusions with infusion reactions compared to the proportion of 2-h infusions with infusion reaction. In addition, we sought to identify predictors of infusion reactions. Methods: A retrospective chart analysis of all IBD patients treated with infliximab was performed. Infusions in scheduled maintenance for at least 6 months from December 1994 until March 2009 were included. All patients were treated at the infusion unit or during hospitalization under standard operating procedures.Infusion parameters were prospectively recorded. From 2004, in patients tolerating at least four 2-h infusions, infusions were given over 1 h. Infusions at start up, after a drug holiday, after a documented infusion reaction and all infusions before 2004 were given over 2 h or longer. The study was approved byour institution's ethics committee. Results: As of March 2009, 953 patients with IBD (77.6% CD, 22.4% UC) had been treated with infliximab. 474 patients met the criteria of scheduled maintenance therapy. In total, 9155 maintenance infusions were administered (4307 over 1h). No severe infusion reactions were documented. Mild acute reactions occurred in 0.6% (27/4307) of 1-h and 1.7% (80/4848) of 2-h infusions (p=0.0034).Delayed infusion reactions occurred in 0.2% of 1-h and 0.5% of 2-h infusions(p=0.277). Loss of tolerability due to infusion reactions (1-h group 2.9%versus 2-h group 4.1%) was evenly distributed (p=0.34). None of the prespecified variables (gender, disease subtype, disease duration, age at moment of first infusion, use of an induction scheme (0-2-6 weeks), maintenance therapy, concomitant immunosuppression and use of corticosteroids) were predictive of infusion reactions in a multivariate analysis.
Conclusion: In patients with IBD tolerating 2-h infusions of infliximab scheduled maintenance therapy, the infusion time can be shortened to 1 h with good tolerability. No severe reactions were observed and no predictors of infusion reactions were identified. Optimizing infusion procedures and accelerated infusion times with acceptable safety offer perspectives for a decreased impact of the treatment on activities of daily life.

Effectiveness and tolerability of maintenance methotrexate therapy in Crohn's disease patients; analysis of a referral hospital-based 10-years intercept cohort

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Background & Aim: Methotrexate (MTX) is a frequently administered immunomodulating drug for the treatment of Crohn's disease (CD). Unfortunately, limited longterm data are available. The aim of this study is to assess the maintenance effectiveness and tolerability of methotrexate (MTX) as maintenance therapy in Crohn's disease patients. Material and methods: A referral hospital-based, intercept cohort from January 1st, 2000, until January 1st, 2010 was explored to evaluate all consecutive MTX-using CD-patients. In this retrospective study, these patients were selected from a prospectively maintained database concerning all IBD-patients. MTX was initiated in patients after previous immunosuppressive therapies (mostly thiopurine, or combination with anti-TNFα), according to a step-up protocol. Therapeutic effectiveness was assessed by calculating the cumulative number of patients still using MTX with a dosage of at least 15 mg/week at 6, 12, 24 and 60 months after initiation of MTX therapy and were considered to be in clinical remission, based on global physician's assessment, laboratory, radiological and/or endoscopic findings. Reasons for discontinuation of MTX were subclassified into adverse events, ineffectiveness, patient's request, pregnancy wish and others. Results: Seventy-eight CD-patients (57 females) were included. The median duration of IBD at initiating MTX therapy was 4 years (IQR 2-13 years) with a median age of 36 years (IQR 26-45 years). Fourty-eight patients (62%) initiated MTX therapy due to an adverse reaction to thiopurines, 17 patients due ineffectiveness of thiopurines, 3 patients had an adverse reaction to combination therapy of thiopurine and a biological and in 9 patients ineffectiveness of combination therapy. MTX therapy was discontinued in 49 patients (63%) after a median duration of 33 weeks (IQR 12-99 weeks) due to adverse events (35%), ineffectiveness (39%), patient's request (10%), pregnancy wish (8%), others (6%) and 1 unknown. Median duration of MTX use in the 29 patients who continued therapy was 162 weeks (IQR 101-231 weeks). In 8 of these 29 patients a biological agent was added after initiating MTX therapy due to ineffectiveness of monotherapy with MTX. The proportion of patients still using MTX at 6, 12, 24 and 60 months was, 73%, 59%, 44% and 9% respectively.
Conclusion: After one year of MTX-therapy, effectiveness was established in 59 percent in CD patients. This percentage decreased to 9% after 5 years, mainly due to ineffectiveness or adverse reactions.

Primary sclerosing cholangitis is associated with pancolitis and not backwash ileitis

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PSC-IBD is reported to represent a distinct phenotype of IBD characterized by colitis, rectal sparing and backwash ileitis, but this has so far not been confirmed in large well-phenotyped cohorts. The aim of this study was to assess the IBD phenotype associated with PSC in a large Dutch PSC cohort using endoscopic and histo-pathological criteria. PSC cases were identified and ascertained, fulfilling well-established serological, histological and radiological criteria in 30 hospitals in The Netherlands. IBD location was recorded according to the Montreal classification. To assess the occurrence of backwash ileitis a subgroup analysis was performed in 40 cases and 80 age- and sex-matched IBD controls with at least one complete ileo-colonoscopy including terminal ileum histology, reviewing 370 endoscopy and pathology reports written between 2001 and 2010.324 (64%) of a total of 506 PSC patients had coexistent IBD, mainly ulcerative colitis (UC, 72%). 147 (80%) of the PSC-UC patients had a pancolitis, 28 (15%) a left sided colitis and eight (4%) a proctitis. Sixty (95%) PSC-Crohn's disease (CD) patients had an (ileo)colitis and three ileitis only (5%). In the subgroup analysis of 40 PSC-IBD patients twenty-seven (68%) PSC-UC patients were identified, as well as twelve (30%) PSC-CD patients and one (2%) PSC-undetermined IBD patient. Twenty-five (93%) PSC-UC patients had a pancolitis, compared to thirty-three (61%) matched UC patients ($p = 0.034$). Left sided colitis was seen in seventeen (32%) UC controls and in none of the PSC-UC patients ($p = 0.001$). Backwash ileitis was seen in only one (4%) PSC-UC patient and in none of the UC controls.
Conclusion: PSC-IBD represents a distinct IBD phenotype. The majority of Dutch PSC-UC patients have a pancolitis. In case of PSC-CD, colonic inflammation is involved in 95% of patients. Backwash ileitis is not a prominent finding in Dutch PSC-UC cases.

Immune-mediated diseases in primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease. An immune etiology is suggested by associations between PSC and inflammatory bowel disease (IBD). Not much data exist on the concomitant prevalence of other immune mediated diseases. Therefore, we studied the prevalence of concomitant immune-mediated diseases and the impact of these diseases on outcome in a large PSC cohort. We included 241 PSC patients, who were seen at the department of Gastroenterology and Hepatology at the University Medical Center Groningen between January 1990 and January 2010. Medical charts were reviewed retrospectively for relevant epidemiological and clinical data. The influence of immune mediated diseases on survival till death or liver transplantation was assessed using Kaplan-Meier curves and log-rank analysis.
Altogether 172 (71.4%) patients had concomitant immune-mediated disease. IBD, autoimmune hepatitis, and other immune-mediated diseases were present in 149 (61.8%), 15 (6.2%), and 47 (19.5%) patients, respectively. Thirty nine of these patients (22.7%) had more than one additional immune-mediated disease. The most frequent immune-mediated diseases other than IBD and autoimmune hepatitis were sarcoidosis, thyroid disease, and type I diabetes mellitus. In patients with IBD, age at diagnosis of PSC was lower than in patients who did not have IBD. In patients with additional extra-hepatic, non-IBD immune-mediated diseases, age at diagnosis of PSC was higher than in patients without these diseases. Younger age at diagnosis of PSC and concomitant IBD related to better outcome defined as survival till death or liver transplantation.
Conclusions: In a large PSC population, a high prevalence of concomitant immune- mediated diseases was found. IBD seemed to occur more often in early-acquired PSC, and the other immune-mediated diseases more often in later-acquired PSC. No effect on survival till death or liver transplantation was found for non-IBD immune mediated disease. The high prevalence of various immune related diseases in PSC further supports an important role for immunological factors in PSC pathogenesis.

Arthropathies in inflammatory bowel disease patients

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Arthropathies are a major medical problem in inflammatory bowel disease (IBD) patients. The aim of this study was to characterize arthropathies in IBD patients.A cohort of 510 consecutive IBD patients, 321 (63%) Crohn's Disease (CD), 186 (37%) ulcerative colitis (UC) and 3 (1%) indeterminate colitis, were questioned about joint pain. A complete rheumatologic examination was performed in 94 patients that reported articular complaints. Peripheral arthralgia was defined as joint pain without swelling, arthritis as joint pain and swelling. Enthesopathy was scored using the Maastricht Ankylosing Spondylitis Enthesitis Score and dactylitis was defined as a 'sausage digit'. Inflammatory back pain (IBP) was defined using the Assessment of SpondyloArthritis international Society (ASAS) criteria. The modified New York criteria were used to classify ankylosing spondylitis (AS). Human leukocyte antigen (HLA)-B27 was typed. Axial and peripheral spondyloarthritis (SpA) were defined using the recently published ASAS criteria.310/510 (61%) IBD patients suffered from joint pain. Joint pain was more frequently reported by CD than UC patients: 67% vs. 31% (OR 1.62 95% CI 1.12-2.34) and more in female than in male patients (67% vs. 34%), (OR 2.19 95% CI 1.52-3.15). 142/ 510 (28%) IBD patients reported back pain for more than three months, 272 (53%) patients had peripheral joint pain and/or swelling and 105 (21%) had back pain and peripheral joint pain and/or swelling. Of the 94 patients that were rheunatological examined axial involvement occurred in 8 (9%) patients, peripheral involvement in 45 (48%) patients and 41 (44%) patients had axial, as well as peripheral involvement. No differences in manifestations were observed between CD and UC. IBP was diagnosed in 21/94 (22%) patients and AS was found in 2 (2%) of the patients with IBP. HLA-B27 was positive in 5 (5%) patients and was more frequently seen in IBD patients with IBP than in IBD patients without IBP (26 vs. 1%). The most frequently involved peripheral arthropathies were arthralgia 82/94 (87%) and enthesopathy 19 (20%). In patients with arthralgia, the knees (25/84, 31%) and hands (19/84, 23%) were most often seen. Three (3%) patients could be classified as axial SpA and 4 (4%) as peripheral SpA.
In conclusion, joint complaints are reported by the majority of IBD patients, more frequent in CD and in female patients. Arthralgia is the most often encountered joint manifestation in IBD patients and mainly affects the knees and small joints of the hands. Joint manifestations did not differ between CD and UC. A positive HLA-B27 was more frequently observed in IBD patients with IBP.

Work disability in inflammatory bowel disease: first results from the COIN study

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Chronic work disability is an important medical and social consequence of inflammatory bowel disease (IBD) and is associated with a substantial economic burden to society. To date, only few data exist on factors predicting work disability. The study on 'Costs Of IBD in the Netherlands' (COIN) aims to assess work disability, quality of life and direct and indirect costs in a large cohort of IBD patients in the Netherlands and to determine demographic, disease and work specific factors associated with these endpoints. Here, we report the base characteristics of the first 942 patients enrolled in this trial.Between October 1st 2010 and December 1st 2010, a total of 15,000 patients with IBD were invited by post to participate in the COIN study, which consists of a base and follow up web-based questionnaire every 3 months for a total of 2 years. The base data includes questions on demographic, disease and work specific characteristics, and a health-related quality of life questionnaire (HRQoL). All data from questionnaires 'returned' until November 25th 2010 were analyzed. Descriptive statistics were used to characterize patients with Crohn's disease (CD) and Ulcerative colitis (UC). Multivariate logistic regression analyses were performed to assess the association between chronic work disability and disease characteristics. A total of 942 patients were included, of which 537 (57%) CD patients (35% males, mean age 46 ±14 years) and 405 (43%) UC patients (52% males, mean age 50±13 years). Patients were included from university medical centers (n=487; 52%) and general hospitals (n=455; 48%). Twenty six percent (n=139) of CD patients were chronically disabled, compared to 17% (n=68) of UC patients (Odds ratio (OR) 0.58, 95%CI 0.42-0.80). Disabled CD and UC patients had a lower EQ-5D as compared to employed patients (0.67 ±0.24 vs. 0.87 ±0.14, p<0.01) and (0.73 ±0.21 vs. 0.89 ±0.15, p<0.01). In patients with CD, we found that age > 40 years (adjusted (adj.) OR 2.02; 95%CI 1.21-3.36), smoking (adj. OR 1.69, 95% 1.02-2.81), disease duration (adj. OR 1.02, 95%CI 1.001-1.05) and endostomy (adj. OR 2.73, 95%CI 1.49-5.00) were independently associated with work disability. In UC patients, only age > 40 was associated with disability (adj. OR 2.20, 95%CI 1.01-4.79).
In conclusion, almost a quarter of all IBD patients have disabling disease. This is more pronounced in CD than UC. Patients at risk for work disability are those at older age (>40 years) and with a low quality of life in both CD and UC, whereas in CD patients, also smoking, a longer disease duration and an endostomy are involved.

Large part of poor Health Related Quality of Life in IBD patients explained by Fatigue, Depression and IBS

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Traditionally, patients with IBD (Crohn's Disease (CD) and Ulcerative Colitis(UC)) are monitored for disease activity. When exacerbation is suspected the anti-inflammatory medication is adapted accordingly. Disease activity is regarded to have a major impact on the Health Related Quality of Life (HRQoL) in IBD patients. Recently, other factors have been identified that may negatively affect the HRQoL. We studied the influence of depression, fatigue and symptoms of Irritable Bowel Syndrome (IBS) on the HRQoL in a IBD population of two large teaching hospitals in The Netherlands. A questionnaire was sent to 904 adult IBD patients (history > 1 yr). This questionnaire consisted of four components: (1) IBDQ (Inflammatory Bowel Disease Questionnaire, range 32 - 160) in an abbreviated version, (2) MFI-20 (Multidimensional Fatigue Index, dimension 'general fatigue', range 4 -20), (3) ZUNG (Depression questionnaire, range 20 – 80) and (4) IBS-QOL (Irritable Bowel Syndrome QOL questionnaire, range 34 - 170). For all components a higher score represents a worse condition. Results: 572 questionnaires (63%) were returned. Ultimately 487 (54%) were available for analysis. This population consisted of 217 males (CD 95, UC 122) and 270 females (CD 148, UC 122). Patients with IBS (n=167, 34 %) were identified based on the ROME III criteria. The average scores (±SD) were IBDQ 76 (20), MFI-20 dimension 'general fatigue' 13 (4), ZUNG 37 (9) and IBS-QOL 72 (24). Prevalence of a poor HRQoL (IBDQ score>100) was 17%, fatigue (MFI-20 dimension 'general fatigue' > 14) was 49%, depression (ZUNG score >50) 10% and poor HRQoL based on symptoms of IBS (IBSQOL score >90) 7%. Multivariate analysis explained 41% of the variance in HRQoL ($p < 0,001$) with female gender, fatigue, depression and IBS as negative predictors for the overall HRQoL as measured by the abbreviated version of the IBDQ.
Conclusions: It is well known that IBD patients suffer from a poor HRQoL. This study corroborates that in addition to disease activity, also fatigue, depression and IBS contribute significantly to a poor HRQoL. In a follow up of this study we will investigate whether subsequent symptomatic treatment of these aspects will improve the HRQoL of IBD patients.

Identification of the gene underlying Congenital Short Bowel Syndrome, pointing to its major role in intestinal development

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Congenital Short Bowel Syndrome is characterized by substantial shortening of the small intestine and by intestinal malrotation. Sixty percent of the cases are familial. Because both boys and girls are affected and as in twenty-five percent of the cases the parents are consanguineous, an autosomal recessive pattern of inheritance has been suggested. The aim of our study was to identify and characterize the causative gene. Homozygosity mapping was performed using 610K SNP arrays of Illumina on five patients of four different families, including one consanguineous family with two affected siblings and one unaffected child. We found an overlapping homozygous region in four of the five patients. In this region a homozygous deletion concerning one exon of a gene encoding a tight-junction protein, was detected in one of the patients. Furthermore, a homozygous deletion in the first intron of this gene was detected in the affected siblings of the consanguineous family, this deletion co-segregates with the disease phenotype in this family. Sequencing of the gene in three other patients resulted in the identification of additional mutations: one patient proved to have a heterozygous frameshift mutation and a heterozygous splice site mutation, whereas two other patients were homozygous for a nonsense mutation and a missense mutation, respectively. The gene is expressed in the intestine of human embryos throughout development. The missense mutation abrogated the normal localization of the encoded protein at the cell membrane. Knock-down experiments in zebrafish resulted in general developmental defects, including shortening of the intestine and absence of goblet cells, which are characteristic for the mid-intestine. Therefore, loss-of-function of the identified gene leads to Congenital Short Bowel Syndrome, likely by interfering with tight-junction formation, with intestinal development and with gut length determination. Note: we will mention the gene name in our presentation.

The human colon is capable of limiting epithelial damage and inflammation following ischemia-reperfusion

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Ischemia/reperfusion (IR) of the colon is a frequent event in clinical practice. It can result from alterations in the systemic circulation as observed during major surgery, trauma and sepsis, or can be caused by anatomic or functional changes in the mesenteric vasculature. Surprisingly, colon-IR is rarely associated with bacterial translocation and severe systemic inflammatory responses. Such IR-induced complications could be suspected, since the intraluminal milieu of the colon is highly pro-inflammatory. This discrepancy let us to hypothesize that the human colon is able to prevent excessive damage to the epithelial lining and to rapidly restore IR-induced wounds. To increase insight into the pathophysiology of colon-IR in man, we developed a unique human experimental colon-IR model. This study was approved by the Medical Ethical Committee, and 10 patients were included in this study. In this model, we take advantage of the fact that during colonic surgery for colon cancer, also a small part of the healthy colon has to be removed for surgical reasons. During surgery, a 6 centimeter segment of this part was isolated on two sides and selectively exposed to 60 minutes of ischemia, followed by 0 (60I), 30 (60I 30R) or 60 minutes (60I 60R) of reperfusion. Tissue was collected at all timepoints to assess morphological changes (hematoxylin/eosin (HE) staining, tight junction loss (zonula-occludens-1 (ZO-1) staining), apoptosis (M30 staining) and neutrophil influx (myeloperoxidase (MPO) staining). In addition, mRNA expression of the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) was assessed using quantitative polymerase chain reaction (qPCR). HE staining revealed appearance of subepithelial spaces in colon tissue exposed to 60I, whereas the epithelial lining remained intact. After 30 minutes of reperfusion, apoptosis of IR-damaged cells was observed in the upper part of the colon crypts, and IR damaged cells were rapidly pinched off. In with this observation, we demonstrated that ZO-1 staining was decreased after 30R, indicating tight junction loss. Interestingly though, the epithelial barrier was fully restored after 60I 60R. In with our hypothesis, we further demonstrated that neutrophil influx was not increased during colon-IR and expression of IL-6 and TNF-α remained unchanged.
In conclusion, we present a novel human experimental colon-IR model, in which we demonstrate that the human colon is capable of preventing excessive epithelial damage and rapidly resolving IR-induced barrier integrity loss, thereby preventing an excessive inflammatory response.

The human small intestine is equipped with a unique mechanism to reduce wound size and rapidly restore ischemia-induced damage to the epithelial lining

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To ensure a sufficient barrier between host and noxious luminal content, the intestinal epithelium must be equipped with efficient mechanisms to limit and/or rapidly restore epithelial damage. Insight into the restorative capacity of the human gut is important to develop strategies to prevent or reduce complications as a result of intestinal epithelial wounding. Using an innovative in vivo human jejunal ischemia-reperfusion (IR) model, we were able to investigate wound induction and healing in the human gut over the time course of 150 minutes. This study was approved by the Medical Ethical Committee and was conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul). In 10 patients, a part of healthy jejunum, to be removed for surgical reasons, was selectively exposed to IR. Control tissue was collected, as well as tissue exposed to 30 minutes of ischemia with 0, 30 or 120 minutes of reperfusion. Directly after ischemia, villus retraction was observed in HE staining, resulting in the appearance of subepithelial spaces. This was paralleled by an increase in myosin light chain kinase (MLCK) protein levels, assessed with Western blot. Co-localization of MLCK and phosphorylated MLC (pMLC) in lamina propria muscle fibers demonstrated active villus contraction. Early during reperfusion, epithelial sheets that lost contact with the basal membrane were pulled together even before these IR-damaged cells were shed. This purse-string contraction, verified by increased F-actin and pMLC staining at the basal side of these epithelial cells, accounted for a 45% reduction in wound surface area during early reperfusion ($P<.001$). Small gaps that remained were sealed by ring-like contraction, resulting in a morphologically fully restored epithelial lining at 120 minutes of reperfusion.

In conclusion, we reveal a novel role for purse-string contraction in an in vivo human IR-model. Purse-string contraction is not merely involved in restoring small epithelial defects in the human gut, but is also critical for the prevention of extensive tissue damage, thereby limiting host exposure to noxious luminal content. Interventions aimed at activating these mechanisms could therefore be a potential new strategy to prevent and/or reduce intestinal epithelial damage.

Modulation of intestinal epithelial barrier function by fatty acid ethyl esters in a three dimensional (3D) epithelial cell culture model: role of nonoxidative ethanol metabolism

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Ethanol has been shown to decrease intestinal epithelial barrier function both, in vivo and in vitro. Fatty acid ethyl esters (FAEEs) are nonoxidative ethanol metabolites that are detectable in the blood after ethanol ingestion. FAEEs have been implicated as mediators of ethanol-induced cytotoxicity and have been shown to cause hepatocellular and pancreatic injury. So far, the effects of FAEEs on intestinal epithelial cells have not been studied. The aims of the study are to investigate in 3D integrity model of human colon carcinoma cells (Caco-2), the effects of FAEEs on functional and structural tight junctions (TJs) integrity and on cellular oxidative stress and mitochondrial function as markers of cytotoxicity. Caco-2 cells were grown for 5 days to form fully polarised spheroids and were exposed to (20 or 40 µM) ethyl oleate, ethyl palmitate or ethyl stearate for 24 h. Culture medium and 2 mM EGTA were used as negative and positive control, respectively. Barrier function was assessed by the flux of fluorescein isothiocyanate-conjugated dextran 4KD (FD4) from the basal to the luminal compartment using live cell imaging. Integrity of the TJs was analyzed by immunocytology staining of ZO-1 and occludin using confocal microscopy. Intracellular oxidative stress and mitochondrial function were measured by dichlorofluorescein and methyltetrazolium assays, respectively. The 3D cultured Caco2 cells form fully polarised spheroids with the lumen inside. After 24 h, the mean fluorescence intensity of FD4 was expressed as the ratio of the luminal over the basal compartment, given as mean of 8 spheroids from 4 different fields of 3 independent experiments. A dose-dependent increase of the FD4 ratio was found at 20 and 40 µM ethyl oleate versus control [0.3455 ± 0.02176 and 0.4474 ± 0.06162, respectively, vs 0.006429 ± 0.001420, $p<0.0001$]. Similarly, 20 and 40 µM ethyl palmitate as well as ethyl stearate, increased the ratio dose dependently versus control [$p<0.0001$]. Ethyl oleate at 20 and 40 µM, induced redistribution of ZO-1 and occludin, increased intracellular oxidative stress [35.44±5.912 and 46.06±7.69 respectively, vs 30.39±0.58%, $p<0.0001$] and decreased mitochondrial function [53.95±4.30 and 48.54±1.98%, respectively vs 100±00, $p<0.0001$].
Our findings show for the first time that FAEEs at concentrations detectable in the blood after ethanol ingestion, dose dependently decrease barrier function and disrupt TJs integrity. Moreover, FAEEs increased intracellular oxidative stress and decrease mitochondrial function. These findings support a role of FAEEs in ethanol- induced intestinal injury.

The serotonin precursor 5-hydroxytryptophan reinforces intestinal barrier function

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Tight junctions between intestinal epithelial cells form a selective barrier that contributes to gut homeostasis. Alterations in intestinal barrier function are considered to be early factors in the pathogenesis of irritable bowel syndrome (IBS). Changes in serotonergic metabolism have also been associated with IBS. The direct precursor of 5-HT, 5-hydroxytryptophan (5-HTP), is available as over-the-counter dietary supplement and is a potential substance to influence serotonin availability and possibly also intestinal barrier function. Aim was to assess the effect of an oral bolus of 5-HTP on intestinal barrier function and mucosal 5-HT metabolism.15 healthy volunteers participated in this randomized double-blind placebo-controlled crossover study. Intestinal permeability was measured by determining the plasma recovery of an orally ingested multi-sugar drink on two separate occasions. Plasma samples were taken prior to, at 60, 90 and 120 min after intake of 100 mg 5-HTP or placebo. At the end of each of both test days, a gastroduodenoscopy was performed to obtain mucosal samples from the duodenum. Plasma concentrations of the sugars and mucosal concentrations of 5-HTP, 5-HT and 5-hydroxyindoleacetic acid (5-HIAA, the main metabolite of 5-HT) were determined by HPLC-MS. In mucosal samples, the expression of tight junction proteins occludin and ZO-1 was analyzed by qPCR and immunohistochemistry. Data are expressed as mean ± SEM. Intestinal permeability as defined by the plasma recovery ratios of lactulose/rhamnose (L/R) and sucralose/erythritol (S/E) was significantly reduced after 5-HTP (L/R 0.005±0.002 vs 0.006±0.002, $p<0.05$, S/E 0.004±0.001 vs 0.005±0.001, $p<0.05$; 5-HTP vs placebo). The mRNA expression of ZO-1 was significantly increased after 5-HTP (1.27±0.24 vs 0.87±0.12; $p<0.05$), whereas the expression of occludin was not altered by 5-HTP. Immunohistochemical staining for the ZO-1 and occludin proteins showed that the proteins were located significantly closer to each other after 5-HTP. Administration of 5-HTP significantly increased mucosal 5-HTP levels (12.7±9.1 vs 1.6±1.5 pmol/mg; $p=0.001$), but did not affect 5-HT levels (57±21 vs 47±18 pmol/mg; $p=0.68$), while 5-HIAA levels increased significantly (7.1±1.7 vs 2.5±0.7 pmol/mg; $p<0.05$). Oral administration of 5-HTP reinforces small intestinal barrier function by lowering intestinal sugar permeability, inducing the expression of the tight junction protein ZO-1 and rearranging tight junction proteins. These changes are associated with 5-HTP-induced alterations in mucosal serotonin metabolism. These data point to a role for serotonergic metabolism in reinforcing intestinal barrier function.

ATP8B1-deficiency reduces the functional CFTR pool in intestinal T84 cells

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Progressive Intrahepatic Cholestasis Type 1 is caused by mutations in ATP8B1, which encodes a phosphatidylserine (PS) flippase. We and others have previously shown that the apical membrane of ATP8B1-deficient hepatocytes is more prone to bile salt-induced damage, with a resulting impairment in the activity of (a.o.) the major bile salt export pump, which most likely causes the cholestasis. Besides cholestasis, patients often develop diarrhea of unknown etiology. We hypothesized that ATP8B1 deficiency in the apical membrane of enterocytes impairs membrane protein stability and/or function. We studied the activity of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel in ATP8B1-deficient mouse intestine by short-circuit current (Isc) measurements in Ussing chambers. In addition, CFTR function was studied in T84 cells in which ATP8B1 protein expression was knocked-down by 95% using Ussing chambers and by a stably expressed intracellular fluorescent chloride sensor. Forskolin-induced, CFTR-mediated Cl^- currents were not significantly different in colon or muscle-stripped jejunum and ileum of ATP8B1-deficient and wild type mice. Likewise, forskolin-induced Cl^- secretory currents across polarized T84 monolayers grown on Transwell filters were similar in ATP8B1 knockdown and control cells (71.0 ± 15.0 μA/cm^2 vs. 60.7 ± 23.1 μA/cm^2). However, a more direct assessment of CFTR activity following permeabilization of the basolateral membrane by nystatin unequivocally demonstrated a significant reduction in forskolin-activated CFTR activity in the apical membrane in ATP8B1-knockdown T84 cells (81.0 ± 27.0μA/cm^2 vs. 148.6 ± 67.8μA/cm^2 in control cells; $p<0.05$). This was paralleled by a reduction in CFTR protein (~40%) and mRNA (~30%) expression levels. A similar reduction in CFTR activity in ATP8B1 knockdown T84 cells was observed in measurements of iodide quenching rates of a stably expressed intracellular fluorescent chloride sensor (0.060 ± 0.020 vs. 0.144 ± 0.066 in ATP8B1-knockdown and control T84 cells, respectively; $p<0.05$).
We conclude that ATB8B1 deficiency (1) does not significantly affect CFTR-mediated transepithelial transport of chloride across mouse intestine, (2) does reduce the functional pool of CFTR in the apical membrane of T84 human colonocytes, possibly by effecting CFTR mRNA expression.

Reduced Paneth cell antimicrobial protein levels correlate with activation of the unfolded protein response in the gut of obese individuals

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The intestinal microbiota is increasingly acknowledged to play a crucial role in the development of obesity. A shift in intestinal microbiota composition favouring the presence of Firmicutes over Bacteroidetes has been observed in obese subjects. A similar shift has been observed in mice with a deficiency in active Paneth cell α-defensins. We aimed at investigating changes in Paneth cell antimicrobial levels in the gut of obese subjects as a possible cause of the obesity-associated microbiota shift. In addition, we studied activation of the unfolded protein response (UPR) as a possible mechanism involved in altered Paneth cell function.Paneth cell numbers were counted in jejunal sections of 15 severely obese (BMI>35) and 15 normal weight subjects. Expression of Paneth cell antimicrobials human α-defensin 5 (HD5) and lysozyme were investigated using immunohistochemistry, qPCR, and western blot. Activation of the UPR was assessed with western blot.Severely obese subjects showed decreased protein levels of both HD5 and lysozyme, while Paneth cell numbers were unchanged. Lysozyme protein levels correlated inversely with BMI. Increased expression of HD5 and lysozyme transcripts in the intestine of obese subjects prompted us to investigate a possible translational block caused by UPR activation. Binding protein (BiP) and activeting transcription factor 4 (ATF4) levels were increased, confirming activation of the UPR in the gut of obese subjects. Moreover, levels of both proteins correlated with BMI. Involvement of the UPR in the lowered antimicrobial protein levels in obese subjects was strongly suggested by a negative correlation between BiP levels and lysozyme levels.
Our findings provide the first evidence for altered Paneth cell function in obesity, which may have important implications for the obesity-associated shift in microbiota composition. In addition, we show activation of the UPR in the intestine of obese subjects which may underlie the observed Paneth cell compromise.

Oral availability of cefadroxil depends on Abcc3 and Abcc4

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Cephalosporins are bactericidal compounds belonging to the class of β-lactam antibiotics. Some cephalosporins, like cefadroxil, are orally available. Orally available cephalosporins enter enterocytes across the apical membrane through active transport mediated by PepT1. Presently, it is not clear which mechanism is responsible for the efficient basolateral transport. ABCC2 is known to mediate transport of cephalosporins, but is expressed apically. Furthermore, the related transporters ABCC3 and ABCC4 share substrates with ABCC2. ABCC3 is expressed on the basolateral side, while this is unknown for ABCC4. The aim of this study was to investigate the contribution of ABCC3 and ABCC4 in the basolateral transport of cefadroxil from enterocyte into blood. Transport studies were performed in plasma membrane vesicles from ABCC1, ABCC2, ABCC3, ABCC4 and ABCG2 expressing Sf21 insect cells. Furthermore, intestinal explants from wild-type, Abcc3$^{-/-}$, Abcc4$^{-/-}$ and Abcc3$^{-/-}$/Abcc4$^{-/-}$ mice were used to study vectorial transport in an Ussing chamber setup. Finally, appearance of cefadroxil in portal blood was investigated in vivo after jejunal delivery of cefadroxil in wild-type, Abcc3$^{-/-}$, Abcc4$^{-/-}$ and Abcc3$^{-/-}$/Abcc4$^{-/-}$ mice. ABCC2-, ABCC3- and ABCC4-mediated transport of estradiol-17ß-glucuronide ($E_2$17ßG) was dose dependently inhibited by cephalosporins. ABCC1, ABCC2, ABCC3 and ABCC4 mediated transport of cefadroxil was concentration- and time dependent. The K_m and V_{max} values for ABCC1, ABCC2, ABCC3 and ABCC4 mediated transport of cefadroxil were 3.9±0.6, 11.8, 2.5±0.7 and 0.25±0.07 mM nmol cefadroxil/mg protein/min, respectively, and 12.4±6.8, 12.3, 0.6±0.3 and 1.2±0.2 nmol cefadroxil/mg protein/min, respectively. No transport was seen using ABCG2-protein containing membrane vesicles. In the Ussing chamber transport of cefadroxil from the apical to the basolateral side was unchanged in jejunal tissue of Abcc3$^{-/-}$ and significantly reduced in jejunal (50%) tissue of Abcc4$^{-/-}$ and Abcc3$^{-/-}$/Abcc4$^{-/-}$ compared to wild-type mice. Portal- and peripheral blood concentrations of cefadroxil were unchanged in Abcc3$^{-/-}$ and Abcc4$^{-/-}$ and diminished to about 50% in Abcc3$^{-/-}$/Abcc4$^{-/-}$ vs wild type mice.These data demonstrate that intestinal uptake depends partly on Abcc3 and Abcc4.

Loss of heterozygosity in liver cysts of autosomal dominant polycystic liver disease (PCLD) depends on germ mutation of the patient

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Autosomal dominant polycystic liver disease (PCLD) is an inherited disorder characterised by a massive increase in liver volume due to multiple fluid filled cysts. Heterozygous germline *PRKCSH* and *SEC63* gene mutations cause PCLD and lead to clinically identical phenotypes. There is loss of heterozygosity of *PRKCSH* in ~80% of cyst epithelial cells from *PRKCSH* mutant patients. Here, we determined whether a similar mechanism is involved in cyst formation in *SEC63* mutant patients.
We collected freshly frozen liver tissue from 2 female PCLD patients with a heterozygous *SEC63* c.1702_1704delGAA germline mutation. We collected between 300 and 800 cyst epithelial cells from 23 liver cysts through laser micro dissection in order to isolate cyst DNA. We used DNA from whole blood and laser dissected hepatocytes as control samples. The loss of heterozygosity status was determined using site specific PCR and sequencing.
We sequenced exon 17 from *SEC63* in all DNA samples available. This demonstrated that the *SEC63* germline mutation c.1702_1704delGAA was present in a heterozygous state in DNA isolated from whole blood, control hepatocytes, and laser dissected cyst epithelium. There was no loss of *SEC63* heterozygosity in any of the 23 cyst epithelial samples.
Conclusions: These results imply that the molecular mechanism controlling hepatic cyst formation depends on the genetic background of the patient. While there is loss of heterozygosity in the majority of cysts from *PRKCSH* mutant patients, this is not the case in *SEC63* mutant patients. This suggests that, at the genetic level, liver cyst formation is differently controlled in *SEC63* mutant patients.

Dynamic changes in the biliary glycocalyx impact cholangiocyte resistance to bile salt induced toxicity

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Cholangiocytes are higly resistant to millimolar concentrations of bile salt monomers in the biliary tree lumen. The mechanism of defence of biliary epithelial cells (BEC) against bile salts, which are toxic to many other cell types already in the micromolar range, is incompletely understood. We recently observed that biliary HCO_3^- secretion is crucial to prevent BEC damage inflicted by protonated bile acids. We hypothesize that BEC stabilize a HCO_3^--umbrella on their apical surface by maintaining a layer of glycosylated mucins and other proteins analogous to the glycocalyx on the luminal side of the intestinal epithelium. Changes in this biliary glycocalyx may confer vulnerability to bile acid induced damage to cholangiocytes. Here we aimed to study the molecular structure of the cholangiocyte glycocalyx and the effect of glycocalyx disruption on cholangiocyte resistance to protonated, hydrophobic bile acids.

A human, non-malignant BEC line was evaluated by FACS for the expression of the mucin MUC1 and the surface glycan profile was investigated using a lectin panel. BEC were exposed to apical neuraminidase (1U/ml) to test the effect of desialylation on BEC susceptibility to toxic bile salts. Chenodeoxycholate (CDC, pKa>4) and its glycine- and taurine conjugates (GCDC, pKa >4 and TCDC, pKa<2) were administered at 0.25-2mM for 18h at pH7.1. WST-1 metabolic assays were performed as readout for cell viability.

Human BEC expressed significant levels of membrane-bound MUC1. O-glycans exposed on mucins and other membrane proteins were dominated by T antigen (core1 glycan), but not Tn antigen. The main N-glycans were sialylated biantennary structures. The H-antigen (α1-2-fucose) was highly expressed, while the Lewis X epitope was absent. Apical neuraminidase treatment induced marked desialylation without affecting baseline viability. Sialylation status as measured by FACS mirrored bile salt susceptibility: pruning of the glycocalyx by neuraminidase treatment exacerbated GCDC toxicity and decreased metabolic activity by 45.2±20.9% as compared to 11.2±18.4% for cells not pretreated with neuraminidase (1mM GCDC, $p<0.01$, $n=6$). CDC but not TCDC toxicity was also significantly increased by neuraminidase pretreatment. Increased bile salt susceptibility could be reversed by 24-hr reconstitution of the glycocalyx before bile salt exposure.

Conclusion: A biliary glycocalyx with glycosylated mucins and other glycan-bearing membrane proteins may stabilize the biliary HCO_3^- umbrella and thereby protect human cholangiocytes against pH-dependent toxicity of bile salt monomers.

Three genetic susceptibility loci indicate a role for IL2, REL and CARD9 in primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the bile ducts. Both environmental and genetic factors are likely to contribute to its pathogenesis. To further clarify its genetic background, we investigated susceptibility loci recently identified for ulcerative colitis (UC) in a large PSC cohort. Single nucleotide polymorphisms (SNPs) tagging 13 UC susceptibility loci were genotyped in 854 PSC patients and 1491 controls from the Benelux (331 cases, 735 controls), Germany (265 cases, 368 controls) and Scandinavia (258 cases, 388 controls). We applied additional analyses to identify likely candidate genes at three newly identified PSC susceptibility loci, and six loci that showed an association with PSC in previous studies. To identify non-random, evidence-based links between these nine PSC susceptibility loci we used GRAIL analysis. GRAIL is a statistical tool that uses text mining to annotate candidate genes in loci associated with disease risk. For the same nine loci we also performed an expression quantitative trait locus (eQTL) analysis using genetical genomics data of 1469 peripheral blood DNA and RNA samples from Dutch and UK individuals. SNPs at chromosomes 2p16 (p value 0.0026), 4q27 (p value 0.00069) and 9q34 (p value 0.0022) were associated with PSC in the combined analysis after correcting for multiple testing. In a subset of PSC patients without inflammatory bowel disease (IBD), SNPs at 4q27, 9q34 and 20q13, were found to be nominally associated ($p < 0.05$). GRAIL analysis showed interconnectivity between genes in six out of in total nine PSC-associated regions. Expression quantitative trait analysis demonstrated that five out of nine SNPs had an effect on cis-gene expression. These analyses prioritized IL2, CARD9 and REL as novel candidate genes in PSC. Conclusions: We have identified three new PSC associated loci harboring the putative candidate genes IL2, CARD9 and REL; Together with the previous association with IL2RA this implies an important role for IL2 signaling in PSC pathogenesis. These results add to the scarce knowledge on the genetic background of PSC and imply an important role for both innate and adaptive immunological factors in PSC pathogenesis.

A HCO_3^- umbrella protects human biliary epithelia against bile acid-induced injury

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Human biliary epithelial cells (BEC) are exposed to millimolar concentrations of mainly glycine-conjugated bile acids, which are toxic to other cell types including hepatocytes already in the micromolar range after cell entry. Apolar protonated bile acids rather than polar deprotonated bile salts may passively enter BEC. Protonation status of bile acids in bile depends on their pKa and biliary pH. We hypothesize that biliary HCO_3^- secretion in humans fosters deprotonation of apolar bile acids to polar bile salts near the apical surface of cholangiocytes. This 'biliary HCO_3^- umbrella' might be a key protective mechanism of human BEC against glycine-conjugated bile acids. Our aim was to test if toxicity of unconjugated, glycine-conjugated (pKa 4-5) and taurine-conjugated (pKa <2) bile acids in BEC is (i) pH-dependent, and (ii) antagonized by anion exchanger 2 (AE2), a candidate for apical HCO_3^- secretion. Methods: A human immortalized BEC and two human cholangiocarcinoma cell lines were exposed to chenodeoxycholate (CDC), or its glycine- and taurine-conjugates, or with an alternative inducer of apoptosis, etoposide, (i) at pH 7.4, 7.1, 6.7 and 6.4, or (ii) after knockdown of AE2 by shRNA. After four hours, cell viability and apoptosis were determined by WST and caspase-3/-7 assays, respectively. Results: CDC- and GCDC- induced cholangiocyte toxicity is pH dependent and increases significantly in all tested cell lines when pH is lowered from 7.4 to 7.1, 6.7 or 6.4. While at a pH of 7.4, 0.5mM CDC and 1mM GCDC did not affect cell viability, they decreased viability in immortalized BEC by 80.8±5.3 and 83.5±9.7% ($p<0.01$ vs. pH 7.4, n=5) and increased caspase activity 9- and 27-fold, respectively ($p<0.001$ vs. pH 7.4, n=5) when pH was lowered to 6.4. As expected from its low pKa and thus complete deprotonation at physiologic pH, TCDC was not toxic within the tested pH range. Etoposide-induced toxicity was not pH-dependent. AE2 knockdown led to 3- and 2-fold enhanced apoptosis induced by 0.75mM CDC or 2mM GCDC at pH 7.4 ($p<0.01$, n=6).
Conclusions: Our data strongly support the presence of a biliary HCO_3^- umbrella protecting human cholangiocytes against injury induced by glycine conjugated hydrophobic bile salts. AE2 might be a key element maintaining this umbrella. Genetic and acquired functional defects leading to destabilization of the biliary HCO_3^- umbrella may contribute to development and progression of various cholangiopathies.

Significant Contribution of the Portal Vein to Blood Flow through the Common Bile Duct

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Introduction: Non-anastomotic biliary strictures (NAS) are a common cause of graft loss after liver transplantation. NAS can occur in the context of a hepatic artery thrombosis, or with an open hepatic artery and are then called ischemic type biliary lesions (ITBL). The hepatic artery is considered to be the sole provider of blood flow to the bile ducts through a network of vessels called the peribiliary plexus (PBP), which is hypothesized to play an important role in the pathogenesis of ITBL. However, the contribution of the portal vein and the gastroduodenal artery to the PBP is unknown, as well as whether disturbances in portal venous blood flow contribute to the formation of ITBL. The aim of this study was to determine the contribution of the hepatic artery, gastroduodenal artery, and portal vein to the microvascular blood flow in the common bile duct (CBD). Methods: Microvascular blood flow in the CBD was determined in 15 patients undergoing pancreaticoduodenectomy, during which the CBD is transected as in liver transplantation. The microvascular blood flow through the CBD was measured combining laser Doppler flowmetry and reflectance spectrophotometry during baseline, after clamping the portal vein, the hepatic artery, and both. After transection of the CBD these measurements were repeated.
Results: Compared to base measurements, microvascular blood flow through the CBD decreased to 62% after clamping the portal vein, 51% after clamping the hepatic artery and 31% after clamping both. After transection of the CBD, microvascular blood flow decreased to 60%, 31% and 20% while clamping the portal vein, hepatic artery and both respectively.
Conclusion: Historically, the hepatic artery is considered mainly responsible for biliary blood flow. We show that after transection of the CBD the contribution of the portal vein to the microvascular blood flow through the CBD is 40%. This study emphasizes the importance of the portal vein with regard to the blood flow through the PBP, particularly after liver transplantation. Thus disturbances in portal venous blood flow could contribute to the formation of biliary complications after liver transplantation.

Quality of colonoscopy from a patient's perspective using the Global Rating Scale

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Patient experience is important in quality assurance (QA) in colonoscopy. The Global Rating Scale (GRS) has proven to be an effective tool for QA in the United Kingdom (UK) to assess patient-centered care. As standardized QA program, the GRS receives international attention but its applicability in other settings remains undetermined. The aim was to evaluate patient experiences in colonoscopy in Dutch endoscopy units using the GRS items. In 12 endoscopy units a previously used, GRS-based survey (a pre- and post-procedure part) was given to outpatients undergoing colonoscopy. The pre-procedure part contained questions about admission, timeliness, and information provision, and was completed before the procedure. The post-procedure part was completed at home. This part involved questions about privacy, comfort, staff's skills, information, aftercare, and willingness to return. In total, 1,904 pre-procedure and 1,532 post-procedure parts returned (response: 81%; mean age=59 yrs, SD=14; male 49%). Previous colonoscopy experience was reported by 47%. Mean waiting for their colonoscopy was 4.3 weeks (range: 3.1-5.8). Patients who had to wait >4 weeks were more dissatisfied with timeliness compared to those who had the procedure within 4 weeks (30 vs. 6%, p<0.01). The reason for colonoscopy was not recalled by 7%. Information about the risk of perforation and bleeding given by a professional was not recalled in 54% (range between units: 1-79%, p<0.01) respectively 50% (range: 12-78%, p<0.01). Satisfactory scores were found in the nurses' courtesy (94%) and endoscopists' competency (93%). Discomfort was reported by 20% (range: 8-40%, p<0.01); 5% reported an unacceptable procedure. Privacy in the recovery area was satisfactory in 76% (range: 66-90%, p<0.05). Adequate explanation about the findings was provided to 75% (range: 52-86%, p<0.01). A majority (79%) reported to be sufficiently informed about what to do when problems after discharge would arise (range: 43-98%, p<0.01). 85% of subjects were willing to return for colonoscopy (range: 72-91%, p<0.01). Factors associated with willingness to return were male gender (OR: 1.7, p=0.02), cecal intubation (OR: 2.9, p<0.01), low levels of discomfort during bowel preparation (OR: 4.4, p<0.01), high acceptance of the experience (OR: 3.4, p<0.01) and less discomfort than expected (OR: 2.7, p<0.01).

In conclusion, the overall experience in colonoscopy procedures in Dutch endoscopy units was satisfactory, reflected in a high willingness to return for colonoscopy. However, differences were found between units in GRS items information and privacy. This study shows that GRS items are applicable to endoscopy units outside the UK.

Quality of colonoscopy reporting and performance

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High quality colonoscopy is of major importance to optimize colonoscopy. Complete procedure reporting is mandatory for valid quality assurance. Limited data are available on quality of reporting in daily practice and assessment of performance based on these reports. This study aimed to assess the quality of colonoscopy reporting and performance in daily clinical practice.Twelve endoscopy units in the Netherlands each provided 400 consecutive colonoscopy reports.Quality of reporting was assessed by compliance of reporting indication, sedation, quality of bowel preparation, extent of procedure, photo documentation, and procedure time. Mean compliance, range between units and statistical difference between the highest and lowest scores were calculated. Quality of performance was assessed based on the adjusted cecal intubation rate, and adenoma detection rate.A total of 4,800 colonoscopies were included from 4,738 patients (male gender: 47%, mean age: 59 yrs), performed by 116 endoscopists (male gender: 76%; median colonoscopy experience: 7 yrs, interquartile range: 4-17 yrs).High compliance in reporting was found for defining indication (98%, range between units: 94-100%, p<0.01), sedation practice (94%, range: 70-100%, p<0.01), and procedure extent (99%, range: 98-100%, p<0.01). Suboptimal compliance was found for reporting on procedure time (47%, range: 0-99%, p=0.01), quality of bowel preparation (62%, range: 7-100%, p<0.01), and photo documentation of cecal landmarks (71%, range: 22-97%, p<0.01). The adjusted cecal intubation rate was 92% (range: 84-97%, p<0.01). The ADR was 26% (range: 14-33%, p<0.01): 32% in male patients and 21% in females.Cecal intubation was higher in males (OR: 1.75, p<0.01), younger patients (OR: 1.01, p<0.01), and with good bowel preparation (vs. poor OR: 23.6; vs. moderate OR: 4.90, p<0.01), the use of sedation was not associated (p=0.39). Gastroenterologists (GE) had higher cecal intubation rates than surgeons and internists (OR: 3.91 and 3.13, p<0.01).Adenomas were more common in males (OR: 1.85, p<0.01), older patients (OR: 1.04, p<0.01), those with a personal history of adenomas (OR: 1.63, p<0.01), with good quality of bowel preparation (vs. poor, OR: 2.23, p<0.01), and when sedation was used (OR: 1.50, p<0.01). GE found more adenomas compared to internists and surgeons (OR: 1.41 and 5.24, p=0.01).

In conclusion did this study show that the quality of colonoscopy reporting is diverse and suboptimal in daily clinical practice. The quality of colonoscopy performance meets the accepted quality indicators, although variance between endoscopy units is found. This underlines the importance of continuous quality monitoring and feedback in order to optimize the procedure.

Interval colorectal cancers frequently have subtle macroscopic appearance: a 10 year-experience in an academic center

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In routine practice, interval colorectal cancers (CRCs) are more common than previously expected. Operator-dependent variability in detection and effective treatment of pre-cursor lesions may be a critical factor, yet its precise contribution remains unclear. We hypothesized that interval CRCs are frequently associated to more subtle (small or flat) macroscopic appearance. Methods: We identified all patients who were diagnosed with CRC at our academic medical center between January 2001 and July 2010, using a national pathology database (PALGA) and data from the Comprehensive Cancer Centre. Patients with hereditary forms of CRC or inflammatory bowel disease were not included. Digital colonoscopy and histopathology reports from all patients were studied. Interval CRCs were defined as cancers occurring within 5 years after a colonoscopy, excluding those with incomplete colonoscopy, poor bowel preparation or inadequate surveillance. We categorized CRCs according to their macroscopic appearance into flat or protruded and according to location into proximal (cecum to splenic flexure) or distal (descending colon to rectum). We classified potential explanations for interval CRCs into i) small (<10 mm), flat or depressed appearance, ii) incomplete removal, defined as CRCs occurring in the same segment as a previous polypectomy or iii) unclear cause. Results: We included a total of 1,176 patients (mean age 70.3 yrs, 55.2% males) with 1,241 CRCs (4.2% synchronous and 2.3% metachronous). Of all CRCs, 4.1% (n=51) developed in patients with previous (<5 yrs) colonoscopy. Of them, 17 were excluded due to incomplete colonoscopy (7), poor bowel preparation (1) or inadequate surveillance (9). Thirty-four interval CRCs (2.7% of all CRCs) in 34 patients (mean age, 71.6 years, 76.5% men) were finally analyzed. Of all interval CRCs, 47.1% (16) were small, flat or depressed cancers, 14.7% (5) occurred in the same segment as previous polypectomy, whereas in 38.2% (13) of cases no explanation could be found. Interval CRCs were predominantly located in the proximal colon (60.6% vs 33.5%, OR 3.3, 95% CI 1.6 – 6.7, p=0.001), smaller in size (3.1 cm vs 4.5 cm, OR 0.69, 95% CI 0.55 - 0.86, p=0.001) and more often flat (43.8% vs 20.0%, OR 3.3, 95% CI 1.3 – 6.7, p=0.001) than non-interval CRCs.
Conclusion: In this Dutch population, interval CRCs accounted for 2.7% of all cancers detected, and of them, the majority were related to a more subtle (depressed or small) macroscopic appearance or incomplete removal. Systematic training on detection and effective treatment of subtle colorectal neoplasms is essential to improve effectiveness of CRC prevention programs.

Adenoma detection with cap-assisted colonoscopy versus regular colonoscopy: a randomized controlled trial

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Colonoscopy is widely accepted as the gold standard for detection of colorectal neoplasia, but it is also known to be an imperfect test. Adenoma detection miss-rates were reported in tandem colonoscopy studies to be as high as 22% for all size adenomas. Performing colonoscopy with a transparent plastic cap attached to the tip of the colonoscope (cap-assisted colonoscopy) may enhance adenoma detection due to improved visualization of the mucosal surface. Aim of this study was to compare adenoma detection with cap-assisted colonoscopy (CAC) to regular colonoscopy (RC). Secondary outcomes were total number of detected adenomas per patient, cecal intubation time and rate. All asymptomatic individuals (50-75 years) who participated in the Dutch primary colonoscopy screening program for colorectal cancer were invited to participate. Consenting screenees were 1:1 randomized to either CAC or RC. All colonoscopies were done by experienced colonoscopists (≥ 1000 colonoscopies) and trained in CAC. The quality of bowel prep was assessed by the validated Ottawa scale (0-14). The primary outcome measure was adenoma detection, defined as the proportion of patients with at least one adenoma. Total number of adenomas per patient was defined as the total number of detected adenomas in each group divided by the number of allocated subjects. A total of 1227 patients (male 52%, median age 60) were allocated to CAC (N=607) or RC (N=620). Cecal intubation rate was similar in both groups (99% vs. 98%; p=0.37). Cecal intubation time was significantly lower in CAC (8.0 vs. 9.4 minutes; p<0.001). Withdrawal time (12.3 vs. 12.4 minutes; p=0.85) and quality of the bowel prep (5.7 ± 3.1 vs. 5.5 ± 3.2; p=0.32) did not differ between the groups. Adenoma detection was not significantly higher in CAC (29% vs. 29%; p=0.87, OR 1.02 (95% CI 0.79 to 1.32)), nor was the number of adenomas per patient (0.51 vs. 0.52; p=0.83). Fewer advanced adenomas per patient were observed with CAC (0.09 vs. 0.14; p=0.04). Conclusions: Cap-assisted colonoscopy does not improve adenoma detection but does reduce cecal intubation times in asymptomatic individuals.

The occurrence of adeverse events in a 30-day period after colonoscopy

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There is increasing attention for quality assurance in colonoscopy. The main focus in this topic is on adenoma detection rates and serious complications. Few data is available on the rate of long-term adverse events (AE). This study aimed to assess the rate of AE in the 30 days after colonoscopy.Outpatients from 12 endoscopy units were contacted 30 days after their colonoscopy. A telephone interview was used to assess the occurrence of any AE (all newly occurring health problems). AE were classified as severe when requiring a hospital visit. Distinction was made between endoscopy-related, possibly related, and unrelated AE.A total of 1,144 (75%) from 1,530 patients were successfully contacted (males: 49%; mean age: 59 yrs). Severe AE were reported by 78 patients (7%), 10 patients (1%) had endoscopy-related severe AE, 13 patients (1%) had possibly related severe AE, and 55 patients (5%) unrelated severe AE. Endoscopy-related severe AE included rectal blood loss (RBL, n=5), abdominal pain (4), and perforation (1). Possibly related severe AE included cardiovascular events (5), vertigo (3), cystitis (2), epididymitis (1), syncope (1), and a ruptured abdominal aneurysm (1). Patients with (possibly) related severe AE were admitted to the hospital for a mean of 3.5 days (range: 1-21).Any AE was reported by 369 patients (32%): endoscopy-related AE in 250 patients (22%), possibly related AE in 54 patients (5%), and unrelated AE in 65 patients (6%). The endoscopy-related AE included abdominal discomfort (115), RBL (65), change in bowel habits (47), tiredness (9), nausea (8), hematoma at the IV-needle site (2), prolaps/hernia inguinalis (2), allergic reaction to the bowel preparation (1), and perforation (1).The occurrence of (possible) related severe AE was not associated with gender, age, sedation, intervention, or cecal intubation ($p > 0.05$). However, any (possible) related AE were more reported by females (OR: 1.41, $p = 0.02$), whereas the other variables were not of influence.Patients reported to have missed a mean of 2.3 days from work, including the procedure day. Patients who did not experience any (possible) related AE were more willing to return for colonoscopy compared to patients who did (88 vs. 80%, $p < 0.01$).
In conclusion, the occurrence of direct-related severe adverse events in the 30 days after a colonoscopy is low. However, less serious adverse events do occur in a significant portion of the patients. It is therefore of paramount importance to inform patients about the possible, minor adverse events that can occur in the weeks after the procedure, and closely monitor the rate of adverse events.

Clipped versus standard nasoenteral feeding tubes: a randomized controlled trial

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Background and aim: Despite the availability of various minimally invasive techniques for nasoenteral feeding tube placement, incorrect placement and spontaneous tube migration remain bothersome issues. Endoscopic clipping of a feeding tube may overcome these problems, thereby preventing repeat endoscopies for tube repositioning. The aim of this study was to compare total endoscopic reposition rates of clipped vs. standard nasoenteral feeding tube placement.Methods: From Aug. 2009 to Nov. 2010, 124 consecutive patients admitted to the medical ward or ICU of a tertiary referral center, were randomly assigned to standard (n=61) or clipped feeding tube placement (n=63). Standard tube placement was performed over a guidewire in the duodenum with a transnasal endoscope, followed by endoscope removal and insertion of a feeding tube over the guidewire. The clipped tube was introduced with a suture fixed to the distal tip, picked up in the stomach with a hemoclip through the working channel of the endoscope and attached to the duodenal wall. Primary endpoint was the total endoscopic tube reposition rate (for spontaneous migration and incorrect placement), secondary endpoints were procedure time, technical difficulty (Visual Analogue Scale (VAS) 0-10) and complications. Tube position was radiologically evaluated <3 hours after placement, in case of suspicion of tube migration and prior to tube removal. Results: Both groups were not different with regard to age, gender, indication for tube feeding, medication use, WHO score and experience of endoscopist. Incorrect tube placement occurred significantly less frequently in the clip group (4; 6%) when compared to the standard group (15; 25%, relative risk (RR) 0.26; 95%CI 0.09-0.73). For standard tube placement, procedure time was shorter (9±10 min.vs. 14±7 min; p<0.01) and procedures were considered easier (mean VAS score 3±2 vs. 5±2, p<0.01). If adequately placed, standard tubes were also positioned more distally in the duodenum (D1-2 vs. D3-4, Standard:4 vs.54, Clip: 24 vs.34, p<0,001). Spontaneous migration occurred only rarely (clip: 1 vs. standard: 2;p=0.73). Total tube reposition rate was significantly lower with clipped (5; 8%) vs. standard tubes (n=16; 26%, RR 0.29; 95%CI 0.11-0.78).Total days of tube feeding (clip vs. standard: 6±14vs.5±13, p=0.38) and complications (2 vs.0, p=0.24) were not different.
Conclusion: Clipped nasoenteral tube placement significantly reduces total endoscopic reposition rate, due to more correctly placed feeding tubes. Although the procedure takes a few minutes longer and was considered more difficult, clipped tube placement is a safe and effective in daily clinical practice.

Prague C & M classification in Barrett's esophagus: is it really reliable in daily practice?

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The Prague C&M classification to describe Barrett's esophagus (BE) length during endoscopy has found rapidly widespread application by endoscopists. It has, however, been validated by scoring video sequences by expert endoscopists, and up to now validation data on its application during real time endoscopy in daily practice are lacking. Aim was to evaluate interobserver agreement (IOA) and absolute agreement (AA) of BE and hiatal hernia (HH) length according to the Prague C&M classification by experts and non-experts, during real time endoscopy. We conducted 2 randomized cross-over trials comparing video endoscopy with endoscopic tri-modal imaging for dysplasia detection in BE. All pts underwent endoscopy twice by 2 different endoscopists who were blinded for the results of any previous endoscopy. According to the Prague C&M criteria, distance from the incisors to diaphragm, gastric folds (GF) and circular and maximal extent of BE were prospectively collected at both endoscopies. BE length was the distance between GF and circular extent (C) and between GF and maximal extent (M). HH length was the distance between diaphragm and GF. The study population consisted of 2 groups. Group I: pts with C≥2M≥2cm or C<2M≥4cm BE studied in a tertiary referral setting by 8 endoscopists with extensive expertise in imaging and endoscopic treatment of BE. Group II: pts with any BE length studied in a community hospital setting by 9 endoscopists with no specific expertise in BE. Endpoints were IOA and AA. IOA was assessed with the interclass correlation coefficient (ICC) and interpreted as a kappa value. AA was defined as 0cm or ≤1cm difference at both endoscopies for BE and HH length. 187 pts were included with median BE length C3M5cm (IQR C1-7M4-9) and median HH 3cm (IQR 2-5). Median interval between endoscopies was 8 weeks (IQR7-10). Overall IOA for M, C and HH length were 0.91 (95%CI 0.88-0.93), 0.92 (0.90-0.94) and 0.59 (0.49-0.68) respectively. Overall AA for M, C and HH length was 31% (24-37%), 39% (32-46%) and 29% (22-35%), respectively when defined as 0cm difference and 68% (62-75%), 74% (68-80%) and 63% (56-70%), respectively when defined as ≤1cm difference. IOA and AA in group I and II did not differ significantly.

Conclusion The use of the Prague C&M criteria during real time endoscopy is associated with a high IOA for C&M BE length and a reasonable IOA for HH length. Absolute agreement ≤1cm for the length of BE and HH is achieved in the majority of patients. We observed no differences in agreement between expert and non-expert endoscopists. These findings strengthen the value of the Prague C&M criteria to describe BE length but also quantify its variability.

Sampling bias/misclassification in the diagnosis of high-grade dysplasia in Barrett's esophagus: a Dutch population-based study

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Previous studies have shown that detecting dysplastic changes in Barrett's esophagus (BE), including high-grade dysplasia (HGD), is susceptible to sampling bias by the endoscopist or misclassification by the pathologist. The extent of sampling bias/ misclassification is important for determining the follow-up strategy when HGD is found. The aim of this study was to identify 1) the prevalence of sampling bias/ misclassification of HGD in BE patients and 2) predictors of re-detecting HGD or esophageal adenocarcinoma (EAC) after sampling bias/misclassification. All patients diagnosed with HGD in BE between 1999 and 2008 in the Netherlands were identified using the nationwide histopathological registry (PALGA). Patients without histologic evaluations after a diagnosis of HGD and patients who underwent endoscopic ablation were excluded. Sampling bias/misclassification was defined as >1 histologic evaluation(s) following HGD diagnosis which was scored as less severe than HGD, including both biopsies and resection specimens. Multivariate Cox proportional hazards regression analysis was performed to identify independent predictors for the (re-)detection of HGD or EAC after sampling bias/misclassification. In total, 515 patients with HGD in BE were included. After an initial HGD diagnosis, 291 (57%) patients had no HGD or EAC in >1 histologic evaluation(s) and were classified as sampling bias/ misclassification. In 102/291 (35%) patients, HGD or EAC was (re-)detected at a later stage during follow-up. Multivariate Cox proportional hazards regression analysis showed that the risk of (re-)detecting HGD or EAC after sampling bias/misclassification was increased when patients underwent endoscopic/surgical resection compared to histologic follow-up (Hazard ratio (HR) 5.06, 95%CI 2.81-9.13) and when follow-up was performed in a university hospital compared to a general hospital (HR 2.03, 95%CI 1.17-3.52). The risk of (re-)detecting HGD or EAC was decreased when 2-3 (HR 0.28, 95%CI 0.17-0.47) or >4 (HR 0.04, 95%CI 0.02-0.08) histologic evaluations following a diagnosis of HGD were scored as less severe than HGD, compared to 1 histologic evaluation.
Conclusion: This large population-based study shows that in more than half of BE patients diagnosed with HGD, sampling bias/misclassification is involved during subsequent histologic follow-up evaluations. The risk of (re-)detecting HGD or EAC during endoscopic follow-up is increased when follow-up is performed in a university hospital and resection is performed some time after initial diagnosis and reduced with increasing numbers of histologic evaluations with a diagnosis less severe than HGD.

Validation of a DNA FISH biomarker set in a random Barrett's esophagus surveillance population

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Current surveillance of Barrett's esophagus (BE) patients have proven to be inadequate. Several of the previously identified biomarkers in BE can be efficiently assessed using DNA-fluorescent in situ hybridization (DNA FISH) on brush cytology specimens of BE patients. Previously, we showed in an academic setting that a DNA FISH marker set consisting of centromeric DNA probes specific for chromosome 7, 17, and the locus specific probes for Her-2(17q11.2-12), 20q13.2, C-myc (8q24.12-13) have high sensitivity and specificity for diagnosing HGD and EAC. Additionally, the combination of CEP 7, 17, and p53 (17p13.1), p16 (9p21) proved to be potentially prognostic. To validate a diagnostic and "potentially" prognostic DNA FISH marker set in an unselected community based BE surveillance population. Between January 2007 until November 2010, prospectively collected brush cytology specimens of 200 unselected BE patients from six hospitals in the Amsterdam/North Holland region were evaluated for the seven FISH markers. All patients underwent upper GI endoscopy for routine surveillance of BE following the 4-quadrant standard biopsy protocol. Biopsies were processed routinely for histopathological staging of dysplasia. Brush specimens were taken from the normal squamous epithelium and the Barrett segment. FISH for the seven biomarker set was carried out on the cytology specimens. Results were evaluated manually and by an automated FISH microscope using spot scoring software. Cut off values were determined in the cytology samples of the normal squamous mucosa. Finally, FISH results were correlated with histological stage. In the cohort of 200 patients, 173 patients were diagnosed with IM, 24 patients with LGD and 3 patients with HGD. The most frequent cytogenetic abnormality through the sequence of dysplasia was loss of p16: IM (53/173) 30%, LGD (17/24) 71%, HGD (3/3) 100%, (Figure1). Loss of P53 was observed in two cases of IM (1%), in 2 LGD (25%) and in one HGD (33%). Trisomy and/or tetrasomy of chromosome 17 and 7 were present in 8 (5%) and 6 (3%) of IM cases, in 5 (20%) and 2 (8%) of LGD cases respectively. Two out of three cases of HGD had trisomy of chromosome 17. There was no abnormality seen with 20q13.2, and Her-2 in the IM and LGD cases. All HGD cases showed gain of C-myc and Her-2, while in only two out of three cases gain of 20q was observed. For the prognostic markers p16 and p53 and CEP 7 and 17 there is a significant trend ($P<0.05$, Trend test) with an increasing frequency of genetic abnormalities through the sequences of dysplasia. The true prognostic potential of these markers will be determined after prospective follow up of the cohort. C-myc, 20q and Her-2 are confirmed as highly sensitive and specific diagnostic markers as they were seen only in HGD.

Radiofrequency Ablation +/- Endoscopic Resection for Barrett's Esophagus with High-Grade Dysplasia and/or Early Cancer: Durability of the Post-Treatment Neosquamous Epithelium at 5-year Follow-up

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Radiofrequency ablation (RFA) is safe and effective for complete eradication of Barrett's esophagus (BE) with high-grade dysplasia (HGD) and/or early cancer (EC) and may be safely preceded by focal endoscopic resection (ER) to remove visible lesions. Less is known regarding the long-term (5-year) durability of the neosquamous epithelium (NSE) that repopulates the esophagus after RFA. In a prospective cohort of BE patients with HGD/EC, all of whom achieved complete epithelial reversion after RFA+/-focal ER at 1-year follow-up (FU), we assessed the 5-year durability of the treatment response. At study entry patients had BE ≤10cm with HGD or EC (<T1sm1) confirmed by an expert pathologist. We removed visible lesions with focal ER followed by repeat biopsy to establish the post-ER diagnosis. We performed RFA at 2-mo intervals until all BE was visibly eradicated. Annually thereafter we performed high-resolution endoscopy with NBI, taking biopsies (4Qbx/2cm) from the NSE above the top of the gastric folds. Additionally, bx were obtained distal to the neosquamocolumnar junction (gastric cardia, analyzed separately). During and after treatment pts received high-dose PPI maintenance medication. Primary outcomes: 1) complete histological remission of HGD/EC (CR-neo), 2) complete histological remission of intestinal metaplasia (CR-IM) in esophageal bx. Secondary outcome: presence of IM in gastric cardia bx. 23 patients were included (17 men, mean age 63.4, median BE C4M7). Entry ER was performed in 13 pts for lesions showing: EC (n=4), HGD (n=6) or LGD (n=3). Worst grade post-ER (pre-RFA): HGD(n=20), LGD(n=3). All pts achieved CR-neo/CR-IM at 1-year (2 required focal escape ER). 3 pts exited study at 16, 28 and 44 mo due to unrelated comorbidity. All were CR-neo/CR-IM at last FU. Median FU (n=23) since study entry was 52 mo (IQR 44-55). FU endoscopy with bx was performed a median of 5 (IQR 4-5) times per patient (mean 77±38 bx per patient (61 NSE, 17 cardia)). All patients (n=23, 100%) demonstrated sustained CR-neo and CR-IM at every biopsy session during FU. None of the 1780 NSE bx demonstrated subsquamous IM. In 37/379 gastric cardia bx (9 pts) focal non-dysplastic IM was demonstrated (not treated). We have previously reported that RFA +/- focal ER for BE with HGD/EC is safe and effective, resulting in 100% CR-neo and CR-IM at 1-year. The results of the present long-term FU of this cohort suggest that the histologically normal NSE achieved after treatment at 1-year is further durable at 5-year FU. No patient in this cohort developed invasive cancer or sustained BE-related morbidity. The clinical relevance of focal IM in a normal appearing cardia remains unknown.

The learning curve of endoscopic resection of esophageal neoplasia is associated with significant complications even in a structured training program

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Background: Endoscopic resection (ER) is the cornerstone of endoscopic treatment of esophageal high-grade dysplasia (HGD) or intramucosal cancer (IMC). ER, however, is a technically demanding procedure requiring specific training and expertise. AIMS: to prospectively evaluate efficacy and safety of the first 119 ERs of early esophageal neoplasia performed by 6 endoscopists (20 ERs per endoscopist) participating in a structured ER training program. Methods: The program (www.endosurgery.nl) consisted of 4 trimonthly one-day courses with lectures on endoscopic work-up and ER, live-demo's, and hands-on training (HOT) on animal models. Participants performed supervised ER procedures during 4 individual HOT-days. Non-supervised ERs were recorded on video and reviewed by the program committee. Participants were full-time gastroenterologists at centres with multidisciplinary expertise in upper GI oncology and participated with an endoscopy nurse and a pathologist. All ER procedures were prospectively registered. The first 20 ERs of all participants were evaluated for: 1) rate of complete endoscopic removal of the target area including all coagulation markings; 2) complications. Results: 119 esophageal ER procedures (84 ER-cap, 35 MBM) were performed by 6 endoscopists. There were 35 en-bloc (EB) and 84 piecemeal (PM) ERs (median 3 (IQR 2-4) specimens). There were 108 ERs in Barrett's esophagus and 11 ERs for squamous neoplasia. Complete endoscopic removal of the target area was achieved in 110/119 (92%) cases. Acute complications included 6 perforations (5.0%): 5 were effectively treated with endoscopic (clips, covered stent) and conservative measures; 1 underwent esophagectomy the same day. Perforations occurred in ER procedures of 4 participants, all ER-cap procedures (7% ER-cap vs 0% MBM, p=0.18), including 4 piecemeal ERs (5% PM vs 6% EB, p=1.00). Ten acute mild bleedings (8%) were managed endoscopically. The rate of acute bleedings plus perforations did not differ between the first 10 ERs per endoscopist vs second 10 ERs (8% vs 19%, p=0.14) or EB vs PM ERs (20% vs 11%, p=0.24). Similarly, no difference in perforation rate alone was found between first 10 ERs per endoscopist vs second 10 ERs (2% vs 9%, p=0.11). Conclusion: In this intense, structured training program, the first 20 esophageal ERs of each participant were associated with a 5% (6/119) perforation rate, which is significantly higher than the 0.9% (2/216) reported for the leading center of the training program.[1] Although perforations were adequately managed, performing 20 ERs may not be sufficient to reach the peak of the learning curve in ER. 1. Peters FP, et al. Dis Esophagus 2007;20:510-5.

First prospective assessment of multiband mucosectomy for endoscopic resection of mucosal squamous neoplasia in the esophagus

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Endoscopic Resection (ER) is an appealing treatment option for early esophageal squamous neoplasia (EESN). The ER-cap technique is most widely used but is technically difficult, requires submucosal lifting and the use of multiple snares for piecemeal resections. Multi Band Mucosectomy (MBM) is a new technique based on a modified variceal-band ligator. By sucking the mucosa into the cap and releasing a rubber band, a pseudopolyp is created that can be removed using a hexagonal snare. MBM does not require submucosal lifting and all resections are performed with the same snare. The procedure has recently been evaluated in Barrett's esophagus, but no data is available on its use in early squamous neoplasia. The aim was to prospectively evaluate MBM for piecemeal ER of squamous neoplasia of the esophagus. Patients with High Grade Intraepithelial Neoplasia/Cancer and no signs of sm-invasion or metastatic disease on EUS and CT were included. Lesions were inspected with white light endoscopy (WLE), narrow band imaging and 1.25% Lugol staining, deliniated with electrocoagulation and resected with MBM. Endpoints were procedure time, endoscopic radicality, complications, histology of ER specimens, and the absence of HGIN/cancer at the site of the ER scar at 3 months follow-up. 36 patients (22 male, median 60 yrs (IQR: 57-64)) underwent MBM; all lesions were visible with WLE (Paris classification: 0-IIa: 1, 0-IIb: 27, 0-IIc: 4, combination: 4; median length: 4 cm (IQR: 3-5); median circumferential extent: 25% (IQR: 17-42)). Median procedure time was 10 min (IQR: 7-18) for a median of 3 resections (IQR: 3-6). Endoscopic complete resection was achieved in all lesions. Two mild bleedings were effectively treated during the initial endoscopy; no other complications were observed. Median max diameter of the resected lesions was 30 mm (IQR: 22-32), with a thickness of 1600 µm (IQR: 1281-1987) and a submucosal thickness of 700 µm (IQR: 500-1000). Worst histology was HGIN (n=17) or cancer (n=19; max penetration: m2: 6, m3: 8, sm: 5; max differentiation: G1: 1, G2: 12, G3: 6) with positive deep margin in 1 case (G2, sm) and lymphatic infiltration in 1 case (G2, m3). Endoscopic follow-up (median interval 13 weeks (IQR: 11-41) showed HGIN at the site of the ER scar in 1 patient which was effectively treated with APC.
Conclusion: This is the first prospective study on the use of MBM for piecemeal ER of EESN. The results suggest that MBM allows complete removal of lesions with short procedure time, few complications, and effective histological assessment of resected specimens.This technique may have significant advantages over the ER-cap technique.

Expandable Metal Stents for Malignant Esophageal Stenosis: a randomized controlled comparison of the new Evolution stent versus the Ultraflex stent

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IntroductionSelf-expanding metal stents (SEMS) provide effective palliation in patients with malignant dysphagia. However, although life expectancy is generally limited, reintervention rates due to stent dysfunction are significant. New SEMS are being designed to overcome this drawback. Compared to existing SEMS they differ in various characteristics: covering, mesh, radial force, body diameter and flanges. In the present study, we investigated whether results of SEMS placement could be improved with a new SEMS design. MethodsIn a multi-center randomized clinical trial consecutive patients with dysphagia due to a malignant esophageal stenosis were randomized to placement of a conventional Ultraflex® stent (Boston Scientific) or the new Evolution® stent (Cook Medical). Patients with a stenosis within 2 cm from the upper esophageal sphincter were excluded. Patients were followed by scheduled telephone calls at one and three months after SEMS insertion. The primary parameter was reintervention rate. Technical and functional outcome, complications, and survival were analyzed with chi-square tests, Kaplan-Meier curves, and log-rank tests.Results:A total of 80 patients (70% male; median age 66 years (range: 40-92 years)) were included in the study. Of these 71 (89%) have currently completed follow-up. Technical success was 100% in both groups. Reintervention rate was 8/35 [23%] for the Ultraflex and 2/36 [5.5%] for the Evolution stent (p=0.046). One month after stent insertion, the mean dysphagia score improved significantly in both the Ultraflex and the Evolution stent group as compared to base (from 2.83 and 3.14 to 0.67 and 0.33, respectively; p=0.000). Major complications including aspiration pneumonia and bleeding occurred more frequently with the Ultraflex (9/35 [26%]) compared to the Evolution group (2/35 [5.7%]) (p=0.045) There was no difference in overall survival between the two groups.
Conclusions. In this randomized controlled trial, the newly-developed Evolution is more effective in the palliation of malignant dysphagia than the Ultraflex. This is likely due to the larger diameter. Furthermore, treatment with the Evolution stent was associated with fewer complications. The difference in reintervention rate, however, did not reach statistical significance.

Partially versus fully covered self-expandable stent for esophageal perforations and fistula: a randomized controlled study

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Introduction:Previous results on stent therapy for benign esophageal perforations, anastomotic leaks and fistula (1) have led to increased use of self-expandable stents (SEMS). To date no prospective randomized trials have been published comparing different types of removable SEMS. We therefore compared the clinical efficacy of fully covered (FC) versus partially covered (PC) SEMS in patients with benign esophageal leaks.Methods:Between 2008 and 2010, we conducted a prospective randomized controlled, clinical trial in subsequent patients referred for treatment of benign esophageal leaks. After informed consent, patients were randomized to placement of an FC Hanaro stent (MI tech, Korea) or a PC Ultraflex stent (Boston Scientific, USA). SEMS removal was scheduled after a time-interval of 4 weeks. On removal the position of the upper flange was measured in cm from the dental verge and compared to the position at insertion to establish stent movement. The primary outcome measure was reintervention rate prior to scheduled removal. Secondary outcome measures included procedural complication rates, stent displacement, and primary stent removal success.
Results:Thirty-eight patients (82% male); median age 65 years (range: 26-82 years) were randomized to the FC group (n=19) or PC group (n=19). Esophageal leaks included iatrogenic perforations (n=17), surgical anastomotic leaks (n=14), Boerhaave's syndrome (n=6), and a fistula of unknown origin (n=1). Placement was technically successful in all patients (100%). Thirty-five patients (92%) underwent SEMS removal. Two (5%) patients died 12 and 30 days after SEMS placement, 1 (3%) patient had progression of underlying disease impeding further intervention or stent removal.In the remaining 35 (92%) patients, no significant difference was found in reintervention rate between FC (8/18) and PC (5/17) SEMS (p=0.36). Stent movement occurred more frequent in the FC group than PC (FC n=12/18; PC n=7/17, p=0.13). Four (11%) patients needed endoscopic stent repositioning due to migration uncovering the leak. In 7 (20%) the SEMS was replaced by a second SEMS, one SEMS was replaced by a duodenal feeding tube. All 35 patients succesfully underwent SEMS removal after a median of 28 days (range 1 – 60 days). During one SEMS (PC) a self-limiting bleeding occurred and subsequently a stenosis requiring repeated dilation (n.s.).
Conclusions:Temporary SEMS placement is effective in sealing benign esophageal fistulae and perforations. Although SEMS movement occurs much more frequently with fully covered as compared to partially covered SEMS, no difference was found in the reintervention rate. Since fully covered SEMS are technically easier to remove placement of a fully covered SEMS is preferred in these patients.

Long term efficacy and safety of biodegradable stent placement for refractory benign esophageal strictures: a prospective follow-up study

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Background and aim: Fully covered stents nowadays are an accepted treatment option for refractory benign esophageal strictures (RBES). Major drawbacks of these stents are high migration rates and the need for stent removal. The recently developed biodegradable (BD) stent (Ella-CS, Hradec-Kralove, Czech Republic) avoids the need for removal, but data on complications and long term efficacy are limited. The aim of the study was to evaluate safety and long term efficacy of 46 BD stent placements in patients with RBES.Methods: All consecutive patients who underwent BD stent placement for RBES between August 2008 and September 2010 were contacted 14 days after treatment and monthly thereafter. Data were collected with respect to technical success (adequate placement without need for repositioning) clinical success (>6 months dysphagia free), recurrent dysphagia and complications. Time to recurrent dysphagia was calculated using Kaplan Meier analysis. Results: In total, 46 stents were placed in 26 patients (15 males, median age 58 years (range 22-88)). Stricture origin was peptic (9), anastomotic (6), corrosive (2) radiotherapy-induced (2), lichen planus (1) or other/ unknown (6). Previous treatments consisted of multiple dilations (46%) or multiple dilations and one or more metal or plastic stent placements (54%). Ten patients had more than one BD stent placed (median 2.5, range 2-6). Stent placement was technically successful in 44 (96%) stents. Two-thirds of stents (65%) had a diameter of 25 mm and a median stent length of 9 (range 6-12) cm. Dysphagia score improved from a median of 3 (ability to swallow liquids only) to 1 (ability to eat most solid foods) 4 weeks after stent placement. Clinical success on a per stent basis (>6 months dysphagia free) was 18%, after a median FU of 240 days (range 180-760). Clinical success was achieved after a median of 2 (range 1-3) stents. Recurrent dysphagia occurred in 37/46 stent placements (80%, after a median of 66 days, range 4-270), due to stricture recurrence (58%), stent migration (13%) and food impaction (9%). In 11 (24%) stent placements, major complications occurred (severe retrosternal pain and vomiting (n=3), hemorrhage (n=3), severe retrosternal pain (n=3), fever (n=1) and aspiration pneumonia (n=1)). Minor complications included retrosternal pain, reflux or vomiting in 4 (9%) of 46 stents. Conclusion: Placement of a single BD stent is safe but only temporarily effective in the vast majority of patients with RBES treated in a tertiary referral center. Nonetheless, this treatment option may still be favored by patients as it avoids repeat endoscopy for stent removal.

Feasibility and accuracy of a new 19G EUS histology needle: an international multicenter prospective study

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Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is an established procedure in the diagnosis of lesions of the gastrointestinal tract and of adjacent organs and mainly relies on cytological specimens. A convenient and reliable method to obtain histological material does not exist but might increase accuracy. For this reason a new 19G EUS needle was developed and assessed in a prospective multicenter study. Methods: In 5 European centers 50 consecutive patients underwent a EUS- guided biopsy to evaluate intraintestinal or extraintestinal mass lesions and/or lymph nodes. All EUS procedures were done by experienced endosonographers using a convex array echoendoscope. EUS fine needle biopsies (FNBs) were performed with the newly developed 19G needle (EchoTip ProCore needle, Cook Medical Inc, Limerick Ireland) using the same technique in all centers. Only a single pass was performed. The specimen was processed for histological analysis. A dedicated local pathologist evaluated specimens in each individual center. The gold standard used to establish the final diagnosis was based on definite surgical pathology or clinical follow-up including repeated imaging examinations.A total of 50 patients were enrolled (median age 67.7). The indications were pancreatic masses(23), lymphnodes(16), submucosal lesions (6), abdominal masses(2), mediastinal mass(1), left liver lesion(1) and left adrenal gland(1). EUS-biopsy with the histology needle was technically feasible in all cases (100%). Adequate tissue samples for histological evaluation were obtained in 98% of cases (49/50). The final histologic diagnosis obtained with the 19G-ProCore needle was pancreatic adenocarcinoma(19), focal pancreatitis(1), GIST(4), leiomyoma(3), neuro-endocrine tumor(1), metastatic nodes(6), lymphoma(3), reactive nodes(6) including 1 sarcoidosis and 1 TB , epidermoid cancer(1), oat cell cancer(1) and liver metastasis(1). EUS-FNB was inconclusive in 3 cases with a suspicious of pancreatic cancer, in whom a second biopsy showed pancreatic adenocarcinoma in all cases. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the histologic diagnosis were 93.3%, 100%, 100%, 57.1% and 93.9% respectively.
Conclusions: EUS-FNB using the19G ProCore needle provided adequate histological samples in almost all cases (98%). Its overall accuracy with regard to the final gold standard diagnosis reached 94%. These promising results open up the possibility for a histological rather than the conventional cytological diagnosis when harvesting EUS guided tissue samples, including the application for immunohistochemistry for more accurate subtyping of lesions.

Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis; long-term outcome

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Previously we have reported a randomized trial that compared endoscopic and surgical drainage of the pancreatic duct in patients with advanced chronic pancreatitis, which revealed a significant benefit of surgery after a 2-year follow-up. Five years later, the long-term outcome of these patients was evaluated.Between 2000 and 2004, 39 symptomatic patients were randomly assigned to undergo endoscopic drainage or operative pancreaticojejunostomy. In 2009, follow-up information was obtained regarding pain, physical and mental health, morbidity, mortality, length of hospital stay, number of procedures undergone, and changes in pancreatic function. In addition, costs were evaluated. Analysis was performed according to an intention-to-treat principle.During the 84 months of follow-up, one patient was lost to follow-up and seven patients died from unrelated causes. Of the endoscopically treated patients, 68% required additional drainage procedures, as opposed to 5% of the patients who underwent surgery (P=0.001) and the complication rate of endoscopic treatment was higher (74% vs. 37%, P=0.022). Overall, patients assigned to endoscopy underwent more procedures (a median of twelve vs. four, P=0.001). In addition, 47% of the patients in the endoscopic group were converted to surgical treatment. Although the Izbicki painscore difference in favor of the surgical group was no longer significant at the end of the follow-up period (39 vs. 22, P=0.12), surgery was still superior in terms of pain relief (80% vs. 38%, P=0.042). Physical and mental health,length of hospital stay, changes in pancreatic function, and costs were comparable.
Conclusions: In the long term, surgery remains superior to endoscopic drainage of the pancreatic duct in symptomatic patients with advanced calcifying chronic pancreatitis. Importantly, almost half of the endoscopically treated patients were converted to surgery.

The first prospective, group sequential study evaluating a new type of fully covered self expandable metal stent for the treatment of benign biliary strictures

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Fully-covered self expandable metal stents (fcSEMS) are an alternative for progressive plastic stenting to treat benign biliary strictures (BBS) and might reduce patient burden and possibly costs. Key is a safe stent removal. Aim: We investigated the feasibility and safety of removing a fcSEMS (MITech, Korea) with a proximal retrieval lasso: a long wire thread integrated in the proximal ends of the wire mesh that enables gradual removal of the stent inside-out. The secondary aim was to evaluate stricture resolution.Methods: Non-randomized, prospective follow-up study with 3 sequential groups of 8 patients with a BBS. Patients had strictures either postsurgical (post-cholecystectomy (LCx) or liver transplantation (OLT)), 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 by 3 months if the stricture had not resolved. The second and third cohort started with 3 months and 4 months, respectively, both followed by another 4 months if indicated. Treatment success was defined by stricture resolution at cholangiography and clinical follow-up (for at least 6 months).Results: 23 patients (11 female; 20–67 yrs) were eligible for final analysis. Strictures were caused by CP (13), OLT (6), LCx (3) and PF(1). In total 37 fcSEMS were placed and removed. All removals were easy and without complications. Transient pain after insertion was common (56%) but easily managed by oral analgesics in all patients. Other complications occurred in 6 patients (26%), consisting of cholecystitis (1), cholangitis due to stent migration (1, stent replaced), or stent clogging (2, managed endoscopically by debridement of the fcSEMS), and worsening of CP (2). In the latter two patients, the fcSEMS was removed and replaced after pancreatic sphincterotomy and PD stent placement. Median follow-up was 12 months (range 8 – 22). Overall treatment success was 65% (15/23); 54% in the CP group and 80% in the remaining patients ($p<0.05$). Patients with stricture resolution after removal of the first stent (n=7; success 6/7) did better than the cohort of patients that underwent a 2nd stent placement (n=16; success 8/16); $p<0.05$.
Conclusions: fcSEMS offer a new option for treatment of BBS. Their placement and removal with a proximal retrieval lasso proved easy and uncomplicated. Treatment success for CP strictures was higher compared to what is known from results of progressive plastic stenting protocols. For other indications treatment success was similar to progressive plastic stenting, but with the prospect of fewer ERCP procedures.

Enteropathy Associated T-cell Lymphoma: a clinical prognostic model to identify high risk patients

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Enteropathy-associated T-cell lymphoma (EATL) is a rare intestinal lymphoma that arises from intraepithelial lymphocytes. In Western countries EATL accounts for 5% of all gastrointestinal lymphomas and in 80-90% of all cases this lymphoma is associated with celiac disease (CD). Based on clinical presentation, EATL can be divided into two subtypes: primary and secondary EATL. Primary EATL develops without a preceding history of CD. The first presentation is often perforation or obstruction, which leads to diagnosis of both EATL and CD. Secondary EATL is diagnosed in patients with well-established CD or refractory CD. These patients deteriorate and eventually develop EATL. The current standard treatment for both types of EATL consists of surgery and chemotherapy, but overall survival (OS) is poor and new therapeutic strategies are urgently needed. For risk-based selection of patients for new therapies and clinical trials, prognostic models as the International Prognostic Index (IPI) are generally used. Since IPI is not predictive for EATL, we determined a prognostic model specifically for EATL, which can identify high-risk patients who need more aggressive therapy.Forty-one patients were diagnosed with EATL and retrospectively analyzed. Two- and 5-years OS were 18% and 10% respectively (range: 0 - 97 months). In multivariate analysis, 3 risk factors were predictive for survival: serum LDH > normal ($P < 0.001$; RR 6.65; 95% CI 1.96 to 9.89), presence of B-symptoms ($P < 0.001$; RR 4.41; 95% CI 2.73 to 16.18) and subtype secondary EATL ($P = 0.036$; RR 2.33; 95% CI 1.06 to 5.13). A weighted point score was assigned to each of these 3 factors and a prognostic model was constructed. Four risk groups were identified ($P < 0.0001$). Group I showed most favorable outcome: 2- and 5-years OS were 55% and 30% respectively. Although survival rates in groups II, III and IV were significantly different, in none of these groups 2-years survival was achieved. Therefore, the model was simplified to a low risk and a high risk group ($P < 0.0001$). The low risk group represented patients with no risk factors, i.e. primary EATL with no B-symptoms and normal LDH. In the high risk group, patients had 1 or more of the risk factors elevated serum LDH, B-symptoms or subtype secondary EATL. The new prognostic model showed superior predictive capacity as compared to IPI.
In conclusion, our new prognostic model clearly identifies a high and a low risk group. Patients with one of the risk factors serum LDH > normal, B-symptoms or subtype secondary EATL are at high risk. Therefore especially for this group new therapies are urgently needed.

The origin of aberrant IEL in RCD II patients

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Background & Aims: Aberrant intra-epithelial lymphocytes (IEL) are the hallmark of refractory celiac disease type II (RCD II) and considered a premalignant cell population from which aggressive enteropathy-associated T cell lymphoma (EATL) can evolve. Elucidating the origin and phenotype of aberrant IEL enables a better understanding of this cell population, possibly leading to new therapeutic options. The aim of this study was to gain further insight in the origin of aberrant IEL by analyzing T-cell receptor (TCR) rearrangements, and by immunophenotypic characterization of aberrant IEL in comparison with their normal counterparts. Material & Methods: Biopsies obtained from RCD II patients that visited the out-patient gastroenterology department at the VU University Medical Centre in the Netherlands between 2003-2010 were analyzed for the presence of T-cell receptor (TCR) gamma, delta and beta chain rearrangements. Furthermore, IEL were isolated from biopsies and analyzed for expression of Ki-67, PCNA, HLA-DR, NKG2D, IL-15Ralpha and granzyme B using four color FACS analyses. Results: TCR rearrangement analyses were performed on biopsies obtained from 14 RCD II patients at time of diagnosis and from 4 patients previously treated. Biopsies of four patients displayed polyclonality, three patients revealed gamma and delta chain clonality, whereas in eight patients an incomplete beta chain was present as well. Biopsies of three patients contained a clonal, complete beta chain and remarkably, all three patients developed an EATL during follow-up. Isolated IEL from biopsies obtained during follow-up were immunophenotypically analyzed in 6 to 14 [median:9] RCD II patients. Noteworthy findings included a significantly decreased expression of PCNA in aberrant IEL as compared to normal IEL with a concomitant non-different Ki-67 expression. Furthermore, aberrant IEL showed a significantly upregulated expression of granzyme B and decreased expression of IL-15Ralpha, whereas a similar HLA-DR and NKG2D expression was observed.
Conclusions: Aberrant IEL in RCD II patients showed a heterogeneic pattern of TCR rearrangements, nevertheless clearly revealed a dominant commitment to the T cell lineage. We show that aberrant IEL originate from deranged developing precursor T-IEL and display clear differentiation to a cytotoxic phenotype. Furthermore, a decreased PCNA expression was found in the aberrant IEL with concomitant non-different Ki-67 expression. These findings support the idea of impaired DNA-mismatch repair in aberrant IEL which may result in chromosomal instability.

Multi-sugar permeability test: a promising new tool for accurate gut permeability assessment in health and disease

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Many pathophysiological situations increase intestinal permeability (IP), thereby posing a considerable threat to the human body. IP changes are classically determined by calculating the ratio of a urinary excreted large and small sugar probes after oral intake. Current assays require the administration of high sugar doses, especially lactulose, thereby decreasing the sensitivity of IP analysis. To improve IP analysis, we developed a sensitive detection method, allowing a substantial dose reduction of lactulose and the addition of low doses of sucrose, sucralose and erythritol for whole gut permeability assessment. The current study was performed to validate this new test in urine in an established in vivo human model of increased permeability of the small intestine. Ten healthy volunteers completed four test days to determine the usefulness of the new IP assay (1 g sucrose, lactulose, sucralose, erythritol, 0.5 g rhamnose dissolved in water) by comparing it to the classical dual sugar test (5 g lactulose, 0.5 g rhamnose). Both IP tests were performed in basal and indomethacin-challenged state. Urine samples were collected at base and every hour up to 5 h after oral test mix intake. Moreover, 5-24 h urine was collected. Samples were analyzed with isocratic ion-exchange chromatography and mass spectrometry. The Wilcoxon signed rank test was used for data analysis. Indomethacin significantly increased the 0-5h urinary lactulose/rhamnose (L/R) ratio in both the new assay ($P<0.01$) and classical assay ($P<0.05$). In the classical assay however, the excreted amount of rhamnose decreased ($P<0.05$), while the excreted amount of lactulose did not increase significantly, indicating less transcellular passage and unaltered paracellular passage after indomethacin intake. In the new assay, the excreted amount of lactulose increased ($P<0.01$), while rhamnose excretion was not significantly changed, reflecting increased paracellular passage, a hallmark of increased IP. Urinary sucrose levels were inconsistent, and could not be used to test upper IP. As expected, no significant change in the 5-24 h urinary sucralose/erythritol ratio was observed, indicating that colon permeability did not change after intake of indomethacin. Our results indicate that reducing the oral lactulose dose improves permeability analysis, as the indomethacin-induced increase in L/R ratio now reflects increased paracellular passage of lactulose instead of decreased rhamnose excretion. Therefore, our new assay provides a more accurate analysis of indomethacin-induced IP changes in urine, and is a promising tool in the assessment of small intestinal permeability.

Pregabalin for pain treatment in chronic pancreatitis

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Pain is a disabling symptom in chronic pancreatitis patients and difficult to treat. Recently, evidence from basic and human experimental pain research has indicated that pain processing by the central nervous system is abnormal in many of these patients and resembles that seen in neuropathic pain disorders. Drugs effective in treating neuropathic pain may therefore be of clinical value. We conducted a randomized, double-blinded, placebo-controlled trial to evaluate the effects of pregabalin as an adjuvant analgesic on pain relief, health status, quality of life and tolerability in patients with pain due to chronic pancreatitis. Sixty-four patients mostly on stable opioid-based analgesia were randomly assigned to receive increasing doses of pregabalin or placebo for three consecutive weeks. The primary endpoint was pain relief based on a visual analogue scale documented by a pain diary. Secondary endpoints included patients' global impression of change (PGIC), changes in physical and functional scales, pain character, quality of life and tolerability. Pregabalin, as compared to placebo, achieved more effective pain relief during the study period (28% vs. 20%, P=0.003). The incidence of patients with improved health status (PGIC score) at the end of the study was higher in the pregabalin group (44% vs. 21%, P=0.048). Changes in physical and functional scales, pain character and quality of life, as well as number of serious adverse events, were comparable in the two study groups.
Conclusion: Pregabalin was superior to placebo for adjuvant treatment of pain in chronic pancreatitis. (ClinicalTrials.gov number, NCT 00755573)

Lipid- and protein-enriched enteral nutrition attenuates the innate immune response during human experimental endotoxemia

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Introduction: A dysregulated inflammatory response is an important cause of morbidity and mortality in surgical and critically ill patients. Modulation of the early inflammatory response represents a potential therapeutic option to improve outcome. Previously, our group demonstrated that enteral administration of lipid-enriched nutrition effectively limits inflammation via a cholecystokinin (CCK)-mediated vagovagal reflex in rodents. Aim: The current proof-of-principle study investigates the immunomodulatory potential of continuous administration of enteral lipid- and protein-enriched (enriched) nutrition, developed to result in prolonged CCK release, during experimental human endotoxemia. Methods: After an overnight fast, 18 healthy male subjects received an intravenous bolus of Escherichia coli lipopolysaccharide (LPS; 2 ng/kg). Fasted subjects (n = 6) were deprived of food throughout the study, while subjects in the intervention groups were fed either enriched (n = 6) or isocaloric control nutrition (n = 6) via nasojejunal tube, starting 1 hour prior to LPS administration until 6 hours afterwards. Circulating levels of pro- and anti-inflammatory cytokines as well as CCK were determined in plasma, that was drawn before the start of postpyloric feeding and serially thereafter up to 8 hours following LPS administration. Two-way analysis of variance was used to detect differences between groups for serial data. $p < 0.05$ was considered statistically significant. Results: LPS administration resulted in a marked inflammatory response. Continuous postpyloric administration of nutrition increased plasma cholecystokinin levels throughout the experimental protocol. Enriched nutrition attenuated plasma levels of the pro-inflammatory cytokines TNF-α and IL-6 and the IL-1 receptor antagonist compared with control nutrition (all: $p<0.01$) and fasted subjects (all: $p<0.05$). Additionally, enriched nutrition augmented the anti-inflammatory response, reflected by increased IL-10 release compared with fasted subjects ($p<0.0001$). Peak levels of TNF-α, IL-6, IL-1 receptor antagonist were reduced by 40 ± 8%, 41 ± 9% and 37 ± 8%, respectively, while peak IL-10 levels were increased with 231 ± 19% compared with fasted subjects.

Conclusions: The current study establishes the anti-inflammatory potential of enriched nutrition in humans. The immediate anti-inflammatory effect of enriched nutrition suggests that the beneficial effects are mediated via the cholecystokinin-dependent vagovagal reflex. Our data implicate continuous enteral administration of enriched nutrition as a promising intervention to modulate the immune response in the early course of systemic inflammation.

Assessment of small bowel function in critically ill MODS patients using the citrul generation test

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Introduction. Small bowel dysfunction is a significant clinical problem in critically ill patients, associated with malabsorption, sepsis and multiple organ dysfunction syndrome (MODS). Small bowel dysfunction often unnoticed, partly due to lack of a gold standard test to assess small bowel function. A novel test, the Citrul Generation Test (CGT), is suggested to quantify enterocyte function and mass, hence, representing a measure of major intestinal function. The aim of this study is to evaluate the value and feasibility of CGT to assess intestinal function in critically ill patients with and without MODS. Patients and MethodsThe CGT was performed in 19 ICU patients with MODS (> 2 organ failures) and a control group of 16 stable ICU patients with normal renal and hepatic function, who were mechanically ventilated but not dependent of vasopressors. Median age was 69 years (64-76) and 63 (53-68) years in MODS and control patients, respectively. The MODS group had a median SOFA score of 10 (8-14), whereas it was 4 (3-5) in the control group. ($p<0.001$). APACHE II score was 28 (20-34) and 25 (20-27) in MODS and control patients, respectively ($p=0.2$).The CGT was performed following a 5 hour fast, after which 20 gr of glutamine-alanine was administered intravenously. Subsequently, plasma citrul levels were measured at fixed time points using HPLC. The area under the curve of citrul T=0 to T=75 minutes (iAUCT75) was calculated to establish citrul generation. The slope from base to peak concentrations was measured as well. Small bowel function was defined by both the citrul iAUCT75 and the slope. ResultsFasting citrul plasma concentration did not show a difference between MODS and control patients group, 37 µmol/l (23-45) and 31 µmol/l (25-38), respectively (medians, (IQR)). Peak citrul concentration was 46 µmol/l (32-65) in MODS, and 52 µmol/l (37-59) in controls ($p=0.8$). Time to peak was also similar in both groups.The slope was 0.17 µmol/l.min (0.1-0.25) in MODS, which was lower than in controls, 0,22 µmol/l.min (0.19-0.3), $p<0.05$. The iAUCT75 was lower in MODS than in controls, 461 µmol/l.min (289-726) vs 691 µmol/l/min (564-781), respectively ($p<0.05$).
Conclusions. CGT clearly identifies ICU-patients with a disturbed intestinal function, Our data are the first to indicate this novel and unique test to quantify small bowel (dys)function in at-risk populations such as patients with MODS . Future studies will delineate feasibility and accuracy of CGT in daily clinical practice.

Gender disparities in performance of a fecal immunochemical test for detection of advanced neoplasia

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Introduction. Fecal immunochemical tests (FITs) are commonly used in screening for colorectal cancer (CRC) and advanced adenomas. It has been suggested that FIT performance may be different in males and females, what could lead to over- or under-estimation of overall test accuracy. However, these disparities might also be caused by gender related differences in age of onset and advanced neoplasia distribution. Thus far, little data exist on potential dissimilarities in test characteristics between the sexes. Aims & MethodsAim of the present study is to compare the confounding influence of gender on the sensitivity and specificity of a frequently used FIT, for the detection of advanced neoplasia. In this prospective cohort study, all individuals referred for elective colonoscopy were invited to perform a semi-quantitative FIT (OC sensor®) prior to the start of bowel preparation for colonoscopy. Subjects in which colonoscopies were performed for evaluation of rectal bleeding or anemia were excluded to correct for potential work-up bias. In addition, participants with incomplete colonoscopy were excluded. Advanced neoplasia was defined as CRC and/or an advanced adenoma. Sensitivity and specificity for advanced neoplasia were compared at different cut-off values (50-200ng/ml), and multivariate logistic regression was used to study potential confounding on sensitivity and specificity of gender, age, number of advanced adenomas, and number of adenomas ≥1cm. Results In 1682 subjects (46% males), 213 participants were found to have at least one advanced neoplasm (54% present in males), i.e. CRC in 40 and advanced adenomas in 173 subjects. At 50ng/ml, sensitivity for advanced neoplasia was 47% (55% for men, 38% for women), and specificity was 92,0% (91,4% for men and 92,4% for women). At each cut-off level, females were found to have a significantly lower sensitivity (range of difference: 17,0-20,5%), but specificity was similar (difference -1,0 - 0,0%; see table 1). Multivariate logistic regression analysis showed that gender significantly influences the sensitivity for advanced neoplasia with or without correction for age, number of advanced adenomas, and number of adenomas ≥1cm.
Conclusions Gender could significantly affect sensitivity of a fecal immunochemical test for the detection of advanced neoplasia. Adjusting for gender disparity when reporting test performance should be considered in designing a screening program.

Attendance and diagnostic yield of repeated fecal immunochemical test screening with intervals of 1, 2, or 3 years: a comparative population-based colorectal cancer screening trial

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Introduction: Fecal immunochemical tests (FIT) have suboptimal sensitivity for advanced neoplasia and require successive screening rounds for an optimal preventive effect. However, data about the influence of screening interval length on attendance and diagnostic yield are lacking, nor is it known whether the increased sensitivity of FIT compared to the conventional guaiac-based FOBT allows for longer screening intervals.Methods: Three representative samples of the Dutch population (total=7,500) aged 50-75 years were randomly selected prior to invitation. Individuals were invited for two 1-sample FIT screening rounds (cut-off ≥ 50 ng Hb/mL) with intervals of respectively 1 (group A), 2 (B), or 3 years (C). Subjects with a positive FIT in the 1st screening round, and those who had moved away/died were not invited for the 2nd round.Results: In group A, attendance was 64.6% (1,544/2,391) in the 1st and 62.7% (n=1,302/2,077) in the 2nd screening round. Of the 1st round participants, 89.8% also attended the 2nd screening round. Of the non-participants in the 1st screening round, 16.3% did participate in the 2nd round. We refer to Table 1 for group B and C. Corrected for 1st round attendance, a longer screening interval improved participation in the 2nd FIT-based screening round (group A (reference) 89.8% vs. group B 90.9%, and vs. group C 91.4%; p<0.05). Attendance of 1st round non-participants was also higher in group B and C compared to the reference group A (respectively 19.3%, and 18.9%, vs. 16.3%; p<0.05). The proportion of participants attending at least one screening round did not significantly differ between the screening intervals (group A: 67.4%, group B: 66.1%, group C 67.0%; p=0.60). The overall positivity rate (PR) in the 2nd screening round was significantly lower compared to the 1st (6.0% vs. 8.4%, OR 0.69; CI 0.58-0.82). However, a longer interval was not associated with higher PR at repeated screening (p=0.36). Similarly, the overall detection rate (DR) of advanced neoplasia was significantly lower in the 2nd round (1.8%, OR 0.55; CI 0.41-0.74) compared to the 1st screening round (3.3%). Colorectal cancers were found in 0.44% of 1st round participants vs. 0.17% in 2nd round participants (OR 0.39; CI 0.16-0.98). The length of screening interval did not affect the DR of advanced neoplasia in the 2nd round (p=0.33).
Conclusion: Attendance of repeated FIT screening is moderately high with uptake percentages approximating 70%. A longer screening interval of 2 or 3 years results in significantly higher participation compared to annual screening. In the 2nd screening round, positivity and detection rates were significantly lower than in the 1st screening round. However, both were not affected by the length of the screening interval.

FOBT accuracy in subjects using acetylsalicylic acid, non steroidal anti-inflammatory drugs and warfarin: a meta-analysis

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Background. Population based screening for colorectal cancer with faecal occult blood test (FOBT) has shown to be cost-effective and is widely implemented in the Western world. The use of antiplatelet therapy, anticoagulants and non steroidal anti-inflammatory drugs (NSAID) are common in the CRC screening population. These medications are all associated with a higher risk of gastrointestinal bleeding which may affect the performance of FOBT by introducing an increased number of false positive test results. There is inconclusive evidence whether the use of these drugs should be discontinued prior to FOBT.AimTo conduct a systematic review and meta-analysis to determine the effect of antiplatelet therapy, anticoagulants and NSAID use on the FOBT detection rate of CRC and advanced colorectal neoplasia. Methods We searched the COCHRANE LIBRARY, Pubmed and EMBASE electronic databases to identify all eligible studies up to August 2010 that investigated the incidence of CRC, significant polyps and advanced colorectal neoplasia (CRC and significant polyps combined) in subjects undergoing colonoscopy after positive FOBT (guaiac or immunochemical). Subjects using low-dose aspirin, NSAID or warfarin were compared to the total population (the sum of users and controls). We performed a meta-analysis and calculated the pooled incidence of CRC, significant polyps and advanced colorectal neoplasia after positive FOBT (positive predictive value, PPV). In order to compare the incidence of CRC, significant polyps and advanced colorectal neoplasia between the two groups, the pooled relative risk (RR) and 95% confidence interval (95%CI) was calculated. ResultsOut of 315 studies, 6 studies were eligible. Three studied aspirin/NSAID use (2 differentiated between aspirin and NSAIDs) and/or 4 warfarin use. None of the three studies investigating aspirin/NSAID use found a significant effect on the PPV for CRC and/or colonic polyps (pooled RR 0.98; 95%CI 0.87-1.10). Warfarin use however was significantly associated with a higher PPV for colonic polyps (RR 1.34; 95%CI 1.13-1.59), advanced colonic neoplasia (RR 1.40; 95%CI 1.21-1.63) and CRC (RR 1.84 95%CI 1.27-2.65).
Conclusions. This systematic review and meta-analysis does not demonstrate a significant effect of aspirin and/or NSAID on the performance of FOBT. Warfarin however was associated with a significant increase in CRC and advanced colonic neoplasia. These results suggest that the use of these drugs does not need to be restricted before FOBT screening.

Antithrombotic and/or anticoagulant use is not associated with a higher false positivity rate in FIT screening

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No consensus exists on what to do with antithrombotics and anticoagulants in the setting of fecal occult blood testing. It has been argued that their use could have an adverse effect on test characteristics yet discontinuation of these drugs is associated with an increased risk of thromboembolic disease. Little is known on the effect of the use of antithrombotics and anticoagulants on the outcome of the newer fecal immune-histochemical test (FIT). The aim was to compare the positive predictive value of FIT for neoplasia in users and non-users of antithrombotic/anticoagulant agents, using colonoscopy as the reference standard. Data were collected in a Dutch FOBT based colorectal cancer screening pilot in the Amsterdam region. In 2006 and 2008 asymptomatic persons aged 50 to 74 from a predefined target area were invited to participate in FIT screening. A single OC-sensor was used with a cut-off value of 50ngHb/ml. In the absence of contraindications, a colonoscopy was advised in FOBT positives. Antithrombotic and/or anticoagulant use >3 times weekly (warfarin, aceno-coumarol, carbasalate calcium and/or clopidogrel) was recorded at the outpatient clinic in all FOBT positive persons prior to the colonoscopy. Positive predictive value (PPV) of FIT for neoplasia was defined as the proportion of persons with at least one adenoma or CRC at colonoscopy. Advanced neoplasia was defined as any adenoma ≥10mm or an adenoma with a villous component >20% or high-grade dysplasia. Colonoscopy results and data on anticoagulant use were available for 510 FIT positives: 88 persons (16%) were on anticoagulant use and 422 (76%) were not (63 carbasalate calcium; 22 warfarin or acenocoumarol; 7 clopidogrel). Patients on anticoagulants were more likely to be male (66% versus 50%), the average age was 61±7 in non-users and 65±7 in users. No significant difference in PPV for neoplasia was observed between the two groups: 74% in non-anticoagulant users versus 68% in anticoagulant users (p=0.31). Also, no difference in PPV for advanced neoplasia was detected: 47% in non-anticoagulant users versus 44% in anticoagulant users (p=0.69).
Conclusion: Patients on anticoagulants or antithrombotics at the time of performing a FIT are not more likely to have a false positive FIT result at colonoscopy. Continuation of anticoagulant or antithrombotic medication during screening with FIT does not seem to affect test accuracy.

Pathology of cancers diagnosed in participants that tested negative in the first round of a FOBT based screening pilot

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Mass-screening for colorectal cancer (CRC) using fecal occult blood tests (FOBT) is aimed at detecting cancer in an early stage. FOBT has an imperfect sensitivity for the presence of CRC, thus leaving a proportion of CRCs undetected. This may either be caused by a relatively decreased vascularisation of these CRCs undetected by FOBT or by an increased progression rate to CRC in these patients. We aimed to analyze the histopathological and molecular characteristics of CRCs that were not detected by FOBT. In 2006 and 2008, a cohort of around 10,000 average risk persons aged 50 to 74 were invited to participate in a Dutch FOBT based CRC screening pilot randomizing guaiac and FIT. All persons that tested negative in the first round but who were diagnosed with CRC within the following 3 years were identified through a cross-linkage between the study database and the database of the National Cancer Registry. Of all identified cases, clinical information was obtained from the hospital where the patient is treated. After revision, microsatellite instability- (MSI) and somatic mutation analysis was performed in the APC (mutation cluster region), KRAS (exon 2) and BRAF (exon 15) genes of all specimens.In 2006, 10,054 (49% male, median age 59) persons were invited of which 4,990 (50%) returned the test. Of these, 4,697 (94%) persons tested negative. In 17 (0.4%) persons (65% male, median age 62 (range 55 to 76) CRC was diagnosed within 3 years after the negative FOBT (median interval 27 months (range 3 to 31)). In 9 persons, a guaiac test had been performed and in 8 persons a FIT. Eight cancer cases were diagnosed clinically, through regular care based on symptoms; 9 cases were screen - detected in the second round using FIT. CRC family history was negative in 16 out of 17 cases. Location was proximal in 3 cases and distal in 14. In 3 cases coincident serrated polyps and in 7 cases coincident adenomas were identified at endoscopy or at surgical resection. One patient (6%) had multiple serrated polyps, satisfying the criteria for hyperplastic polyposis syndrome. Molecular analysis could be performed in 16 of the 17 CRC cases. APC mutations were detected in 4 (25%) and KRAS mutations in 7 (44%); one CRC had both an APC and KRAS mutation. No BRAF mutations were identified. One tumour (6%) was MSI-high, the others were microsatellite stable. Conclusion: In FOBT screening, interval CRCs are observed in a minority of individuals. These CRCs represent a molecular heterogeneous group involving both APC- and KRAS mutations, in the absence of BRAF mutations.

Sensitivity and specificity of FIT in an average risk screening population

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Early detection and removal of colorectal cancer (CRC) or its precursor lesions through population screening can reduce CRC-related mortality. Faecal immunochemical stool testing (FIT) is widely accepted as a screening test in average risk individuals. The accuracy of FIT in this population is unknown because solid comparative data between FIT and colonoscopy (reference standard) are missing. Aim of this study was to estimate sensitivity and specificity of FIT in an average risk population using colonoscopy as the reference standard. All average risk adults (50-75 years) who participated in the Dutch primary colonoscopy screening program were asked to complete one sample FIT (OC-sensor) prior to colonoscopy. FIT sensitivity was defined as the number of FIT-positives among screenees with one or more advanced neoplasias (carcinomas and advanced adenomas altogether) divided by the total number of subjects with advanced neoplasia. FIT specificity was defined as the number of FIT-negatives without advanced neoplasia divided by the total number of subjects without advanced neoplasia. An advanced adenoma was defined as an adenoma ≥ 10 mm, with villous histology (≥25% villous) or with high grade dysplasia. Sensitivity and specificity were estimated for cut-off levels of 50 (FIT50), 75 (FIT75) and 100 (FIT100) ngHb/ml. In addition, performance of FIT was evaluated by estimating the corresponding area under the ROC curve (AUC). 1,236 subjects underwent screening colonoscopy of whom 996 (81%) returned the FIT (51% male, median age 60 yrs). Of the latter group, 88 (9%) were diagnosed with advanced neoplasia, 6 (0.6%) of which with CRC. For FIT50, 100 had a positive test result (10%); 33 (33%) of them were diagnosed with advanced neoplasia and 5 (5%) with CRC. Among 896 FIT negatives, 55 (6%) screenees had advanced neoplasia and 1 (0.1%) CRC. FIT50 had a sensitivity of 38% (95% CI: 29 to 49) for advanced neoplasia and 83% (95% CI 36 to 99) for CRC with respectively a specificity of 93% (95% CI 91 to 94) and 90% (95% CI 88 to 92). For FIT75, sensitivity and specificity for advanced neoplasia was 33% (95% CI 24 to 44) and 95% (95% CI 94 to 97). Corresponding numbers for FIT100 were 31% (95% CI 22 to 42) and 97% (95% CI 96 to 98). The AUC of FIT was 0.69 (95% CI: 0.62 to 0.76).

Conclusions: In an average risk screening population, FIT50 has a high sensitivity for detection of CRC and only a moderate sensitivity for advanced neoplasia. A higher FIT cut-off level lowers sensitivity but has limited impact on specificity. One out of three screening participants with advanced neoplasia are being detected using one single FIT50.

A randomized controlled trial comparing participation and diagnostic yield in colonoscopy and CT-colonography for population based colorectal cancer screening

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Screening for colorectal cancer (CRC) is widely recommended, but the preferred strategy remains to be determined. We conducted a randomized controlled trial comparing the participation rate and diagnostic yield of colonoscopy versus CT-colonography (CTC) screening. A random selection of the Dutch population, aged 50-75 years, was 2:1 randomized to colonoscopy or CTC for primary CRC screening. CTC participants with lesions ≥10mm were offered colonoscopy, those with one or more 6-10mm lesions were offered a surveillance CT. Primary endpoints were participation rates defined as the number of participants undergoing the screening test relative to the total number of those invited to screening, and detection rate of advanced neoplasia defined as either advanced adenoma or carcinoma. Advanced adenoma was defined as those with a diameter ≥10 mm, a ≥25% villous component, or high grade dysplasia. Participants were classified based on the most advanced lesion found. A total of 8844 persons were randomly allocated to colonoscopy (n=5,924) or to CTC (n=2,920). A total of 1,236 (21%) invitees had a colonoscopy in the colonoscopy arm and 935 (32%) invitees had a CTC ($p<0.001$). Of the latter, 75 (8%) participants were offered surveillance while 70 (7%) CTC participants were referred for colonoscopy. In the colonoscopy group, 91 (8%) participants had one or more advanced adenomas while 7 (0.6%) had a carcinoma. In the CTC group, 44 (5%) participants referred for colonoscopy had one or more advanced adenomas while 5 (0.5%) had a carcinoma. The diagnostic yield of advanced neoplasia was 8.4 per 100 participants in the colonoscopy group versus 5.2 per 100 participants in the CTC group ($p<0.001$); relative to the number of invitees, these numbers were 1.7 per 100 invitees in both arms ($p=0.909$). In this randomized population-based CRC-screening trial significantly more persons responded to a CTC-based invitation, but colonoscopy identified significantly more advanced neoplasia in colonoscopy screening participants than in referred CTC participants. In combination, the proportion of invitees in whom advanced neoplasia was detected was similar with both strategies.

Perceived burden and time investment of colorectal cancer screening by colonoscopy or CT-colonography: a randomized controlled trial

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CT-colonography (CTC) is thought to be less burdensome and time-consuming than colonoscopy in population-based colorectal cancer (CRC) screening, but there are no data to substantiate this difference. We compared perceived burden and time investment in an RCT of colonoscopy versus CTC in primary CRC screening. In total, 8,844 Dutch citizens aged 50-74 were randomly invited to undergo CRC screening either by regular colonoscopy (n=5,924) or CTC (n=2,920). Colonoscopy was performed under conscious sedation with 2L Moviprep and 2L clear fluid, CTC was performed with 3x 50mL Telebrix. Perceived burden was measured 2 weeks after the procedure by a validated questionnaire. A total of 490 consecutive screenees was willing to complete a diary and to record a series of time intervals until feeling back to normal. The perceived burden questionnaire was completed by 74% (913/1,236) of colonoscopy and 73% (681/935) of CTC screenees. Drinking the bowel prep was rated more burdensome in the colonoscopy group (mean rank3.0 vs. 1.7, p<0.001), while the related bowel movements were rated more burdensome in CTC (2.1 vs. 2.2, p=0.005). 25% of colonoscopy and 52% of CTC screenees experienced abdominal pain after the examination (p<0.001). The whole screening procedure (including preparation and waiting for results) was experienced as more burdensome by CTC than by colonoscopy screenees (1.8 vs. 2.0, p<0.001). 73% of colonoscopy and 32% of CTC screenees reported the bowel prep as most burdensome. 38% of CTC screenees reported the examination itself as most burdensome. Compared to CTC, a larger proportion of colonoscopy screenees rated the procedure less burdensome than expected (mean rank 1.8 vs 2.2, p<0.001). The diary was returned by 75% (240/320) of eligible colonoscopy and 75% (127/170) of CTC screenees. For colonoscopy the median interval between starting the preparation and leaving home for the examination was 17hrs (IQR 15-18) versus 19hrs for CTC (IQR 18-20; p<0.001); leaving home and returning to routine activities the intervals were 6.0hrs (IQR 4.0-17) and 3.2hrs (IQR 2.3-6.2; p<0.001), and for leaving home and feeling completely back to normal 13hrs (IQR 5.1-22) and 24hrs (IQR 6.9-48; p<0.001). 95% of colonoscopy and 93% of CTC screenees would probably or definitely participate in a next screening round.

Conclusions: In a population-based CRC screening program, CTC was experienced as significantly more burdensome than colonoscopy, but differences were small. Time to return to routine activities was shorter for CTC, but time to feeling back to normal was longer for CTC. There was no difference in the number of screenees who intend to participate in a next screening round with the same technique.

Anticipating on implementation of colorectal cancer screening in the Netherlands: endoscopic demand versus capacity

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Introduction. Nation wide colorectal cancer (CRC) screening is advocated, but not yet implemented in the Netherlands. A screening program should not (greatly) interfere with regular health care. The Dutch Health Council has advised to implement a biennial fecal immunochemical test (FIT) based screening program for subjects aged 55-74 years old. Following a gradual introduction, an additional workload of 78.000 colonoscopies after six years is expected. Yet, trends in current endoscopic capacity and manpower are unknown. Aims & Methods: Aim of the present study is to evaluate and compare the current endoscopic capacity and manpower in the Netherlands in 2004 and 2009. In addition, it is determined how many extra colonoscopies are needed per endoscopy unit when a screening program would be implemented. In spring 2009, a questionnaire was sent to all endoscopy units across the Netherlands (N = 101), containing topics ranging from specific endoscopic procedures to current manpower. Data from 2004 obtained by the same questionnaire were used to study the changes over the last five years. Results: The response rate was 97%, representing 48.047 hospital beds. Overall, a 21% increase in endoscopic procedures was found compared to 2004 (495.571 versus 408.982 respectively), whereas the increase in workload was 52% compared to 1999 (325.000 endoscopies). Specifically, a 61% increase in colonoscopies was observed (188.494 in 2009 versus 116.815 in 2004), accompanied by a 20% decrease in sigmoidoscopies. The number of endoscopists increased slightly (598 in 2004 versus 606 in 2009). The number of colonoscopies performed per 100.000 inhabitants over the different Dutch provinces (N = 12) ranged form 879 to 1620. To cope with the additional colonoscopic workload in year six of a screening program, the number of extra colonoscopies needed per unit is 16 a week.
Conclusions: Over the last five years, a 21% increase in endoscopic capacity is observed in the Netherlands without a considerable increase in manpower. The number of colonoscopies is increasing intensively, whereas less sigmoidoscopies are performed. To cope with the anticipated extra colonoscopies needed for a FIT based screening program, workload per clinic may need to increase by 16 procedures a week in year six after implementation.

Evaluation of a quality assurance program for endoscopy services in the Netherlands

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With increasing recognition of variability in quality and safety outcomes in endoscopy there is increasing need for comprehensive quality assurance (QA) programs. A comprehensive QA program in endoscopy, called the Global Rating Scale (GRS), has been successfully implemented in England. The GRS receives wide international attention, but its applicability in other settings has not been established. As no formal standardized QA program does currently exist in the Netherlands, this study aimed to determine the applicability of the English GRS system in the Dutch endoscopy setting. The English GRS consists of 2 main domains: Clinical Quality (CQ) and Quality of Patient Experience (QPE) evaluating all aspects of the endoscopy unit. Each domain is divided in 6 items, all with 4 performance levels: level A (excellent service), B (achieving standards), C (monitor standards), or D (basic care, protocols available). Each level is underpinned by measures that must be achieved to reach a certain level. For the Dutch pilot, the GRS domains CQ and QPE were evaluated after translation into Dutch and back-translated for validation. Eleven Dutch endoscopy units participated in completing a GRS pilot census (6 teaching, 5 general hospitals). A gastroenterologist, nurse, and manager completed the census together. In the CQ domain high scores in ‘Communicating results to the referrer' (45% A, n=5/11 hospitals, Level C) were achieved. CQ items such as ‘Appropriateness' (82% D, n=9/11) and ‘Quality of procedure' (100% D, n=11/11) achieved less favorable scores as Dutch units lack running audit programs in these areas. For QPE items such as ‘Timeliness' (27% A or B, n=3/11) and ‘Booking & Choice' (36% B, n=4/11) relatively high scores were achieved in several hospitals. Improvements can be realized in the items ‘Equality' and ‘Timeliness' for the majority of hospitals (100% D [n=11/11] and 73% D [n=8/11] respectively). The items ‘Privacy' (64% C, n=7/11) and ‘Feedback' (82% C, n=9/11) were moderately addressed as most hospitals received a C performance level. Overall, 7 hospitals reached at least level B for any item (64%); 5/11 were at least Level A. No significant differences were observed in reaching a level B or A in any item between teaching vs. general hospitals (14% vs. 5%, p=0.12). The GRS is internationally applicable. In the Dutch setting, use of the GRS in a range of hospitals identified relevant service gaps, in particular pertaining to monitoring of CQ items, but also in patient experiences. The results indicate that the GRS is a useful QA tool for endoscopy, in both teaching and general hospitals. It may guide further quality initiatives in other countries as well.

Factors affecting miss rate of polyps during colonoscopy: results from a prospective, multicenter back-to-back colonoscopy study

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During colonoscopy, 22-28% of polyps and 20-24% of adenomas are missed. Interval colorectal cancer (CRC), detected after recent colonoscopy, probably originates from these missed lesions. It was estimated that 1.8-3.5 per 1,000 screened patients will develop CRC from a missed adenoma within 5 years after screening. It is unclear which factors contribute to polyp miss rates. The aim of our study was to determine patient and polyp related factors affecting miss rates of polyps and adenomas during colonoscopy. We used the database of the TERRACE study, a prospective, multicenter back-to-back colonoscopy study investigating the Third Eye Retroscope (TER), an imaging device to improve visualization behind colorectal folds. In this study, patients were randomized to undergo standard colonoscopy and then colonoscopy with TER, or vice versa. Colonoscopy results of 448 patients, included between March 2009 and January 2010 in 9 centers were studied. Miss rates were calculated for all polyps, (tubular, tubulovillous, villous or serrated) adenomas and hyperplastic polyps. All lesions were categorized for size (≤5mm, 6-9mm or >10mm) and localization in the colon/rectum. We computed odd ratios (OR) using adjusted logistic regression models to identify patient and polyp related factors that were independently associated with missed lesions. Per patient analyses were corrected for randomization group, gender, age, indication, complications, pain during or after the procedure, Ottawa Bowel Preparation Quality Score, withdrawal and starting time and the number of lesions found during the first colonoscopy. Per polyp analyses were corrected for adenoma type, size, morphology and localization. Mean age was 58.3 years (SD 10.1) and 62% (276/448) were male. Miss rate for all polyps was 24% (150/619) and 25% (90/356) for adenomas. Miss rates were significantly reduced (20% vs. 28%) in patients randomized to TER as first procedure (p=0.03). Taking both randomization groups together, more than 2 polyps detected during the first colonoscopy independently increased the risk of missing additional polyps (adjusted OR=2.91, 95%CI 1.25-6.88). Adenomas in the left colon were more frequently missed than adenomas in the right colon (adjusted OR=1.66, 95%CI 1.07-2.60). Of all factors investigated did not change the risk estimates. A quarter of all polyps is missed during colonoscopy. Factors that increase the risk of missing polyps are the finding of more than 2 polyps during colonoscopy and polyp localization in the left colon. Therefore, endoscopists should be specifically alert on detecting polyps when already polyps have been detected during colonoscopy and in the left colon.

The valuation of the increase in quality of life and health-adjusted life expectancy as a result of colorectal cancer screening in future decades; a population-based study

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Population screening has a major impact on morbidity and mortality due to colorectal cancer (CRC). The cost-efficacy of screening has been widely studied, but these studies mostly did not take savings of reduced CRC treatment into account. Most importantly, the societal gains of screening have not been calculated. Such knowledge is relevant to understand the benefits of screening and to decide on implementation of screening programs.The aim of this study was to calculate the societal gains of implementation of nationwide colon cancer screening in terms of QALY's (quality of life adjusted life years) and HALE (health-adjusted life expectancy) as well as to provide an Euro valuation of these societal gains.Literature studies were performed for data on colon cancer epidemiology, and screening outcomes over time. National / governmental databases in the Netherlands were searched to obtain the input for calculations of QALYs, HALE, and the corresponding financial gain. The mortality due to colon cancer is high, 26/1000 persons of 50 year and older in 2008, with a mean loss of 12.0 life years per patient diagnosed corresponding to 52,000 life years in the total Dutch population per year. Quality of life (QoL) of patients that survive colon cancer was less affected, 1 year after diagnosis the mean QoL of patients was 63/100 compared to 64/100 in the general population. Implementing FIT-screening (Fecal immunochemical test) will lead to diagnosis at an earlier stage, with 60% of cancers diagnosed in stage 1, leading to a mortality reduction of at least 50%-80%, to a mortality of 5-13/1000 50 year olds. This will lead to a rise in the mean HALE with 0.025 year per person in the population. On a population of 16.8 million people this translates to a mean reduction of otherwise lost quality-adjusted life years per year of 5,000 (16.8 million*0.025/average life expectancy at birth). Until 2040 the Dutch population will lose a mean of 70,000 life years by colon cancer per year because of high incidence due to an ageing population. Implementing FIT-screening will gain 35,000 life years every year in this period, which corresponds to 26,000 QALYs per year. The value of a life year varies from €40.000 to €170,000 per person/yr and the true financial gain for society can be calculated in several ways. The implementation of FIT-screening will thus result in a gain for the Dutch society of 1,0-4,4 billion euro/yr depending on the method used.This study demonstrated the implementation of FIT-screening in the coming 3 decades will result in a mean gain of 35,000 life years and 26,000 QALYs in the Dutch population per year, which translates to an amount of 1,0-4,4 billion euro/yr for the society in the Netherlands.

Endoscopy and pH-impedance in children with GERD

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Introduction: Various studies have shown discordance between outcomes of macroscopy, biopsies, pH-metry and gastroesophageal reflux symptoms in children. Multichannel intraluminal impedance monitoring (pHMII) is able to detect acid and non acid reflux episodes and is capable to correlate these with symptoms. Thus far, the relationship between endoscopy, biopsy and pHMII has not been investigated.
Objective: To determine the association between outcomes of endoscopy (macroscopy and biopsy) and pHMII in children with gastroesophageal reflux disease (GERD).
Methods: A retrospective study was performed including infants and children who underwent endoscopy with biopsies of the distal part of the esophagus between 2007 and 2009 and had pHMII performed within 1 to 3 months of the endoscopy respectively. Results of macroscopy were rated by the Los Angeles grade of esophagitis (grade A, B or C). Biopsies of the esophagus were assessed on the presence of increased or severely increased inflammatory cells. Reflux index (RI, <3%: normal, 3-7%: intermediate, >7%: positive), symptom association probability (SAP, >95%; positive) and number of acid and non-acid (pH>4) reflux episodes were derived from the pHMII measurements calculated by MMS auto scan. Statistical analysis, using logistic regression, was performed with SPSS 18.Results: 44 children were included with a median age of 26.5 months (range: 2 months-16.2 years). Table 1 and 2 represent the results of macroscopy and histology respectively, combined with pHMII. Of the children with esophagitis, 73 % had a positive SI and/or SAP (n=11). No significant association was found between the outcome of macroscopy and a positive pHMII measurement (RI >3 and/or SAP >95%) (p=0.609) or number of non acid reflux episodes (p=0.929). Neither for biopsies and a positive pHMII (p=0.070) or number of non acid reflux episodes (p=0.457). Moreover, biopsies and endoscopy did not correlate (p=0.577). Stratifying for age or the use of anti-reflux medication did not significantly change the association between endoscopy, biopsy and pHMII.
Conclusion: No associations were found between macroscopic endoscopy results, histology and/or pHMII results. When clinically suspecting esophagitis, pHMII is not useful, and endoscopy with biopsies should be performed.

Reproducibility of the histological diagnosis of celiac disease

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Aims. A small intestinal biopsy is considered to be the gold standard for the diagnosis of celiac disease (CD). However, the assessment of small intestinal histology may vary between pathologists. Our aim was therefore to determine the interobserver variability in the histological diagnosis of CD. Methods Biopsy specimens of 297 patients suspected of having CD were revised by a single experienced pathologist and compared to the original reports. Mucosal changes were scored using the Marsh classification. Serological data were collected for all patients. In patients with a discrepancy in diagnosis, clinical and serological data were used to determine the most probable diagnosis. The kappa value for inter-observer agreement was calculated. Results Although the interobserver variability for the Marsh classification was found to be moderate with a Kappa value of 0.486, the Kappa value for the diagnosis reached an almost perfect agreement (0.850). Nevertheless, in 22 patients a different diagnosis was made by the second observer. Interestingly, in this subgroup relatively more biopsies were classified to be of suboptimal quality (P-value 0.027). Based on clinical presentation, serology and follow-up, nineteen of those patients truly had CD. In fourteen of them the diagnosis was originally missed by the first observer while five cases were under-diagnosed by the second pathologist. Interestingly, those 14 missed patients were also a large proportion of the 52 patients who were initially thought to have false positive serology. Especially in the 30 patients with combined positivity for EMA and tTGA but apparently normal histology, the initial diagnosis was likely to be revised by the second pathologist (43.3%). By contrast, in only one of the 22 patients with solely elevated EMA and apparently normal histology according to the initial assessment, the diagnosis was revised.
Conclusions. CD can be missed histologically due to assessment variation between pathologists. A final diagnosis of CD should be based on histology, serology as well as response to the diet. Finally, a revision of the biopsy should be considered in case of discrepancy between serology and histology, especially when both EMA and tTGA are positive while histology appears to be normal.

Antibodies against deamidated gliadin peptides outperform anti-endomysium and tissue transglutaminase antibodies in children <2 years

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Aims. Immunoglobulin A (IgA) auto-antibodies against endomysium (EMA) and tissue transglutaminase (tTGA) are considered the most reliable serological tests to screen for celiac disease (CD). However, newly developed commercial ELISA tests using deamidated gliadin peptides (DGP) antigens may be of additional diagnostic value, especially in very young children, where EMA and tTGA have shown to be diagnostically less accurate. The aim of the present study was to determine the diagnostic accuracy of a new commercial ELISA kit (Bindazyme Human Anti-Gliadin EIA Kit IgG and IgA, The Binding Site, Birmingham, UK) and thereby determine whether antibodies against DGP (a-DGP) are useful in clinical practice, especially in young children. Methods The sera of 262 paediatric patients suspected of having CD were tested for EMA, tTGA and IgA and Immunoglobulin G (IgG) a-DGP. All patients had undergone a small intestinal biopsy to confirm or exclude CD. The sensitivity, specificity, positive predictive value (PPV) and the negative predictive value (NPV) were calculated using histology as the gold standard for CD. Additionally, these values were specifically calculated for children <2 years. Results One-hundred and forty-nine (56.9%) patients had a Marsh III lesion and where therefore diagnosed with CD. The sensitivity, specificity, PPV and NPV for IgA a-DGP were 72%, 92%, 92% and 71% respectively. For IgG a-DGP these values were 92%, 84%, 88% and 89% respectively. Sensitivity for EMA and tTGA were clearly better (98% and 97% respectively). However, specificities were disappointing, with values of 66% and 83% for EMA and tTGA respectively. The PPV and NPV for EMA was 79% and 96% and for tTGA 88% and 96%. However when the analysis was restricted to the 55 children <2 years, no misclassifications occurred when using IgG a-DGP: both sensitivity, specificity, PPV and NPV were 100%. Sensitivity for IgA a-DGP, EMA and tTGA was 85%, 95% and 98% respectively, with a specificity of 100%, 93% and 100%. The PPV was 100%, 97% and 100%, while the NPV was 71%, 88% and 94%.
Conclusions. In an overall analysis the antibody assay against deaminated gliadin did not outperform tTGA. However, when used in children <2 years IgG a-DGP had a 100% sensitivity and specificity for CD. In this specific age group IgG a-DGP seems to be preferred above tTGA.

Prevalence and predictive factors of non-alcoholic fatty liver disease in severely obese adolescents. Assessment using Magnetic Resonance Spectroscopy

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Background: Non-alcoholic fatty liver disease (NAFLD) presumably has a high prevalence in obese children. However, limited data are available regarding the exact prevalence of this disorder in unselected cohorts of children due to lack of accurate non-invasive diagnostic tools. Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive tool to detect hepatic fat content and has shown to correlate well with liver biopsy results. Objectives: To prospectively determine prevalence of NAFLD using 1H-MRS in a cohort of severely obese adolescents and identify the clinical parameters related to the presence of hepatic steatosis. Methods: Children with severe obesity (age corrected BMI equivalent >35 kg/m2) admitted to a lifestyle intervention program in a tertiary obesity centre between February 2008 and April 2010 were included. Exclusion criteria were presence of other liver diseases, alcohol abuse and use of steatogenic medication. Clinical evaluation, blood tests and 1H-MRS of the liver were performed before starting the lifestyle intervention. 1H-MRS measurements were performed on a 3.0T Philips Intera scanner. A validation study comparing 1H-MRS measurements in our institution and histopathological assessment of hepatic steatosis has shown an excellent correlation (r = 0.86) and a good sensitivity/specificity for detecting hepatic steatosis(2). Logistic regression analysis was performed to identify clinical parameters related to the presence of hepatic steatosis. All parameters with p <0.10 in univariate analyses were included in multivariate regression analyses. Results: A total of 117 children (59% â™€) were included with a mean age of 14.2 (± 2.1) years, BMI z-score 3.34 (± 0.35) kg/m2 and HOMA-Insulin Resistance index (HOMA) 3.86 (± 2.5). None was diabetic. The prevalence of NAFLD measured using 1H-MRS in this cohort was 48%. In multivariate regression analysis serum ALT (OR 4.8, 95%CI 1.9-12.4; p=0.001) and HOMA (OR 1.5, 95%CI 1.2-1.8; p=0.001) were significantly related to the presence of hepatic steatosis. Positive and negative predictive value of ALT>35 U/L were 75% and 65%, respectively, and the positive and negative predictive value of HOMA> 4.0 were 70% and 70%, respectively. BMI-SD score, abdominal circumference, blood pressure, serum lipids serum AST and GGT did not correlate to the degree of hepatic steatosis in multivariate analyses.
Conclusions: NAFLD is common among severely obese adolescents. Serum ALT and HOMA index are the clinical parameters most strongly related to presence of NAFLD, although their predictive value is limited.

Cognitive Behavior Therapy for children with Functional Abdominal Pain: preliminary results of a randomized controlled trial

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Functional abdominal pain (FAP) is a common complaint in children and adolescents. Three previous randomized controlled trials (RCT) showed that cognitive behavior therapy (CBT) is an effective treatment for children with FAP. However, these studies suffered from methodological flaws like small sample sizes and high drop-out rates. The aim of the current study was to investigate 1) the effectiveness of CBT compared to medical care (MC) on pain symptoms in a large RCT, and 2) the effectiveness of CBT compared to MC in reducing symptoms of anxiety, depression, disability due to FAP, other somatic complaints and quality of life. A total of 104 children were randomized to CBT or MC. Both treatments consisted of 6 weekly sessions with a trained masters-level psychologist in the CBT arm and a pediatric gastroenterologist/pediatric resident in the MC arm. Data were collected pre- and post-treatment and at 6 and 12 months follow-up. As at the time of the conference follow-up data will not be available yet, only complete pre- to post-treatment data were used in the analyses (N=88). Repeated measures ANOVAs were used to analyze differences in effectiveness between treatment conditions for all outcome measures. Additionally, it was calculated what percentage of children was pain free after treatment or had decreased 2 standard deviations in pain, in accordance with Jacobsen and Truax's criterion of clinical significant change. Children in both treatment conditions improved significantly in their level of abdominal pain from pre- to post-treatment (child report: $p<.001$; parent report: $p<.001$). CBT was equally effective as MC in improving abdominal pain (p for time x treatment interaction child report: $p=.421$ and parent report: $p=.218$). According to child report, 20.9% of children receiving CBT and 8.9% of children receiving MC were pain free after 6 weeks of treatment. According to parent report, this percentage was 23.3% for CBT and 13.6% for MC. 25.6% of children reported clinical significant change in the CBT condition, versus 11.1% in the MC condition. These percentages were 37.2% versus 20.5% for parent report. Concerning the other outcome measures, only for social anxiety a significant interaction effect was found, showing that CBT was superior to MC in reducing symptoms of social anxiety (child report: $p=.037$; parent report: $p=.033$).
Conclusions: Six weekly sessions of either CBT or MC both cause a significant decrease in abdominal pain and co-morbid complaints. CBT does not seem to be superior to MC over this short time period, except for it's effects on co-morbid symptoms of social anxiety.

Ursodeoxycholic acid use is associated with fat malabsorption and compromised growth in children with cystic fibrosis and mild liver disease

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Objectives and study: Liver disease in Cystic Fibrosis (CF) affects up to 30% of CF patients and is associated with a more severe CF phenotype as well as malnutrition. It is caused by inspissated bile, inducing bile duct obstruction, progressive fibrosis and eventually cirrhosis. Ursodeoxycholic acid (UDCA) therapy is commonly used for CF related liver disease as it supposedly improves bile viscosity by changing bile acid composition. However UDCA has also an impaired capability to form mixed micelles, which may negatively influence fat absorption and growth in CF patients. Therefore this study investigated longitudinally fat absorption, growth and pulmonary function in CF patients receiving UDCA for either liver cirrhosis or mild liver disease. Methods: A longitudinal, retrospective study was performed in 181 pediatric CF patients, of whom 7% received UDCA for cirrhosis and 17% for mild liver disease. The effect of UDCA on the coefficient of fat absorption (CFA), weight, height and BMI z-scores, FEV_1 and FVC was analyzed, using a multilevel linear regression model. Corrections were made for known confounders of pulmonary function and growth (age, gender, CFTR genotype, P. aeruginosa and S. aureus colonization). For the CFA analysis additional factors influencing CFA were included (PERT dose and gastric acid inhibition use). Results: At ten years of age mild liver disease patients receiving UDCA had compromised fat absorption (mean CFA 84.9% vs. 89.2%, $p<0.001$) and growth parameters (mean z-scores for weight -1.46 vs. -1.23, $p<0.001$; height -1.00 vs. -0.82, $p<0.001$ and BMI -1.20 vs. -1.02, p 0.003) compared to patients without UDCA (controls), while pulmonary function at 10 years of age did not differ. Furthermore in mild liver disease patients the yearly change of weight, height and BMI was compromised (respectively mean z-score change/ year of -0.10 vs. -0.015, p 0.006; -0.031 vs. -0.0011, p 0.014 and -0.22 vs. -0.036, p 0.003) as was yearly change of pulmonary function (mean change/ year for FEV_1 -2.8% vs. -1.5%, p 0.004 and for FVC -0.76% vs. 0.38%, p 0.008). This was in contrast with cirrhosis patients in which yearly change of CFA, growth and pulmonary function and mean values at 10 years did not differ from controls.
Conclusion: Our data suggest serious side effects of UDCA on fat absorption, growth and pulmonary function in CF patients with mild liver disease. As the suggested positive effects of UDCA on the progression of liver disease in CF, for which it is generally prescribed, so far never have been proven, our findings once more generate an urgent need for well performed and prospective randomized clinical trails with UDCA in CF patients.

Viral load reduction in chronic hepatitis B infectionameliorates the interaction of natural killer cells with dendritic cells: a keystep in achieving anti-viral immunity?

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Background: Chronic hepatitis B infection (CHB) is the result of a failing immune response towardsthe virus. Dendritic cells (DC) and natural killer (NK) cells serve as first-defense against viral intruders and regulate virus-specific T cell responses via a reciprocal interaction. We and others previously demonstrated impaired cytokine production by NK cells in CHB when total PBMC were used. The underlying mechanism for the impaired NK cell function could be a consequence of impaired DC-NK interaction. Therefore, we aimed to investigate the functional interaction of DC and NK cells in CHB and the influence of viral loadreduction.
Methods: BDCA1+ mDC and CD56+CD3- NK cells were isolated from blood of 10 healthy controls (HC) or 24 CHB patients at baseline(t=0) and after 6 months of entecavir (0.5 mg daily) therapy (t=6). Afterovernight activation with polyI:C+IFNg, DC were co-cultured with NK cells (ratio 1:5, 48h). In addition, PBMC or purified NK cells were stimulated for 24h with IL12 and IL18 to assess IFNg production. Phenotype and function were analysed by flowcytometry and ELISA.
Results: Upon IL12/18 stimulation, NK cells present in CHB-PBMC produced less IFNg compared to HC. This impairment was also significant, but less pronounced in purified NK cells. In both groups, IL12/18 stimulation of mDC-depleted PBMC resulted in decreased IFNg and addition of mDC to purified NK cells enhanced IFNg production, indicating that DC regulate NK cellfunction. DC-NK cell interaction resulted in reduced NK cell activation, i.e. CD69 expression, in CHB compared to HC. Viral load reduction increased DC-induced NK cell activation and IFNg production. To assess whether the impaired DC-NK interaction in CHB is due to a defect in DC or NK cells, frozen NK cells isolated at t=0 were co-cultured with fresh DC isolated at either t=0 or t=6. These cultures showed improved NK cell activation and IFNg production with $DC_{t=6}$ compared to $DC_{t=0}$, demonstrating impaired DCfunction in CHB with regard to NK cell activation and function that is improved by viral load reduction. In with this, supernatants of DC cultured alone or with NK cells demonstrated a diminished production of DC-derived cytokines (IL6, IL12, IL18), which was significantly improved upon treatment.
Conclusions: These data demonstrate that CHB patients display a diminished functional interaction between DC and NK cells due to impaired DC function, which can be partially restored by viral load reduction. Enhancing this reciprocal interaction could reinforce the innate and thus adaptive T cell response and might be the key step in achieving anti-viral immunity.

In vivo immunosuppressive effects of intravenous immunoglobulin on innate and adaptive immune cells involved in allograft rejection

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Intravenous Immunoglobulin (IVIg) is a safe and effective therapy for unfavorable immune responses in patients with autoimmune diseases. Interestingly, we observed that prophylactic administration of anti-HBs IVIg in hepatitis B-infected liver transplant patients reduces the incidence of acute rejection. To understand these clinical benefits, we studied the immunomodulating effects of IVIg treatment on circulating immune cells and serum cytokine level in patients.

To exclude the immunomodulating effects of other immunosuppressive drugs, the effects of IVIg treatment were not analyzed in liver transplant recipients, but in sixteen patients with hypogammaglobulinemia or autoimmune disease who were on IVIg monotherapy. Blood was collected before IVIg infusion, and 1 and 7 days thereafter. Changes in leukocyte surface markers, serum cytokine and IgG levels were measured by flowcytometry and ELISA.

Serum IgG levels increased from mean 7.0±0.7 to 17.0±2.3 one day after IVIg treatment ($p<0.001$), which was within range of increase in anti-HBs-IVIg in transplant patients in our center. Expression of the activating Fcγ receptor (FcγR) IIa on dendritic cells (DC) decreased at 1 day after treatment (T=0$\rightarrow$T=1: -33.9%, $p=0.02$), while the inhibitory FcγRIIb expression remained unchanged. Hence, IVIg significantly balances DC towards an inhibitory status. After 7 days, IVIg reduced IFNGR2 expression on DC (T=0$\rightarrow$T=7: -61.7%, $p=0.03$), which is part of the signalling receptor for the potent DC activator, IFN-γ. In addition, IVIg treatment selectively activated $CD4^+CD25^+FoxP3^+$ regulatory T-cells (Treg), as revealed by enhanced HLA-DR (T=0$\rightarrow$T=7: +16.7%, $p<0.01$) and FoxP3 (T=0$\rightarrow$T=1: +11.7%; $p=0.01$) expression and reduced CD127 expression (T=0$\rightarrow$T=7: -5.8%, $p=0.03$) post-treatment, while not affecting conventional T-cells. Serum concentration of the anti-inflammatory cytokine IL-10 increased 2.5-fold one day after treatment ($p=0.02$).

Conclusion: IVIg has selective immunomodulating effects on innate and adaptive immune cells involved in allograft rejection in patients. By downregulation of FcγRIIa and IFNGR2 expression, IVIg suppress responsiveness of DC to immune complexes and IFNγ. Additionally, the activation of natural Treg and enhancement of systemic IL-10 levels by IVIg suggest that IVIg can effectively suppress inflammatory responses. Hence, by targeting the immune system *in vivo* at these different levels, IVIg may be a promising candidate for immunosuppression after liver transplantation.

Human hepatoma cell HepaRG based bioartificial liver therapy increases survival time in rats with acute liver failure

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Bioartificial livers (BALs) should bridge liver failure patients to liver transplantation or liver regeneration. BALs comprise a bioreactor loaded with cells, and their efficacy heavily relies on the functionality of the cells applied. In this study, we evaluated the potential of the human hepatoma cell HepaRG for BAL application. HepaRG cells were cultured in laboratory scale AMC-BALs (n=6) for 14 days and analyzed for growth characteristics, expression of various hepatic genes, and liver specific functionality. Next, HepaRG BALs were tested for efficacy in a rat model of acute liver failure (ALF; n=6), induced surgically by liver ischemia. Control rats were treated with an empty BAL. The pimary endpoint was survival time, and secondary endpoints were progression of hepatic encephalopathy (clinical score), plasma ammonia levels, renal function (plasma creatinine), and bleeding tendency (hemoglobin and intra-abdominal blood loss). Total protein content demonstrated a stable culture of HepaRG cells in the BAL for 14 days. Histological inspection revealed liver-like tissue with polarized cells throughout the bioreactor. Expression levels of hepatic genes remained stable or increased by BAL culture. Ammonia elimination and urea production reached 52% and 10% of the rate of a primary porcine hepatocyte BAL. For lactate consumption this level was 62%. Detoxification function and synthetic function, as tested by the production rates of 6β-hydroxytestosterone and apolipoprotein A-1 reached 22% and 192% of primary human hepatocyte cultures. HepaRG BAL treatment of ALF rats increased survival time with 47% from 9.7 to 14.3 hours ($p = 0.002$). In addition, HepaRG BAL treatment significantly and substantially slowed down the progression of hepatic encephalopathy and renal dysfunction, ammonia accumulation (28%) and bleeding tendency.
Conclusion: Utilization of HepaRG cells as a biocomponent in the AMC-BAL results in a BAL with high hepatic functionality that proves efficacy in a rat model of ALF.

Pharmacological inhibition of human Multidrug Resistance-associated Proteins (MRPs) reverses liver fibrosis in vitro

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Background: Chronic liver diseases are characterized by the formation of scar tissue and leads to liver fibrosis. Currently, there are no effective therapies to prevent or reverse liver fibrosis. Chronic liver injury leads activation and proliferation of hepatic stellate cells (HSC) and portal myofibroblasts (PMF) that both produce excessive amounts of extracellular matrix proteins, including collagens.
To understand why HSCs are able to survive and proliferate in a diseased liver, we previously analyzed the expression of ATP-binding cassette (ABC) transporters in rat and human HSCs. ABC-transporters like MDR1 and MRP1 are well-known for their cytoprotective function for normal and malignant cells. We found that HSCs contain high levels of MRP1 and MRP5 and blocking their transport function by MK571 induces necrosis in rat HSCs.
Aim: 1)To determine the MDR/MRP expression profile in rat PMF and human HSC-cell line LX-2; 2) To establish the effect of MK571 and siRNA-mediated inhibition of MRP1 on the expression of fibrotic markers in LX-2 cells.
Material and Methods: The expression of MDR1, MRP1-6, and fibrosis makers (αSMA, collagen1a1, TGF-b, PPARγ) was determined by qPCR. LX-2 cells were treated with MK571 in the presence or absence of human recombinant transforming growth factor-beta (hrTGF-β) and expression levels of markers of liver fibrosis were measured by qPCR and western blotting. MRP1 expression was inhibited by transient transfection of LX-2 cells using MRP1-selective siRNA duplexes. Necrotic cell death was determined by LDH release assays; cell proliferation by BrdU incorporation and metabolic activity by WST assays.
Results: MRP1 is the most dominantly expressed MRP in both PMF and LX-2 cells.. MK571 treatment and/or siRNA-mediated MRP1 inhibition significantly reversed the TGF-β-induced mRNA levels of collagen1a1 and TGF-β and enhanced the expression of the peroxisome proliferator activated receptor-gamma (PPARγ), a marker for quiescent HSCs. 50 μM MK571 induced only limited LDH release, but strongly decreased metabolic activity and cell proliferation. No significant apoptotic cell death was detected.
Conclusion: MRP1 is prominently expressed in the various cell types that contribute to liver fibrosis. MRP1 is involved in HSC activation and viability. MRP1 is therefore a potential target to treat liver fibrosis.

Chronic prednisolone treatment leads to dyslipidemia in mice carrying a dimerization-defective glucocorticoid receptor

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Chronic use of anti-inflammatory synthetic glucocorticoids, such as prednisolone, is limited by the severe side effects they induce. Many of these side effects resemble the metabolic syndrome, such as weight gain, insulin resistance and dyslipidemia. Glucocorticoids act via the glucocorticoid receptor (GR), which shows activity both as dimer or monomer, leading to transcriptional activity or cytosolic protein-protein interactions, respectively. To segregate these effects a mouse model has been developed with a mutation in the dimerization part of the GR, in this GRdim mouse only monomeric GR is active. We aimed to elucidate the effects of chronic prednisolone treatment on metabolic profiles in GRdim and wild type mice. Wild type and GRdim mice received sustained treatment of prednisolone for 6 days, by implantation of a pellet. Before and during the treatment, plasma glucose levels and lipoprotein profiles were determined. After 6 days, livers were collected and analyzed for lipid levels and gene-expression pattern. Six day prednisolone treatment did not influence fasting glucose levels in GRdim mice, but strongly increased plasma triglyceride and cholesterol levels. This was already apparent after one day of treatment. Prednisolone treatment resulted in a dramatic increase of triglycerides (644 vs 72 nmol/fraction, GRdim Pred vs WT ctr), phospholipids (196 vs 15 nmol/fraction) and free cholesterol (201 vs 34 nmol/fraction) in the VLDL fraction of prednisolone treated GRdim mice. Surprisingly, hepatic lipid levels did not change. The unusual lipid profile was not caused by cholestasis since plasma bile acid concentration did not increase. Hepatic gene expression levels showed no major differences in genes involved in cholesterol conversion and HDL metabolism as well as in bile acid secretion and production. Interestingly, gene expression levels of the “starvation” hormone fibroblast growth factor 21 (fgf21) was 10 times induced. In conclusion this study showed that sustained prednisolone treatment in GRdim mice leads to an atypical VLDL particle containing high levels of triglyceride, phospholipids and free cholesterol.
These results indicate an important role of monomeric GR in lipid metabolism and this could contribute to unravelling the mechanisms underlying glucocortoid-induced side effects.

Hepatocyte-derived MicroRNAs in Human Serum are Sensitive Markers for Hepatic Injury in Liver Transplantation

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Background: MicroRNAs (miRNA), a class of small non-coding RNAs, are key regulators of many cellular functions by post-transcriptional suppression of gene expression. MiRNAs are emerging biomarkers for cancer and recent studies in animal models have highlighted the potential of hepatocyte-derived miRNAs (HDmirs) in serum as early and sensitive biomarker for liver injury. However, whether HDmirs are useful markers in humans remains unknown. The aim of this study is to investigate the utility of serum HDmirs in patients with liver disease and after liver transplantation.
Methods: Liver graft biopsies (n = 50) and serum samples from healthy controls (n = 12) and liver transplant recipients and candidates (n = 70) were analyzed. Hepatocyte-derived miRNAs, miR-122 and 148a, were quantified by RT-PCR.
Results: We found the expression of miR-122 and miR-148a in liver tissue showed a significant reverse correlation with the duration of the graft's warm ischemia time (R = -0.31 and R = -0.40 respectively, $P < 0.05$). In patients, levels of serum HDmirs significantly correlated with transaminases (AST and ALT, $R \geq 0.75$, $P < 0.001$) and were significantly elevated as compared to healthy controls. Even in patients with serum transaminases below 50 IU/L, a significant increase of HDmirs was found (> 8-fold, $P < 0.01$). In patients experiencing an episode of acute rejection, serum HDmirs were 9-fold higher as compared to levels six months after rejection was resolved (n = 10, $P < 0.005$). Interestingly, longitudinal analysis in three patients showed the peak of serum miRNAs preceded the elevation of transaminases, suggesting HDmirs are early markers for liver injury. Additional testing showed that repeated freezing and thawing of serum samples did not cause degradation of HDmirs.
In conclusion: This study is the first to show the potential application of miRNAs in serum as biomarkers in the setting of liver transplantation. Our results show that HDmirs represent novel candidates for stable, specific and sensitive biomarkers for liver injury in humans.

FcaRI expressing neutrophils induce severe colitis through binding of IgA-opsonized bacteria

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Ulcerative colitis is a chronically remitting and relapsing disorder, characterized by severe inflammation of the intestinal tract. In ulcerative colitis large neutrophil infiltrates are observed in the lamina propria and we recently demonstrated that neutrophils in the colon of these patients have phagocytosed dimeric IgA-opsonized bacteria via the IgA Fc-receptor FcaRI. Moreover, we recently identified a key role for FcaRI in mucosal defence as cross-linking of FcaRI by IgA-antigen complexes induce leukotriene B4 mediated neutrophil recruitment. These infiltrating neutrophils are very efficient for clearing an impending infection. However, this mechanism of neutrophil recruitment may have detrimental consequences in ulcerative colitis, as this disease displays excessive IgA-antigen complexes in the lamina propria. Therefore, we investigated the role of IgA-FcaRI interactions in experimental colitis in mice. To study this, we generated new transgenic (Tg) mice expressing human FcaRI and human IgA, hereby fully mimicking the human situation. Strikingly, these FcaRI-IgA Tg mice suffered from severe colitis indicated by irreversible and serious weight loss, tissue damage of the intestines and massive neutrophil infiltrates in cryosections of the colon. In contrast, control human IgA-mice lacking FcaRI experienced only mild symptoms of colitis and recovered fast. Thus, FcaRI plays a crucial role in aggravation of ulcerative colitis by continuous neutrophil activation and infiltration. Importantly, blocking FcaRI with a monoclonal antibody abrogated IgA-dependent neutrophil activation and migration in vitro. Therefore, novel therapeutic strategies that block dIgA-FcaRI interactions in ulcerative colitis may dampen the uncontrolled inflammatory processes in these patients and improve quality of life.

A preoperative protein free diet protects against hepatic ischemia and reperfusion injury

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We have previously shown that three days of preoperative fasting protects against hepatic ischemia and reperfusion (I/R) injury. As pre-operative fasting is currently considered an unwanted necessity, the aim of the current study was to design a more clinically applicable diet that protects against hepatic I/R injury. Therefore, we investigated the effect of a three day preoperative protein free diet on hepatic I/R injury.Male C57BL/6 mice were fed a control diet for two weeks. Hereafter, mice were randomized into three groups. They received either control food, no food or protein free food three days prior to I/R injury. I/R was induced by clamping the hepatic artery and vein to 70% of the liver for 75 minutes. Liver damage was assessed by means of serum ALAT and LDH levels, and percentage of hemorrhagic necrosis on haematoxylin and eosin stained sections. Three days of fasting reduced bodyweight by 17.6% (±3.3%), and protein restriction by 9.6% (±1.8%). Ad libitum fed control animals gained 3,2% (±0,7%). At six hours after reperfusion both serum ALAT and LDH of the protein restricted group were significantly lower when compared to the control and the fasted group. At 24 hours after reperfusion they were significantly lower than the control group. Furthermore, preoperative protein restriction significantly reduced the amount of hemorrhagic necrosis at 24 hours after reperfusion when compared to the control group. Conclusions: A preoperative protein free diet reduces preoperative weight loss and results in a more robust protects against hepatic I/R injury as compared to preoperative fasting. This nutritional intervention is a promising new strategy to implement in the clinical setting.

Smoking is an environmental factor that modulates innate immune functions associated with Crohn's disease

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Crohn's disease (CD) is a chronic inflammatory disorder of the intestine that is caused by a complex interplay between genetic and environmental factors. It is estimated that the relative contribution of genetic and environmental factors to CD is approximately 20% and 80%, respectively, where cigarette smoke is the most prominent environmental factor. Genome-wide association studies have revealed a crucial role for innate immunity (phagocytosis) and autophagy (ATG16L1, IRGM, NOD2) in CD development, shifting the primary focus for therapeutic targets for CD to these cellular processes. Our recent data show that the therapeutic drug Azathioprine increases the phagocytotic activity of human monocytes, thereby stimulating innate immunity. As smoking aggravates CD, it is important to determine whether smoke affects innate immune functions, in particular when combined with immunomodulatory drugs like Azathioprine. Peripheral blood monocytes of healthy individuals were isolated by $CD14^+$ magnetic beads and cultured in the presence of different concentrations of cigarette smoke-saturated medium (CSE). The phagocytotic activity was measured by quantifying incorporation of FITC-labeled zymosan particles using fluorescence microscopy. In addition, mouse macrophages (RAW264.7) were treated with different concentration of CSE. Autophagic activity was monitored by the conversion of LC3-I to LC3-II biomarkers using Western blotting.The phagocytotic activity of primary monocytes of healthy controls was dose-dependently decreased after pre-exposure with CSE (0.5%, 1%, 2% and 5%) for 30 min. Similar results were obtained with RAW264.7 cells, though at higher concentrations of CSE (5%, 10%, 20% and 30%). Expression levels of the autophagy marker LC3-II were dose-dependently enhanced after CSE exposure (5%, 10%, 20% and 30%) of RAW264.7. Viability of these cells was not affected at these CSE conditions, as the metabolic activity of the exposed cells was similar compared to control cells.
In conclusion, cigarette smoke strongly affects innate immune responses, although opposite effects were observed on phagocytosis (repression) and autophagy (induction). Smoke-induced aggravation of CD may therefore result from shifting monocytes from their immunological function to cell survival.

Autophagy Regulates Immune Responses through Destabilization of the Immunological Synapse

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Various polymorphisms in the autophagy related genes ATG16L1 and IRGM have been associated with the development of Crohn's disease (CD). 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. Therefore, this study focused on the effects of decreased autophagy on the immunogenicity of dendritic cells (DC).Gene knockdown was achieved in human or mouse primary DC using siRNA. DC-T cell interactions were induced in mixed lymphocytes reactions (MLR), and cytoskeletal changes and interaction times were studied by immunofluorescence and time-lapse microscopy. T cell reactivity was determined by 3H incorporation. For patient studies, monocytes were obtained from peripheral blood of CD patients genotyped for rs_2241880.ATG16L1^{low} and IRGM^{low} DC induced significantly more T-cell proliferation in both an allogeneic MLR and an antigen specific proliferation assay. This finding was consistent in human and mouse cells, suggesting a conserved role for autophagy in the regulation of immune responses. No alterations in cytokine production or surface marker expression of autophagy^{low} DC were seen, indicating the immunostimulatory phenotype is not due to increased maturation. However, clear aberrancies occured at the site of contact between DC and T cells, the so-called immunological synapse (IS). Autophagy^{low} DC displayed increased cytoskeletal polarization towards interacting T cells, and interaction times between DC and lymphocytes were prolonged, pointing to IS hyperstability. To confirm the physiological role of this mechanism, we compared IS formation in CD patients carrying the ATG16L1 risk allele and patients carrying the wild type allele. Indeed, IS formation was increased significantly in homozygous risk allele carriers compared to wild type controls.Finally, autophagy^{low} DC more effectively induced Th17 polarization without affecting Th1 cells, increasing the Th17/Th1 balance. This effect was likely due to the IS hyperstability observed, as destabilizing the synapse pharmacologically had the opposite effect and tilted the balance towards Th1.
Conclusions. Decreased levels of autophagy results in an increased pro-inflammatory capacity in both human and mouse DC. This effect is regulated through hyperstabilization of the IS, leading to increased T cell activation and tilting of immune responses towards a more Th17 phenotype. This phenotype was confirmed in cells obtained from risk allele carriers and is therefore likely to contribute to the increased immune activation as seen in CD patients carrying autophagy-related SNP.

Dietary non-digestible oligosaccharide-induced epithelial galectin-9 secretion correlates with protection against allergic symptoms

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Background: Intestinal epithelial cells (IEC) abundantly express galectins, which are known to modulate T cell responses. In this study, immune modulation and epithelial expression of galectin-9 (Gal-9), induced by a galacto/fructooligosaccharide mixture (scGOS/lcFOS) and TLR9 ligand, and its relevance for the suppression of allergic disease were determined both in vitro and in vivo. Methods: Human IEC were grown on transwell inserts and apically exposed to 0.5% scGOS/lcFOS together with Toll-like receptor ligands and co-cultured with activated healthy donor PBMC in the basolateral compartment. After 24h, cytokines and immune cell phenotype were measured. In vivo, mice were sensitized orally to whey, while being fed a diet containing Bifidobacterium breve M-16V and scGOS/lcFOS (GF/Bb). Gal-9 expression was determined by immunehistochemistry in the intestine and measured in the serum by ELISA. In addition, in a double-blind, placebo-controlled multicentre trial, Gal-9 levels were measured in sera of 90 infants with atopic dermatitis that received hydrolyzed formulae with or without GF/Bb for 12 weeks. Results: IEC-derived Gal-9 mRNA, protein expression, and basolateral secretion increased after combined addition of scGOS/lcFOS and TLR9 ligand in the co-culture model. This coincided with enhanced IL-10 and IFN-g secretion by PBMC and increased percentages of T_h1 and T_{reg} cells. Basolateral neutralization of galectins suppressed IL-10 and IFN-g, but enhanced IL-6, IL-17 and TNF-a secretion. Furthermore, development of T_h1 and T_{reg} cells was enhanced in Gal-9 treated PBMC, resulting in increased IL-10 and IFN-g, but suppressed IL-17 secretion in a dose dependant manner. Immunohistochemistry in mouse intestine revealed expression of Gal-9 in epithelial cells in the small intestine. Interestingly, the GF/Bb diet enhanced serum Gal-9 levels, which correlated with decreased allergic symptoms. In addition, infants suffering from atopic dermatitis receiving the GF/Bb diet also showed enhanced Gal-9 levels in serum, which coincided with less severe allergic symptoms. Conclusion: GF/Bb-induced Gal-9 expression by IEC may protect against the development of allergic disease by modulating the effector T cell response.

Activation of bile salt nuclear receptor FXR is repressed by pro-inflammatory cytokines activating NF-κB signalling in the intestine

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Hyperactivation of NF-κB is a key factor in the patho-physiology of inflammatory bowel disease (IBD). The nuclear receptor and transcription factor Farnesoid X Receptor (FXR) is highly expressed in the liver and intestine and is the master regulator of bile salt homeostasis. We previously showed that FXR counter-regulates intestinal inflammation, possibly via NF-κB repression. Here, we examine whether mutual antagonism between NF-κB and FXR exists. FXR and target gene expression was determined in differentiated HT29 colon carcinoma cell and ex vivo in intestinal specimens of wild type (WT) and Fxr-ko mice, with or without FXR ligands (GW4064 or INT-747) and inflammatory stimuli (TNFα or IL-1β). In addition, FXR activation was studied in vivo in WT and Fxr-ko mice with DSS-colitis and in IBD patients (Crohn's and Ulcerative colitis patients) and healthy controls. Underlying mechanisms were explored in complementary in vitro experiments. FXR target gene expression was highly reduced by inflammatory stimuli in all models, while FXR expression was unaffected. In with this results, Crohn's but not Ulcerative colitis patients displayed 50% decreased expression of the FXR target gene SHP compared to controls, while FXR expression resulted not altered. Indeed, reporter assays showed reduced FXR transcriptional activity upon TNFα or IL-1β stimulation. We next investigated the involvement of NF-κB in the pro-inflammatory- induced repression of FXR activity, and showed that co-transfection with the NF-κB subunits p50 and/or p65 resulted in markedly reduced FXR transcriptional activity. In addition, physical interaction between NF-κB subunits and FXR was observed in GST-pull down assays.
Conclusions: Together, these results indicate that intestinal inflammation strongly reduces FXR activation, probably via NF-κB-dependent tethering of FXR. Therefore, FXR not only inhibits inflammation, but also is targeted by the inflammatory response itself. This could result in a vicious cycle where reduced FXR activity results in less repression of inflammation, contributing to development of chronic intestinal inflammation. Also, decreased FXR activity could lead to derailed bile salt homeostasis potentially relating to liver disease often coexisting in patients with IBD.

Involvement of G -protein coupled receptors in bile acid-induced apoptosis in primary rat hepatocyte

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Background: G-protein coupled receptors (GPCR) represent the largest family of transmembrane receptors. Many studies have investigated the role of GPCRs in liver diseases and have reported the existence of GPCRs for bile acids in Kupffer cells and sinusoidal cells. However, the involvement of GPCRs in bile acid induced –apoptosis in hepatocytes has not been well described. Aim: to investigate the involvement of Gαi-protein coupled receptors in glycochenodeoxycholic acid (GCDCA)-induced apoptosis in primary rat hepatocytes. Methods: Hepatocytes were isolated from Wistar rats. To induce apoptosis, hepatocytes were exposed to GCDCA (50 µmol/L). The Gai inhibitor pertussis toxin (PTX; 200 nmol/L) was added 30 minutes prior to GCDCA. Hepatocytes were treated with sphingosine kinase inhibitor SKI II (1-10 µmol/L), sphingosine-1 phosphate receptor 1/3 antagonist VPC23019 (5 and 10 µmol/L) and sphingosine-1 phosphate receptor 2 antagonist JTE-013 (5 µmol/L) 30 min prior to apoptotic stimuli. Apoptosis was determined by measuring caspase-3 activity and acridine orange staining. Necrosis was determined by Sytox green staining. Results: PTX inhibited GCDCA-induced apoptosis ($p< 0.05$) and did not increase necrosis in hepatocytes. Theses data indicate the involvement of Gαi-protein coupled receptors in GCDCA-induced apoptosis. Previous studies have described a possible role for sphingosine and its metabolite, sphingosine-1 phosphate, the product of sphingosine kinase, in cell survival and apoptosis. Therefore, we inhibited sphingosine kinase with SKI II. Inhibition of sphingosine kinase reduced GCDCA–induced apoptosis in hepatocytes ($p < 0.05$). qPCR revealed that primary cultured hepatocytes express mRNA of both $S1P_1$(Edg 1) and $S1P_2$ (Edg 5) which are known to be Gαi-protein coupled receptors. Pretreatment of cells with $S1P_{1/3}$ antagonist VPC23019 reduced GCDCA-induced apoptosis by 30% while treatment with $S1P_2$ antagonist JTE-013 had no effect on GCDCA–induced apoptosis. These findings indicated that S1P via its receptor, $S1P_1$ (Edg1) may be involved in GCDCA-induced apoptosis in primary rat hepatocytes. Conclusion: Inhibition of Gαi-protein coupled receptors by PTX protects hepatocytes from bile acid-induced apoptosis. Our results indicate that sphingosine-1 phosphate and $S1P_1$ (GαiPCR) are involved in bile acid–induced apoptosis in hepatocytes. Our findings suggest new potential strategies for treatment of bile acid toxicity through pharmacologic inhibition of GPCR.

Vitamin A deficiency strongly aggravates liver damage during obstructive cholestasis; acute vitamin A therapy is the cure

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Background. Vitamin A is an essential nutrient compound that mammals obtain from dietary carotenoids and retinyl esters. Bile salts aid in the intestinal absorption of vitamin A, after wich most is stored in the liver. Vitamin A-metabolites, especially various retinols, are important for regulating cell differentiation, proliferation and immunological processes, in particular by activating the nuclear receptors Retinoic Acid Receptor (RAR) and Retinoid X recpetor (RXR). Both transcription factors also perform key functions in the liver by regulating bile salt, lipid en glucose homeostasis as well is the intrahepatic immune response. Chronic liver diseases are characterized by hepatic vitamin A loss often leading to vitamin A deficiency (VAD). Recently, we showed that VAD strongly aggravates liver damage in the bile duct ligation (BDL) model in rats. Here, we performed a transcriptome analysis to characterize the prominent cell biological processes in the liver that are disturbed in obstructive cholestasis under VAD conditions.
Methods. Rats were made VAD by omitting vitamin A from their diet for 16 weeks, followed by ligation of the common bile duct (BDL). 7 days later, the animals were sacrificed. During the 7 days of BDL, half of the animals received daily IP injections with retinyl-palmitate (vitamin A therapy). Bile salt concentrations and liver damage markers (AST/ALT) were determined in serum. Whole genome gene expression in liver tissue was analyzed with the Illumina platform RatRef-12 beadchip. False discovery rate (FDR) was set at a stringent 1%. Data were confirmed by quantitative real time PCR, Western blotting and/or histochemistry.
Results. BDL induced dramatic liver damage in VAD rats with serum liver damage markers (AST/ALT) approximately 10-fold increased compared to BDL rats receiving a vitamin A-sufficient (VAS) diet. Only 20 genes were differentially expressed between sham-treated VAS and VAD rats and clustered in the vitamin A metabolism, immune response, carbohydrate and lipid homeostasis. In contrast, 1583 genes were differentially expressed between the BDL-treated VAS and VAD rats. The strongest effects were observed in genes from the vitamin A metabolism, immune reponse, collagen production and oxidative stress response. Importantly, all the liver disease markers and most gene expression levels were efficiently reversed by retinyl-palmitate therapy to the levels observed in VAS-BDL rats.
Conclusions. We conclude that vitamin A deficiency dramatically aggravates liver damage caused by obstructive cholestasis. The transcriptome analysis suggests that a disturbed immune reponse may be the predominant causative factor.

Essential fatty acid deficiency induces intestinal cholesterol excretion in mice

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Essential fatty acid (EFA) deficiency in mice is associated with altered small intestinal function, as demonstrated by fat malabsorption and decreased negative feedback on bile salt synthesis via the small intestine. However, effects of EFA deficiency on cholesterol excretion are not known. Induction of fecal cholesterol loss by dietary means could be of therapeutic value, for example in patients with hypercholesterolemia. We determined cholesterol excretion in a mouse model of EFA deficiency to assess mechanistic possibilities to manipulate cholesterol excretion. EFA deficiency was induced in mice by feeding an EFA-deficient diet during 8 weeks. We determined body weight, dietary intake and dietary, biliary, intestinal and fecal cholesterol levels. Dietary cholesterol intake (2.3 ± 0.2 versus 2.1 ± 0.1 µmol/ 100g BW/ day) and biliary cholesterol secretion (3.3 ± 0.9 versus 2.8 ± 1.4 µmol/ 100g BW/ day) were similar in EFA-deficient and control mice. Fecal cholesterol excretion however was significantly increased in EFA-deficient compared with control mice (8.1 ± 1.6 versus 4.5 ± 1.0 µmol/ 100g BW/ day, p=0.003). Cholesterol balance classically is suggested to consist of dietary intake + biliary secretion - fecal cholesterol output. EFA deficient mice had a positive cholesterol balance compared with control mice (p=0.015), indicating non-hepatobiliary cholesterol excretion. In EFA-deficient mice, cholesterol amounts in the intestinal lumen were increased in the mid part of the small intestine (0.08 ± 0.02 versus 0.04 ± 0.02 µmol, p= 0.01) and in the total intestinal tract (0.44 ± 0.08 versus 0.33 ± 0.09 µmol, p= 0.03) compared with controls.
Conclusion: Our data show that EFA deficiency is associated with cholesterol hyper-excretion via the intestine. Induction of intestinal cholesterol excretion by dietary means could represent an attractive target in prevention and treatment of cardiovascular disease.

Phosphorylation of FXR-S228 is necessary for transactivation of bile salt homeostasis genes but not transrepression of inflammatory signalling via NF-κB

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The bile salt nuclear Farnesoid X receptor (FXR), is a key regulator of bile salt, cholesterol, lipid and glucose metabolism via classical transactivation of gene expression. FXR binds as an heterodimer with Retinoid X Receptor (RXR) to the FXR responsive elements on the promoters of target genes. In addition, we have recently shown that FXR also regulates inflammation status via transrepression of NF-κB. Also other nuclear receptors (PXR, PPAR, VDR, GR, ER, etc.) have immune suppressive capacities via transrepression of NF-κB. It is generally accepted that different modifications and different cofactors are necessary for NRs to transactivate and transrepress gene transcription. Here we aimed to start dissecting the moleculair pathways regulating FXR transactivation and transrepression. HEK293T cells transfected with FLAG-FXR were treated with or without GW4064 for 24h. Subsequently, we performed FLAG-immunoprecipitations and ascertained sites of phosphorylation by Orbitrap mass spectrometry. Phosphorylation was detected at Serine 228 (S228). Substitution of S228 into S228A (defective in phosphorylation) resulted in abrogated transcriptional activity of FXR on its target gene promoters (SHP, IBABP and BSEP) in reporter assays. In contrast, transactivation capacity of FXR S228D (phospho- mimicking mutant) was similar or higher than wild type FXR. Electro mobility shift assays show absence of binding of FXR-S228A to BSEP, SHP, and IBABP oligos, in contrast to FXR-WT and FXR-S228D. Heterodimerisation to RXR is unaffected as shown by GST-pull down assays. Interestingly, the ability of FXR-S228A to inhibit NF-κB signalling by transrepression is unaffected in reporter assays. Conclusion: Phosphorylation of FXR-S228 is important for transactivation but not transrepression in vitro. We are currently performing a high-troughput screen cotransfecting a cDNA kinase library in order to identify the kinase responsible for S228 phosphorylation. In addition, we have generated a phospho-specific antibody to FXR-S228 and are currently assessing FXR-S228 phosphorylation in vivo. These findings potentially advance drug design for FXR, since selective FXR ligands which do not result in S228 phosporylation may be useful to treat hepatic/intestinal inflammation without interfering with bile salt, glucose and fat metabolism.

Targeting specific Fxr isoforms; the role in the bile acid biosynthetic pathway

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Farnesoid X receptor (Fxr), a member of the nuclear receptor family, acts as an intracellular bile acid (BA) sensor. Four Fxr splice variants are known, Fxrα 1-4. These isoforms show differences in spatial and tissue specific expression as well as transcriptional activity. Fxr regulates BA homeostasis via modulating hepatic and intestinal transcription of the bile salt export pump (Bsep), small heterodimer partner (Shp) and fibroblast growth factor 15 (Fgf15). The action of each Fxr isoform in these mechanisms is unknown and needs to be established. The aim of this study is to define the role of Fxr isoforms in control of bile acid metabolism.Male Fxr knock-out mice were retro-orbitally injected with hepatic specific self-complementary adeno-associated virus (scAAV) expressing Fxrα2, Fxrα4 or GFP or with PBS. After 3 weeks of stable expression, mice received a 0.5% cholate acid (CA) diet for 1 week. Upon termination, hepatic and plasma parameters were measured as well as hepatic gene expression patterns using qPCR and microarray analysis. In addition, in an in vitro study target gene promoter transcription was determined by luciferase reporter assays. Plasma cholesterol levels were decreased in Fxrα2 (3.12 ± 0.34 mM) and Fxrα4 (3.44 ± 1.19 mM) treated mice, compared to the GFP (7.27 ± 1.53 mM) and PBS (6.24 ± 1.21 mM) controls. Comparing microarray analysis data from Fxrα2 and Fxrα4 showed significant differential gene regulation by both isoforms; upregulated expression ($p<0.001$) of Cyp7b1 (2.7 fold) and Bsep (1.6 fold) in Fxrα2 treated mice and Cyp7A1 (1.4 fold) and Cyp17a1 (4.4 fold) in Fxrα4 treated mice, while Fxr and Shp expression were comparable. Broad scale BA biosynthetic pathway analysis revealed primary involvement of Fxrα2 in the cheno-deoxycholate acid (CDCA) production and of Fxrα4 in CA production. Preliminary in vitro data indicate that the Fxr target gene Bsep is differently transactivated by the different Fxr isoforms.

In conclusion, both Fxrα2 and Fxrα4 normalize the plasma lipid profile in Fxr knock-out mice. Different hepatic expression levels of BA biosynthetic genes between Fxrα2 and Fxrα2 indicate a role of the Fxr isoforms in BA composition in mice. These results indicate distinct roles of Fxrα2 and Fxrα4 in BA homeostasis. This work was performed within the framework of the Dutch Top Institute Pharma project T2-110.

Autotaxin is a Novel Diagnostic Marker for Intrahepatic Cholestasis of Pregnancy

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Introduction: Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic disorder mainly occurring during the third trimester of pregnancy. ICP is characterized by pruritus, elevated serum aminotransferases and serum fasted bile salt levels. In contrast to other pruritic disorders of pregnancy, only ICP is associated with an increased risk of adverse fetal outcomes. Diagnosis of ICP may, however, be difficult when considering other pregnancy associated disorders and liver diseases such as HELLP-syndrome and (pre-)eclampsia. We have recently identified increased autotaxin activity in women with ICP (Gastroenterology 2010;139:1008). Here, we studied whether serum autotaxin could distinguish ICP from other diagnoses. Methods: ICP was diagnosed in pregnant women with pruritus and increased serum transaminases and/or fasted serum bile salt levels in the absence of a dermatosis. Women with pruritus and normal serum transaminases and bile salt levels were summarized as pruritic disorders of pregnancy. Autotaxin activity was measured enzymatically in diluted serum samples of pregnant women with intrahepatic cholestasis of pregnancy (ICP; n=43), other pruritic disorders of pregnancy (n=15), HELLP-syndrome and (pre-)eclampsia (n=17), pregnant (PC; n=44) and healthy controls (HC; n=219). Autotaxin protein was semi-quantified by Western Blotting. Serum bile salts and transaminases were quantified by enzymatic assays. Results: ATX activity was highly increased in women with ICP (52.2 nmol/mL*min ± 21.6 nmol/mL*min, $p<0.0001$) compared to other pruritic disorders of pregnancy (21.7 nmol/mL*min ± 6.5 nmol/mL*min), HELLP-syndrome and (pre-)eclampsia (19.8 nmol/mL*min ± 8.7 nmol/mL*min), and pregnant controls (20.5 nmol/mL*min ± 6.4 nmol/mL*min). Autotaxin protein content correlated with autotaxin activity ($r=0.62$, $p<0.01$). With a cut-off value of 30.0 nmol/mL*min, autotaxin had a sensitivity of 88%, specificity of 93% and positive predictive values (PPV) of 97% in diagnosing ICP from other pruritic disorders and a sensitivity of 80%, specificity of 85%, and PPV of 90% from HELLP-syndrome and (pre-)eclampsia. In a subset of ICP women longitudinal studies during pregnancy revealed that autotaxin activity markedly increases in the third trimester of pregnancy. Sequential blood sampling in healthy controls revealed that autotaxin displayed no circadian rhythm and was not influenced by oral food intake.
Conclusion: Autotaxin levels represent a highly sensitive and specific diagnostic tool in distinguishing ICP from other pruritic disorders of pregnancy and pregnancy-related liver diseases such as HELLP-syndrome, and (pre-)eclampsia.

Real-time PCR for simultaneous detection and identification of Brachyspira species reveals the presence of a novel Brachyspira species in human spirochaetosis

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Infections with Brachyspira species result in a wide range of intestinal disorders in various animal species. While Brachyspira infections have been studied intensively in veterinary science, little is known regarding the infection rates and disease potential in humans. Human intestinal spirochaetosis is thought to be caused by two Brachyspira species: Brachyspira aalborgi and Brachyspira pilosicoli. Prevalence rates are estimated between 1-32% in the general population and up to 63% homosexuals. Diagnosis of human intestinal spirochaetosis is based on histopathology of colon-biopsies and does not allow for definitive species identification. The aim of this study was to design a real-time PCR for the diagnosis of human intestinal spirochaetosis and simultaneously allow for Brachyspira species identification in the positive samples. Formalin fixed colon biopsies were included from histopathology spirochaete positive patients (n=25 patients and n=50 biopsies) and spirochaete negative patients (n=12 patients and n=16 biopsies). All samples were revised by a gastrointestinal pathologist to confirm the diagnosis. Biopsy samples were deparafinized and spiked with phocine herpes virus as internal control. DNA was isolated on a Roche MP96 and real-time PCR and SYBR-green melt-curve analysis of the PCR products was performed on a Roche LC480. Species designation was confirmed by DNA sequence analysis of the PCR fragments. A specific primerset was designed against a region of the 16S rRNA gene that was both specific for, and conserved within all Brachyspira species. All 50 samples from histopathology positive patients showed amplification of the predicted 136 bp 16S rRNA amplicon, whereas all 16 negative controls did not generate a PCR product. SYBR-green based melt-curves of the 50 positive samples indicated that next to the two Brachyspira species known to infect humans, a third Brachyspira species was occasionally present in these samples. Sequence analysis confirmed the presence of single infections with B. aalborgi (12/25), B. pilosicoli (3/25), and a thus far unreported Brachyspira species (3/25). In addition, there were seven double infections: 3/25 B. aalborgi with the novel Brachyspira species, 2/25 B. pilosicoli with the novel Brachyspira species and 2/25 B. aalborgi with B. pilosicoli.

Conclusions: To our knowledge this is the first real-time PCR that allows for simultaneous detection and species discrimination of Brachyspira in routine biopsy materials. The PCR revealed that in human spirochaetosis: 1) a surprisingly high number of double infections is present, and 2) a thus far unknown Brachyspira species is involved.

Clinicians need support in determining familial colorectal cancer risk: results of a national survey

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According to national and international guidelines, individuals with an increased familial colorectal cancer risk are eligible for preventive colonoscopies. Those with a moderate familial risk (2-3 times population risk) are advised to undergo regular colonoscopies; if the familial risk is at least 3 times increased, genetic counselling is recommended as well. Since the identification and referral of these individuals depend on their clinicians, it is important that clinicians are able to determine familial colorectal cancer risk levels and their corresponding follow-up policies. In November 2010, 2,008 clinicians were asked to participate in a national web-based survey. Clinicians included 1,536 surgeons, 370 gastroenterologists, and 102 clinical geneticists, including doctors in training in these fields. They scored familial colorectal cancer risk level and follow-up policy for ten clinical scenarios (4 high, 4 moderate and 2 average risk scenarios). The survey was completed by 275 clinicians (63% men, mean age 41 years). In total, 51% of the scenarios was answered correctly. Clinical geneticists had the highest mean scores (74% correct answers), compared to gastroenterologists (56% correct answers, p=.022) and surgeons (44% correct answers, p<.001). There was no significant correlation between total score and age, gender, experience or being in training or not.Determination of risk levels was better for low-risk scenarios than moderate and high-risk scenarios (63% versus 37% and 47% correct answers, respectively; p=.126). For follow-up policy, participants had slightly higher scores on high-risk scenarios compared to moderate and low-risk scenarios (59% versus 55% and 53% correct answers, respectively; p=.094).
In conclusion, many clinicians need support in determining familial colorectal cancer risk levels and their corresponding follow-up policies. There is much room for improvement in this area, in order to identify those at a high-risk, enabling them to take preventive measures and thus leading to better prevention of colorectal cancer. We are currently conducting a randomized controlled trial to determine whether providing patients and clinicians with web- and paper-based tools improves the determination of colorectal cancer risk levels and their corresponding follow-up policies.

The lack of evidence for treatment of uncomplicated diverticulitis

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Treatment of uncomplicated acute diverticulitis of the sigmoid has not changed over the last 30 years and is still based on low-residue liquid diet and antibiotics. Since surgery has become obsolete after a single episode of uncomplicated diverticulitis, medical treatment options, such as a high fibre diet with or without long-term medical therapy (antibiotics, probiotics and 5-aminosalicylic acid), are commonly used to prevent complications and recurrence. Different surveys in the UK, USA and the Netherlands have shown that practice standards vary widely. Medline, EMBASE and CINAHL databases were systematically searched. All randomized clinical trials (RCT) and prospective or retrospective cohort studies specifically addressing the conservative treatment of uncomplicated left-sided diverticulitis were included. Studies without comparison of an intervention group and a control group were excluded. Treatment options of uncomplicated acute diverticulitis:1) Low-residue liquid diet: no studies were found. 2) Antibiotics: one retrospective study published in 2007 compared a group treated with antibiotics to one treated without antibiotics. No difference in outcomes was found. Treatment options to prevent recurrence after an episode of acute diverticulitis:1) High fibre diet: no studies were found. 2) Probiotics: one RCT (2004) was found showing no significant reduction of recurrence. 3) 5-Aminosalicylic acid: one RCT (2002) was found and showed a significant reduction in recurrence rates in the mesalazine group. 4) Antibiotics: one retrospective study from 1994 was found and showed a significant lower readmission rate in the antibiotic group. In conclusion in the treatment of uncomplicated acute left-sided diverticulitis it is important to separate facts from fiction. Current standard treatment for uncomplicated diverticulitis lacks evidence. However, dietary advise and medical treatment are still widely advocated in many guidelines and reviews (World Gastroenterology Organization 2007, NEJM 2006, American College of Gastroenterology 1999). Also for to the prevention of recurrent diverticulitis, the evidence is based on very limited data. All trials have non-specific and subjective symptom outcomes, diagnosis is not based on imaging and sample sizes are far too small to demonstrate any differences. This systematic review emphasizes the need for prospective well-designed trials in patients with uncomplicated acute diverticulitis and encourages a critical look at experts' opinions treatment guidelines from more than 30 years ago.

Long-term outcome of treatment with temperature-controlled radiofrequency energy (SECCA) in patients with fecal incontinence: sustained improvement after 3 and 5 years

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Background & Aim:The SECCA procedure, which delivers temperature-controlled radiofrequency energy to the anal canal, is a novel treatment for fecal incontinence. The aim of the study was to evaluate the long-term efficacy of the SECCA procedure. Methods: Patients who had failed conservative management for fecal incontinence, received the SECCA procedure and were categorized into two prospective cohort groups according to their treatment year: group-I in 2005 and group-II in 2006-2007. The efficacy of the treatment was graded by patient as improved, slightly improved or not improved. The Vaizey-score was completed at baseline, 3 months, 6 months and 1 year (by both groups), at 3 years (by group-II) or at 5 years (by group-I).. Furthermore, fecal incontinence quality of life questionnaire and Short-Form-36 were also completed by group-II. Anorectal manometry and anal endosonography were performed at base and at 3 months. Results Twenty-four patients (mean age: 59 years [range 44-73]; 23 females [96%]) were treated (group-I: n=11; group-II: n=13). At 1 year, 14/24 patients (58%) experienced improvement and 3/24 (13%) slight improvement. The Vaizey-score improved from 18.0 at base to 14.0 at 1 year (P<0.001) (Figure 1).At 3 years, 4/13 patients (31%) experienced improvement and 6/13 (46%) slight improvement. The Vaizey-score improved from 17.2 at base to 13.3 at 3 years (P=0.03). In the fecal incontinence quality of life questionnaire the parameters lifestyle, coping and depression were improved (Figure 2). The Short-form-36 was not improved. There was no statistical difference in the Vaizey-score between 1 and 3 year.At 5 years, one patient died, 2/11 patients (18%) experienced improvement, 3/11 (27%) slight improvement and 5/11 (45%) no improvement. The Vaizey-score changed from 19.1 at base to 12.1 at 5 years (P=0.004). There was no statistical difference in Vaizey-score between 1 and 5 year. There were no changes in anorectal manometry or endosonography observed. Side effects were anal pain (n=16 [67%]), minor bleeding or hematoma (n=8 [33%]), diarrhea associated with antibiotic intake (n=7 [29%]), urinary tract infection (n=1 [4%]) and temporary discharge of mucus with stool (n=1 [4%]). Due to diarrhea, most of the patients felt worsening of FI during the first week. There were no long-term complications at 3 and 5 years.
Conclusion. The SECCA procedure is a promising treatment for fecally incontinent patients with improvements demonstrated in the Vaizey and fecal incontinence quality of life scores. The response maintains at 3 and 5 years without morbidity.

Gastrointestinal ischemia is an important trigger for athletes with exercise induced abdominal complaints

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Background: gastrointestinal (GI) symptoms during exercise may be caused by GI-ischemia. We report our experience with athletes referred for analysis of GI-symptoms suspected to be caused by GI-ischemia. Methods: Athletes with GI-symptoms during exercise underwent a 30 minutes exercise test with CO2 measurement in stomach and jejunum (exercise tonometry). Study parameters (lactate, heart rate, luminal-arterial CO2 gradient in stomach and jejunum) were related to the presence of symptoms (S+ and S-) during the exercise test. Ischemia was assessed calculating the luminal-arterial CO2 gradient in stomach and jejunum. Data are presented as mean (standard deviation), median (range) or Regression coefficient (95% confidence interval). Results: 12 athletes were specifically referred for GI-symptoms during exercise (5M, 7F, median age 29 yr (15-46). Type of sport was cycling (6), running (4) and triathlon (2). Median duration of symptoms was 32 months (7-240). 10 Athletes underwent the exercise protocol. During the first 10 min, lactate rose from mean 0.9 (0.9) mmol/l to 4.5 (1.7) mmol/l. At maximum intensity exercise, lactate rose to 9.0 (1.7) mmol/l. Six athletes had GI-ischemia during sub maximal exercise. All athletes had GI-ischemia in stomach and/or jejunum at exhaustion. Mean gastric gradient rose from -0.1 (0.5)kPa at rest to 0.5 (0.7) kPa during sub maximal exercise to 2.3 (2.9) kPa during exhaustion. For jejunal gradient these figures were 0.7 (0.6) kPa, 1.4 (0.5) kPa and 2.7 (0.4) kPa, respectively. Seven patients developed symptoms (S+) with mean start of symptoms after 22 minutes. No significant difference was found in gastric (S+ 2.5kPa (0.8) vs S- 1.7kPa (0.9)) or jejunal gradient (S+ 2.7kPa (0.4) vs S- 2.4kPa (0.5)) during maximum intensity exercise. In S+ athletes, the relation between lactate and gastric gradient was significant and stronger than in S – athletes (S+ 0.29, 0.22-0.36 vs S- 0.10, -0.10-0.17). Relation between lactate and jejunal gradient was significant in both groups but again stronger in S+ athletes (S+ 0.22, 0.16-0.28 vs S- 0.22, 0.06-0.32), indicating a steeper rise in PCO2 for each mmol increase in lactate. All athletes were treated conservatively and 66% reported significant improvement by following our treatment advices.
Conclusion: Gastrointestinal ischemia is common during maximum intensity exercise. Symptomatic athletes had a higher rise in gradients per mmol/l lactate than S- athletes suggesting a more pronounced splanchnic vasoconstriction in response to exercise. Our approach and treatment advices helped the majority of the referred athletes to reduce their complaints.

Clinical effect of vasodilating agents in patients diagnosed with non-occlusive mesenteric ischemia

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Chronic non-occlusive mesenteric ischemia (NOMI) is referred to as presence of confirmed mucosal ischemia in patients with open gastrointestinal arteries. NOMI is thought to develop secondary to a low flow state or vasospasm, and to be part of the clinical spectrum of chronic gastrointestinal ischemia (CGI). It has been suggested that vasodilating medication can be effective. The aim of this study was to evaluate the therapeutic effect of vasodilating medication in NOMI patients.Patients referred for evaluation of CGI were prospectively included. All patients had a standard work-up, consisting of evaluation of symptoms, angiography for evaluation of gastrointestinal arterial patency and functional assessment of mucosal perfusion by tonometry or visible light spectroscopy. Patients were diagnosed with NOMI if the symptoms suggested CGI, and functional testing revealed mucosal ischemia, in the absence of gastrointestinal artery stenosis. NOMI was treated with escalating doses of isosorbide dinitrate (ISD; 20 or 40 mg), followed by ketanserin (KTS; 20 or 40 mg) if ISD was not successful or tolerated. A positive treatment response was defined as loss of pain. In 3.5 years, 353 pts were referred for evaluation of suspected CGI. NOMI was diagnosed in 59 (17%) pts; 37 (63%) females, mean age 56 (17-82) yrs. The characteristics were: postprandial pain 46 (78%), weight loss 40 (68%), nausea 23 (39%), diarrhea 13 (22%), the history of cardiac and vascular disease 23 (39%) and diabetes 12 (20%). Vasodilation therapy was initiated in 42 (71%) patients. Of the remaining 17 patients, 11 had conservative treatment with proton pomp inhibition, 5 patients were diagnosed with cardiac dysfunction and were treated accordingly, and one patient with severe COPD had intensification of pulmonary treatment. Sustained response was achieved in 11/42 (26%) pts treated with ISD (mean follow-up 21 months). Of 31 non-responders to ISD, 22 (71%) were treated with KTS. Six (27%) of them had a sustained response (mean follow-up 8 months). Intention to treat and per protocol analysis showed an overall therapy response of 41% and 55%, respectively. There was no difference in base characteristics between responders and non-responders. Responders had a median weight gain of 1 (IQR: -1 – + 6) kg, whereas the non-responders had median weight loss of – 0.6 (IQR: -4 – + 1) kg. Side effects were reported in 18/42 patients (43%), in particular headache, and dizziness.Vasodilating medication is of benefit to approximately half of patients with chronic NOMI. Further studies are needed to optimize the effectiveness of vasodilating agents in these patients, and predict therapeutic response.

Chronic Gastrointestinal Ischemia due to Atherosclerotic Narrowing is related to Classical Risk Factors for Cardiovascular Disease

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Chronic gastrointestinal ischemia (CGI) is most commonly caused by atherosclerotic stenosis of the gastrointestinal arteries. Although CGI is an extracardial manifestation of atherosclerosis, its relationship with classical risk factors of cardiovascular disease (CVD) is unclear. The aim of this study was to determine whether classical risk factors of CVD associate with atherosclerotic CGI (ath-CGI). A prospective cohort study was performed in patients with unexplained chronic abdominal symptoms referred for evaluation of CGI. A standard work-up was conducted including CTA or MRA for imaging the abdominal vessels and gastrointestinal tonometry. Additionally, an extensive evaluation for atherosclerotic risk factors was performed. Healthy subjects from the DiaGene Study population served as controls. The controls were previously not diagnosed with CGI or diabetes.Between 2006 and 2009 195 patients were evaluated. Ath-CGI was diagnosed in 69 patients: 48 (70%) females, median age 66 (IQR 57-75) years. Weight loss was reported in 74% of ath-CGI patients and was reported median 9 (IQR 6 -12) kg. The controls consisted of 132 subjects: 63 (48%) females, median age 66 (IQR 63-72). The prevalence of hypercholesterolemia (38% vs. 24%, p-value = 0.03), personal history of CVD (51% vs. 8%, p-value < 0.01), family history of CVD (51% vs. 33%, p-value < 0.01), smoking (39% vs. 13%, p-value < 0,01), use of statins (46% vs. 17%, p-value < 0.01), and anti-hypertensive agents (52% vs. 30%, p-value < 0.01) were significantly higher in ath-CGI patients compared with controls. Total LDL-cholesterol was lower in ath-CGI vs. controls (median 2.2 (IQR 1.8-2.9) vs. 3.5 (IQR 3.0-3.4), P < 0.01), this can be explained by higher statin use and substantial weight loss.
Conclusion: CGI due to atherosclerotic stenosis is associated with classical CVD risk factors. This advocates secondary prevention therapy for these patients. However, the female preponderance is remarkable.

Epidemiology of Autoimmune hepatitis in the Netherlands: A nationwide study

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Background: Autoimmune Hepatitis (AIH) is a chronic liver disease of unknown etiology. AIH has been considered a disease occurring predominantly in young women, but up to one third of the patients are men, and the disease can develop in all age groups. The incidence of AIH is low, with a reported incidence ranging from 0.85 to 2 per 100.000 and a point prevalence of 10 cases per 100.000 in Northern European countriesAim: To investigate the prevalence, diagnostic criteria and treatment of AIH patients in the Netherlands. Methods: In this multi centre retrospective study regarding AIH, patients were included when the diagnosis of AIH was based on the global physician assessment. The data were obtained from 16 centres in the Netherlands. Analyses were performed in the charts of 800 patients, to determine the patients characteristics, original and simplified diagnostic criteria and treatment. Results: At this moment 800 cases of AIH were identified which covers an estimated 75% of the Dutch AIH population. This indicates a minimal prevalence of 6,25 per 100.000 in the Netherlands. Of these 800 cases 625 (78,1%) were female and 175 (21,9%) male. At diagnosis the average age of females was 44 years (range 6-87) and males were 41 years (range 10-81). In 238 (29,8%) patients concomitant autoimmune diseases were frequently found. In particular there was a high frequency of autoimmune thyroid disease (72 patients) and irritatable bowel syndrome (53 patients). Others autoimmune diseases included rheumatoid arthritis, celiac disease and type I diabetes mellitus. 88% Of the AIH patients satisfy either the original (Alvarez et al 1999) or the simplified (Hennes et al 2008) criteria. The remaining 12% did not satisfy these criteria, most likely due to insufficient data recording at diagnosis. These patients were diagnosed and treated as autoimmune hepatitis based on clinical and histological data. At diagnosis 83 (10,4%) patients had cirrhosis in the liver biopsy, and 322 fibrosis (40,2%).As maintenance treatment 141 AIH patients used corticosteroid (17,6%), 148 thiopurines (18,5%), 300 combination therapy corticosteroid and thiopurines (37,5%), 42 patients other medication (5,3%), 52 used no therapy (6,5%) and in 117 patients the therapy is unknown.
Conclusion: This nationwide detailed investigation indicates that the prevalence of AIH in the Netherlands is lower than reported in previous studies from Europe. Most patients satisfies the original or simple criteria and these criteria are useful in the diagnosis. One third of the AIH patients have an other concomitant auto immune disease.

Percutaneous Radiofrequent Lesioning of the Splanchnic Nerves in Patients with Chronic Pancreatitis. An explorative study in 11 Patients

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Background: Pain is a major problem in patients with chronic pancreatitis (CP). Unfortunately, medical therapy often fails and then endoscopic or surgical treatment is indicated. However, both techniques are invasive and results may vary considerably. Nerve blockades, i.e. celiac plexus block and thoracoscopic splanchnicectomy, are less invasive procedures but serious complications have been reported. Radiofrequent lesioning of the splanchnic nerves (RFSN) is a relatively new and minimal invasive procedure. In an explorative open study we investigated the effect of RFSN on pain scores in CP patients.Materials and methods: We evaluated 18 consecutive RFSN procedures in 11 CP patients performed between March 2006 and November 2010. The diagnosis of CP was based on clinical symptoms, typical morphological changes shown on imaging techniques and exocrine insufficiency when present. All patients were refractory to medical therapy (both NSAID's and opioids). Five patients underwent a second, two patients a third procedure, after subsiding of the effect of the previous intervention. Pain scores (by means of numeric rating scales) were assessed pre-procedure and 6 weeks postprocedure. Complications, usage of analgesics and the eventual pain free period were determined during a mean follow-up of 83 weeks. Special attention was paid to the effect of repeated interventions. Results: RFSN was effective in 15 out of 18 interventions (83%). The mean NRS-score (ranged 0-10) reduced from 7.5 ± 0.9 to 1.5 ± 1.1 6 weeks after treatment with a mean reduction of 5.9 ± 1.1 ($p<0.0001$). The low-pain / pain free period lasted for a median period of 45 weeks. The mean interval between the first and second and second and third intervention were 14.5 and 10.5 months respectively. The effect of repeated interventions was comparable to the effect of the initial procedure. One, minor complication, temporal hypoesthesia of the flank, was reported. Of all responding patients 5 patients significantly reduced their daily dose of analgesics, 3 patients stopped completely.
Conclusion: This explorative study confirms earlier results that RFSN is a simple, effective procedure in patients with CP. After subsiding its effect RFSN can successfully be repeated. RFSN may become an alternative treatment in a selected group of CP patients with invalidating pain. A larger, randomized trial is justified to substantiate these preliminary findings.

Gadolinium-EOB-DTPA enhanced MRI in differentiating focal nodular hyperplasia from hepatocellular adenoma

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Introduction: Unlike Focal Nodular Hyperplasia (FNH), resection is recommended for Hepatocellular Adenoma (HCA)>5cm, because of potential risk of bleeding and malignant transformation. Differentiation between FNH and HCA remains challenging based solely on imaging studies. Gadolineum-EOB-DTPA (Primovist®) combines the properties of a conventional contrast agent, with a hepatobiliary agent, allowing MRI evaluation of hepatocyte uptake and biliary excretion. Objectives: We assessed the accuracy of Gd-EOB-DTPA enhanced MRI compared to conventional contrast enhanced MRI in differentiating FNH from HCA, with histological outcome as standard of reference (SOR). Methods: In this prospective study, 55 consecutive patients suspected of FNH or HCA underwent a Gd-EOB-DTPA MRI of the liver. Conventional series included dynamic contrast-enhanced T1 weighted FS series, T1 in/out of phase, T2, and diffusion, followed by delayed hepatobiliary phase. The two imaging studies were stored separately and evaluated by two blinded abdominal radiologists. The readers made their diagnosis on conventional imaging based on lesion characteristics (bleeding, central scar, and shape) and enhancement pattern. In addition, diagnosis was made after the hepatobiliairy phase of the Gd-EOB-DTPA.The latter series were regarded diagnostic for FNH if accumulation of contrast was seen and diagnostic for HCA without accumulation. Imaging results were compared to histological outcome as standard of reference (SOR) and obtained by biopsy and/or resection. Results: SOR revealed HCA 23 and FNH 32. The conventional MRI (HCA 13, FNH 19, inconclusive 23) showed a sensitivity of 52.2% for HCA with a positive predictive value (PPV) of 92.3% and for FNH of 56.3% (PPV 94.7%). The hepatobiliary phase of the Gd-EOB-DTPA (HCA 24, FNH 31) showed a sensitivity for HCA of 95.7% (PPV 92.7%) and for FNH of 93.8% (PPV 96.8%). Features with significant predictive value for diagnosis included bleeding for HCA (p=0.040) and a central scar for FNH (p=0.001).
Conclusion: The hepatobiliary phase of the Gd-EOB-DTPA contrast significantly increases the sensitivity of MRI in differentiating FNH from HCA.

Interobserver agreement among radiologists for pancreatic cysts using MRI

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Magnetic Resonance Imaging (MRI) is considered the best radiologic imaging modality for the morphologic characterization of pancreatic cysts (PC) but little is known about the interobserver agreement. Aim of this study was to assess the degree of interobserver agreement of MRI in the diagnostic work up of PC among four experienced radiologists. MRI images of 64 patients with PC (32 without, 32 with histological confirmation) were reviewed. In the latter group histological diagnoses were as follows: pseudocyst (4), serous cyst adenoma (2), IPMN (17), mucinous cystic neoplasm (8), cystic neuroendocrine tumor (1). Before reviewing, all radiologists were exposed to a training set demonstrating specific MRI-features of PC. Observers were blinded to clinical and histological results. Features scored included: septations, nodules, solid components, pancreatic duct communication and wall thickening (>2mm). Radiologists were asked whether they considered the PC mucinous and if the PC had malignant features. Furthermore, a presumptive diagnosis had to be specified. Intraclass correlation coefficient (icc) was used to measure agreement within the group. Icc values greater than 0.80 were considered in excellent agreement, 0.61-0.80 were considered good, 0.41-0.60 moderate, 0.21-0.40 fair and <0.20 poor. Interobserver agreement for septations and nodules was fair (icc=0.29 and 0.27). Agreement for the presence of solid components was poor (icc=0.07), agreement for communication with the pancreatic duct was moderate (icc=0.48) and agreement for wall thickening was also moderate (icc=0.44). There was only fair agreement between radiologists for the discrimination between mucinous and non-mucinous PC (icc=0.31). Agreement for a specific diagnosis was border fair (icc=0.22) in the whole set of MRI`s (n=64) and poor (icc=0.05) in the group with histological confirmed PC (n=32). Interobserver agreement for the presence of malignant features was fair (icc=0.32). Accuracy rates to predict if a cyst was mucinous in the group with histological confirmed PC were 66%, 59%, 63% and 69% respectively for the four individual radiologists. Accuracy rates for a specific diagnosis in the group with histological confirmed PC were as follows for each individual radiologist: 56%, 53%, 63% and 76%.

Conclusions: Interobserver agreement was poor to moderate for individual PC features and there was poor agreement for a specific diagnosis in histologically confirmed PC. Accuracy rates for a specific diagnosis were limited but comparable between radiologists. In this study, MRI morphology alone did not allow for a reliable discrimination between different types of PC.

Indication for CDKN2A mutation analysis in familial pancreatic cancer-families without melanomas

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Carriers of a CDKN2A-gene mutation run a high risk of developing melanomas and an additional increased risk of pancreatic cancer (PC). Familial pancreatic cancer (FPC)-patients with a personal or family history of melanomas should therefore be offered CDKN2A-mutation analysis. However, CDKN2A-testing is not recommended in the literature in FPC-families without a history of melanomas. FPC-families were defined as families with clustering of PC (either ≥2 first-degree relatives (FDRs), ≥3 relatives of any degree, or 2 relatives with one <50 years at diagnosis) and not meeting diagnostic criteria of specific other familial cancer syndromes. Medical details of cancer diagnoses were retrieved and revised. Blood samples were obtained for DNA isolation from PC-patients or FDRs and analyzed for mutations in CDKN2A, BRCA1, and BRCA2. Among 34 FPC-families, DNA-analyses was done in 24 families (71%), leading to identification of a causal genetic factor in eight (33%) families; CDKN2A-mutations in five families and BRCA2-mutations in three families. None of the CDKN2A-families fulfilled the diagnostic criteria of familial atypical multiple mole melanoma (FAMMM)- syndrome and in three CDKN2A-families no melanomas and/or dysplastic nevi had been observed. In these latter three families two different CDKN2A-mutations were found; in two families the Dutch founder mutation p16-Leiden (c.225_243del, p.Ala76fs) and in the third family the c.19_23dup.p.Ser8fs-mutation. After disclosure of the CDKN2A-mutation in one of the families, a curable melanoma was diagnosed at dermatological surveillance in a 17-year old female family member. All BRCA2-mutation families included one breast cancer patient per family.
Conclusion: Based upon these results, we postulate that CDKN2A-mutation analysis should be included in genetic testing in FPC-families, even in the absence of reported melanomas. This strategy will enhance the recognition of individuals at risk for PC and may also facilitate the early detection of melanomas.

Plattegrond

Alfabetische lijst van standhouders
B = Beneluxhal D = Doorloop K = Kempenhal ***Standnummer***

Abbott BV	B 17
AstraZeneca BV	K 9
B.Braun Medical	K 4
Boston Scientific nederland B.V.	K 18
Brunschwig Chemie BV / Lans medical	K 17
CameraPil BV	K 6
Cobra Medical B.V.	B 2
COOK Medical	B 13
Crohn&Colitis Ulcerosa ver.Nederland	B 19
Darm	D 4
Dr. Falk Pharma benelux B.V.	B 1
Ella-CS	D 3
Endomed B.V.	B 5
Endoss	B 10
Endotechniek	B 15
Erbe Nederland BV	D 1
Ferring B.V.	B 16
FMH Endoscopy B.V.	B 3
Fresenius Kabi Nederland B.V.	K 10
Getinge bv	B 6
Hitachi Medical Systems	K 2
Janssen-Cilag B.V.	K 12
Meda Pharma B.V.	B 18
Medical Measurements Systems B.V.	D 2
Medicom	B 14
Medicor	K 7
Merck Sharp&Dohme	K 19
Minigrip Nederland BV	K 11
Minntech B.V.	K 5
Movetis	B 8
MTW-Endoskopie	B 11
Nederlandse Coeliakie Vereniging	B 20
Norgine	B 4
Olympus	K 8
PelviTech	B 7
Pentax Medical	K 1
PMT Partners Medische Techniek BV	B 9
Medicom	B 14
Surgical Technologies BV	K 14
The Surgical Company	K 13
TRAMEDICO B.V.	K 15
V&VN MDL	B 21
Vifor Pharma Nederland B.V.	K 20
Wassenburg Medical Devices B.V.	B 12
Zambon Nederland B.V. 2x(3x2)	K 3

Nederlandse Vereniging voor Gastroenterologie

Aanmeldingsformulier lidmaatschap *(doorhalen wat niet van toepassing is)*

naam en voorletters		m / v
voornaam		geb. datum:
titel		
specialisme / functie		
doctoraal examen	neen / ja d.d.	zo ja, studierichting:
arts examen	n.v.t. / ja d.d.	
assistent i.o. voor		einde opleiding:
inschrijving MSRC	neen / ja d.d.	BIG registratie nr.
huisadres		
postcode en plaats		
telefoonnummer		
werkinstelling		
afdeling		
adres		
postcode en plaats		
telefoonnummer		
e-mail adres		
Toezending verenigingspost aan huis- / werkadres		

Tevens wil ondergetekende zich aansluiten bij:

□ Sectie Gastrointestinale Endoscopie*
□ Netherlands Society of Parenteral and Enteral Nutrition*
□ Sectie Neurogastroenterologie en Motiliteit*
□ Sectie Experimentele Gastroenterologie*
□ Sectie Kindergastroenterologie*
□ Nederlandse Vereniging voor Gastrointestinale Chirurgie *(combinatielidmaatschap)*

contributiebedragen: graag aankruisen wat voor u van toepassing is

□ Specialisten € 90,00 (totaal € 140,00 incl. lidmaatschap NVGE € 50,00)
□ Assistenten i.o. € 25,00 (totaal € 75,00 incl. lidmaatschap NVGE € 50,00)

*Aanvullende lidmaatschappen van met * aangegeven secties zijn kosteloos*

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Bank- / girorekening:

Datum en handtekening:

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NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

Aanmeldingsformulier lidmaatschap

Nederlandse Vereniging voor Hepatologie

** Doorhalen wat niet van toepassing is.*

naam en voorletters		m / v
voornaam		geb. datum:
titel		
specialisme / functie		
doctoraal examen	neen / ja d.d.	zo ja, studierichting:
arts examen	n.v.t. / ja d.d.	
assistent i.o. voor		einde opleiding:
inschrijving MSRC	neen / ja d.d.	BIG registratie nr.
huisadres		
postcode en plaats		
telefoonnummer		
werkinstelling		
afdeling		
adres		
postcode en plaats		
telefoonnummer		
e-mail adres		
* Toezending verenigingspost aan huis- / werkadres		

□ Hierbij machtig ik de penningmeester van de Nederlandse Vereniging voor Hepatologie om de verschuldigde contriutie tot wederopzegging automatisch van mijn bank-/girorekening af te laten schrijven. Betaling geschiedt nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen. Indien u geen machtiging tot incasso geeft ontvangt u automatisch een factuur. Voor verzending van facturen worden vanaf volgend jaar administratie-kosten in rekening gebracht.

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