Programma voorjaarsvergadering 13 en 14 maart 2008

NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

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

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

NEDERLANDSE VERENIGING VOOR GASTROINTESTINALE CHIRURGIE

NEDERLANDS GENOOTSCHAP VAN MAAG-DARM-LEVERARTSEN

Locatie:

NH KONINGSHOF VELDHOVEN

INHOUDSOPGAVE pag.

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

Tijdstippen diverse ledenvergaderingen donderdag:

Assistentenvereniging Touché (mdl-artsen i.o.) 13 maart, 12.30 uur - Zaal 82/83
Nederlandse Vereniging voor Hepatologie 13 maart, 11.30 uur - Parkzaal

INHOUDSOPGAVE pag.

VRIJDAG 13 MAART 2008

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

Tijdstippen diverse ledenvergaderingen vrijdag:

Nederlandse Vereniging voor Gastroenterologie	*14 maart, 07.30 uur - Genderzaal*
Ned. Genootschap van Maag-Darm-Leverartsen	*14 maart, 12.00 uur - Genderzaal*
Sectie Endoscopie Verpleegkundigen en Assistenten	*14 maart, 13.15 uur - Diezezaal*
Vereniging Maag Darm Leververpleegkundigen	*14 maart, 11.30 uur - Auditorium*
Sectie Experimentele Gastroenterologie	*14 maart, 15.00 uur - Baroniezaal*

VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering die gehouden wordt op 13 en 14 maart a.s. in Congrescentrum Koningshof te Veldhoven. Zoals gebruikelijk wordt ons congres vooraf gegaan door het cursorisch onderwijs, waarvan u het programma aantreft op bladzijde 7.

Het programma zal donderdag 13 maart om 12.00 uur van start gaan met de begeleide posterrondes die deel uitmaken van 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 13.00 uur zijn er behalve genodigde sprekers en vrije voordrachten van de genoemde DEGH, ook een aantal sessies met vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie, de Nederlandse Vereniging voor Gastroenterologie en de Secties Neurogastroenterologie en Moliteit en de Netherlands Society of Parenteral and Enteral Nutrition.
Om 17.00 uur vindt de Presidential Selection plaats, zoals gebruikelijk plenair in de Brabantzaal. Deze sessie duurt tot 18.00 uur en sluit daarmee het programma van de donderdag af. In de avond zijn er geen verdere lezingen meer ingepland, zodat er ruimer gelegenheid is voor diner en ontspanning. De ledenvergadering van de NVGE vindt plaats op vrijdagochtend om 07.30 (inclusief ontbijtbuffet).

Op vrijdagochtend is er na de ledenvergadering van de NVGE in de Genderzaal (met ontbijtbuffet), casuïstiek in de Brabantzaal, gevolgd door vrije voordrachten van de Sectie Gastrointestinale Endoscopie. Na deze voordrachten staat er een symposium over de nieuwe sedatierichtlijn op het programma.
Gedurende de gehele vrijdag zijn er behalve sessies met genodigde sprekers en vrije voordrachten van de DEGH, ook vrije voordrachten van de Nederlandse Vereniging voor Gastroenterologie. In respectievelijk de Diezezaal en het Auditorium tenslotte, worden door de Sectie Endoscopie Assistenten en Verpleegkundigen en de Vereniging van Maag Darm Lever Verpleegkundigen eigen programma's met lezingen verzorgd.

Een aandachtspunt voor de sprekers: u dient zich strikt te houden aan de beschikbare spreektijd! U vindt dit aangegeven bij de betreffende sessie. Indien u een eigen laptop gebruikt, dan dient u deze aan te sluiten tijdens de discussietijd van de spreker voor u.
In **zaal 25** kunt u uw PowerPoint presentatie tevoren controleren.

Graag tot ziens in Veldhoven!

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

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

Belangrijke mededeling

over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de voorjaarsvergadering

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

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

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

Het bestuur van de NVGE

Cursuscommissie: Dr. E. van der Harst, (chirurg, MCRZ)
Drs. A.D. Koch (aios MDL, Erasmus MC)
Dr. R.A. de Man (voorzitter) (maag-darm-leverarts, Erasmus MC)
Prof. dr. C.J.J. Mulder (maag-darm-leverarts, VUmc)
Dr. R. Timmer (maag-darm-leverarts, Antonius Nieuwegein)
Mw. Dr. A.M.P. de Schryver (aios MDL, UMC Utrecht)

Spoedeisende zorg in de maag-, darm- en leverziekten

Woensdag 12 maart 2008

20.00 – 20.30 Optimale diagnostiek van een patiënt met een acute buik
Mw. Dr. M.A. Boermeester, chirurg, AMC, Amsterdam

20.30 – 21.00 Bovenste tractus dig. bloedingen bij de vasculair gecompromitteerde patiënt
J.W. Poley, MDL-arts, Erasmus MC, Rotterdam

21.00 – 21.30 Interventieradiologie en tractus digestivus bloedingen
Dr. J.A. Vos, radioloog, St.. Antonius Ziekenhuis, Nieuwegein

21.30 – 22.00 Acute slokdarm obstructie: management van corpora aliena in de slokdarm
Dr. E.A.J. Rauws, MDL-arts, AMC, Amsterdam

Donderdag 13 maart 2008

08.00 – 08.30 Acute cholecystitis: drainage of operatie?
Dr. E. van der Harst, chirurg, Medisch Centrum Rijnmond Zuid, Rotterdam

08.30 – 09.00 Acute Maag, Darm ischaemie, door de ogen van de MDL-arts
Dr. J.J. Kolkman, MDL-arts, Medisch Spectrum Twente, Enschede

09.00 – 09.30 Acute Maag, Darm ischaemie, door de ogen van de vaatchirurg
Dr. R.H. Geelkerken, chirurg, Medisch Spectrum Twente, Enschede

09.30 – 10.00 Acuut leverfalen
Prof. dr. H.J. Metselaar, MDL-arts, Erasmus MC, Rotterdam

pauze

10.30 – 11.00 Management van loog/zuur ingestie in de slokdarm
Prof. J.F.W.M. Bartelsman, MDL-arts, AMC , Amsterdam

11.00 – 11.30 Acute slokdarmperforatie
Prof. dr. P.D. Siersema, MDL-arts, UMC Utrecht

11.30 – 12.00 Acute colonobstructie
Dr. F. ter Borg, MDL-arts, Deventer Ziekenhuis, Deventer

12.00 – 12.30 Update beleid bij shock en sepsis
Dr. A.F. Grootendorst, intensivist, Medisch Centrum Rijnmond Zuid, Rotterdam

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

Programma donderdag 13 maart 2008

DONDERDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
12.00		**Begeleide posterrondes van de DEGH in de Meierij Foyer (nabij Baroniezaal**) p. 43-53 *tevens lunchbuffet*			
13.00	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie p. 10	**Genodigde spreker:** **Prof. B. Staels** Gevolgd door vrije voordrachten DEGH- sessie (metabolisme) p. 16	Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit p. 19	Geen programma in deze zaal donderdagmiddag	Geen programma in deze zaal donderdagmiddag
15.00	Theepauze	Theepauze	Theepauze		
15.30	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 12	**Genodigde spreker:** **Prof. R. Xavier** Gevolgd door vrije voordrachten DEGH- sessie (immunologie/IBD) p. 18	Vrije voordrachten Netherlands Society of Parenteral and Enteral Nutrition p. 21		
17.00	**President Select plenair programma**	Geen programma in deze zaal	Geen programma in deze zaal		
18.00	Congresborrel expositiehal	Congresborrel expositiehal	Congresborrel expositiehal		
19.00	Diner in Genderzaal, naborrelen en muziek in de Limburgfoyer	Diner in Genderzaal, naborrelen en muziek in de Limburgfoyer	Diner in Genderzaal, naborrelen en muziek in de Limburgfoyer		
	Geen congresprogramma in de avond	Geen congresprogramma in de avond	Geen congresprogramma in de avond		

Programma vrijdag 14 maart 2008

VRIJDAG	BRABANTZAAL	BARONIEZAAL	PARKZAAL	AUDITORIUM	DIEZEZAAL
07.30	**Ledenvergadering NVGE** in Genderzaal – met ontbijtbuffet	**Meet the speakers Breakfast Zaal 20** (vanaf 08.00 uur)			
08.30 09.00	**Casuïstiek voor de clinicus** Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 24	**Meet the speakers Breakfast** (tot 09.00 uur) **Genodigde spreker:** **Prof. I.N. Crispe,** gevolgd door vrije voordrachten DEGH- sessie (immunologie) p. 27	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 29	09.30 Programma VMDLV p. 42	
10.00	Start symposium	Koffiepauze, expositie	Koffiepauze, expositie	Koffiepauze, expositie	Start programma SEVA
10.30	**Symposium richtlijn Sedatie** **Genodigde sprekers:** **Prof. dr. J.T.A. Knape** **Dr. J.J. Kolkman** **Prof. Chr. Beglinger** **Dr. S.J. van den Hazel** p. 26	Vrije voordrachten DEGH-sessie (immunologie/ celbiologie) p. 27	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 29	Programma Vereniging voor Maag-Darm-Lever Verpleegkundigen p. 42	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten | p. 42
12.00	Lunchbuffet expositiehal	Lunchbuffet expositiehal	Lunchbuffet expositiehal	Lunchbuffet expositiehal	Lunchbuffet expositiehal
13.30	Vrije voordrachten Sectie Gastrointestinale Endoscopie p. 30	**Genodigde spreker:** **Prof. H. Witt,** gevolgd door vrije voordrachten DEGH-sessie (genetica / cancer / other) p. 36	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie p. 37	Programma Vereniging voor Maag-Darm-Lever Verpleegkundigen p. 42	Programma Sectie Endoscopie Verpleeg-kundigen en Assistenten p. 41
15.00	Einde programma, thee	Einde programma, thee	Einde programma 15.10, thee	Einde programma, thee	Einde programma, thee

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

12.30 Inschrijving, koffie

Voorzitters: E. van der Harst en A. Mearadji

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

13.00 Rectocele Repair by Anterolateral Rectopexy; Long-term Functional Outcome (p. 56)
D.M.J. Oom[1], M.P. Gosselink[1], J.J. van Wijk[1], V.R.M. van Dijl[1], W.R. Schouten[1]. Dept of colorectal surgery, Erasmus MC, Rotterdam, The Netherlands

13.10 Fibrin glue and transanal rectal advancement flap for high transsphincteric perianal fistulas; Is there any advantage? (p. 57)
P.J. van Koperen, J. Wind, W.A. Bemelman, J.F.M. Slors, Dept of Surgery, Academic Medical Centre, Amsterdam, The Netherlands

13.20 Accuracy of the clinical diagnosis, a clinical prediction model, or imaging for the diagnosis of acute diverticulitis in patients with abdominal pain. (p.58)
W. Laméris[1], A. van Randen[2], B. van Ramshorst[3], E.J. Hesselink[4], H.G. Gooszen[5], J.W. Juttmann[6], P.M.M. Bossuyt[7], J. Stoker[2], M.A. Boermeester[1]. Depts of Surgery[1], Radiology[2], Clinical Epidemiology[7], Academic Medical Center, Dept of Surgery[3], Antonius Ziekenhuis Nieuwegein, Dept of Surgery[4], Gelre Ziekenhuis Apeldoorn, Dept of Surgery[5], UMC Utrecht, Dept of Surgery[6], Ter Gooi Ziekenhuizen Hilversum, The Netherlands

13.30 Isolated segmental bile duct injury after laparoscopic cholecystectomy. Clinical presentation, diagnosis, and long-term outcome after multidisciplinary treatment (p. 59)
P.R. de Reuver[1], I. Grossmann[2], E.A. Rauws[3], O.R. Busch[1], J.S. Laméris[4], T.M. van Gulik[1], D.J. Gouma[1]. Depts of Surgery[1], Gastroenterology[3] and Radiology[4], Academic Medical Centre, Amsterdam, The Netherlands. Currently working at Medisch Spectrum Twente[2], Enschede, The Netherlands

13.40 Intestinal barrier dysfunction in a randomised placebo-controlled trial of probiotic prophylaxis in acute pancreatitis (p. 60)
M.G. Besselink[1], H.C. van Santvoort, M.A. Boermeester, K. Fischer, W. Renooij, M.B. de Smet, U. Ahmed Ali, G.A. Cirkel, T.L. Bollen, B. van Ramshorst, B.L. Weusten, A.F. Schaapherder, B.J. Witteman, R.J. Ploeg, H. van Goor, C.J. van Laarhoven, A.C. Tan, M.A. Brink, E. van der Harst, P.J. Wahab, C.H. van Eijck, C.H. Dejong, K.J. van Erpecum, L.M. Akkermans, H.G. Gooszen and the members of the Dutch Acute Pancreatitis Study Group[1] UMC Utrecht and the centres participating in the Dutch Acute Pancreatitis Study Group

13.50 Transgastric Peritoneoscopy versus Laparoscopy for the Detection of Peritoneal Metastases (p. 61)
R.P. Voermans[1,2], M.I. van Berge Henegouwen[2], D.O. Faigel[3], S. Conlon[5], J.T. Spivey[5], R. Rowe[5], B. Sheppard[4], P. Fockens[1]. Depts of Gastroenterology and Hepatology[1], and Surgery[2], Academic Medical Center, Amsterdam, The Netherlands, Depts of Gastroenterology and Hepatology[3], and Surgery[4], Oregon Health & Science University, Portland, OR, USA, Ethicon Endosurgery[5], Cincinnati, OH, USA

14.00 Is there a role for post-imatinib surgery in advanced gastrointestinal stromal tumours? (p. 62)
K.F.D. Kuhlmann[1], J.M. Kerst[2], A. Cats[2], F. van Coevorden[1]. Depts of Surgery[1] and Medical Oncology[2], Antoni van Leeuwenhoek Hospital / Netherlands Cancer Institute, Amsterdam, The Netherlands

14.10 In vitro comparison of seven gastric closure modalities for Natural Orifice Transluminal Endoscopic Surgery (NOTES) (p. 63))
R.P. Voermans[1, 2], A.M. Worm[3], M.I. van Berge Henegouwen[2], P. Breedveld[3], W.A. Bemelman[2], P. Fockens[1]. Depts of Gastroenterology and Hepatology[1], and Surgery[2], Academic Medical Center, Amsterdam, Dept of BioMechanical Engineering[3], University of Technology, Delft, The Netherlands

Donderdag 13 maart 2008

14.20 A promising new combined treatment modality for Barrett's esophagus containing early neoplasia: endoscopic resection followed by step-wise circumferential and focal radiofrequency energy ablation (p. 64))
R.E. Pouw[1], J.J. Gondrie[1], F.G. van Vilsteren[1], C.M. Sondermeijer[1], F.J. ten Kate[2], O.R. Busch[3], M.I. van Berge Henegouwen[3], K.K. Krishnadath[1], P. Fockens[1], B.L.A.M. Weusten[4], J.J. Bergman[1]. Depts of Gastroenterology[1], Pathology[2] and Surgery[3], Academic Medical Center, Amsterdam, Dept of Gastroenterology[4], St Antonius Hospital, Nieuwegein, The Netherlands

14.30 Neo-adjuvant radiochemotherapy in esophageal cancer patients results in increased MMP-activity in surrounding healthy esophageal tissue at the time of surgery (p. 65)
E.A. Rieff[1], T. Hendriks[2], G.A.P. Nieuwenhuijzen[1], H.J.T. Rutten[1], M.J. Gosens[1], I.H.J.T. de Hingh[1]. Dept of Surgery[1], Catharina Ziekenhuis Eindhoven, Dept of Surgery[2], UMC St Radboud Nijmegen, The Netherlands

14.40 Good results of surgery after Self-Expanding Metal Stent (SEMS) placement for acute malignant colonic obstruction (p. 66)
H.H. Zwaving[1], J.J. Driest[2], E.H. Eddes[1], M. Ledeboer[2], F. ter Borg[2], R.J.I. Bosker[1], M. Eeftinck Schattenkerk[1]. Depts of Surgery[1] and Gastroenterology[2], Deventer Ziekenhuis, The Netherlands

14.50 Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal origin shows acceptable morbidity and high survival. (p.67)
J. Hagendoorn, E. van der Beek, D. Boerma, M.J. Wiezer, B. van Ramshorst. Dept of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands

15.00 Theepauze

Nederlandse Vereniging voor Gastroenterologie **Brabantzaal**

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

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

15.30 A high incidence of MSH6 mutations in Amsterdam Criteria II negative families tested in a clinical setting (p. 68)
D. Ramsoekh[1,2], A. Wagner[3], M.E. van Leerdam[1], W.N.M. Dinjens[4], E.W. Steyerberg[2], E.J. Kuipers[1], D. Dooijes[3]. Depts of Gastroenterology and Hepatology[1], Public Health[2], Clinical Genetics[3] and Pathology[4], Erasmus MC University Medical Center, Rotterdam, The Netherlands

15.40 Poor compliance with MSI-analysis in patients with colorectal cancer at high risk for Lynch Syndrome (p. 69)
M.G.F. van Lier[1], J.H.W. de Wilt[2], J.J.M.F. Wagemakers[3], W.N.M. Dinjens[4], R.A.M. Damhuis[3], E.J. Kuipers[1], M.E. van Leerdam[1]. Depts of Gastroenterology and Hepatology[1], Surgery[2] and Pathology[4], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

15.50 Individualized prediction of MLH1 and MSH2 Mutations in Lynch Syndrome (p. 70)
C. Liem[1], D. Ramsoekh[1,2], J. Balmana[3], S. Syngal[4], E.W. Steyerberg[1]. Depts of Public Health[1] and Gastroenterology and Hepatology[2], Erasmus MC University Medical Center, Rotterdam, The Netherlands, Dept of Medical Oncology[3], Hospital Vall d'Hebron, Barcelona, Spain, Dana-Farber Cancer Insitute[4], Boston, Massachutes, United States of America

16.00 Prognostic impact of MMP-2 and MMP-9 gene promoter polymorphisms and their corresponding protein levels in colorectal cancer (p.71)
A.M.J. Langers, C.F.M. Sier, F.J.G.M. Kubben, W. van Duijn, J.J. van der Reijden, L.J.A.C. Hawinkels, P.J. Koelink, C.B.H.W. Lamers, D.W. Hommes, H.W. Verspaget. Dept of Gastroenterology and Hepatology, Leiden University Medical Center, The Netherlands

16.10 Usefulness of genetically engineered bacteria for the treatment and prevention of colorectal cancer (p. 72)
N. Bos, S. Yuvaraj, M. Stoel, V. Puerta, M. Peppelenbosch. Dept of Cell Biology, University Medical Center Groningen, University of Groningen, The Netherlands

Donderdag 13 maart 2008

16.20 Accept or decline fecal occult blood test screening for colorectal cancer: the participants view (p. 73)
A.F. van Rijn[1], L.G.M. van Rossum[2], M. Deutekom[3], R.J.F. Laheij[2], P. Fockens[1], P.M.M. Bossuyt[3], E. Dekker[1] J.B.M.J. Jansen[2]. Depts of Gastroenterology[1] and Epidemiology and Biostatistics[3], Academic Medical Centre, Amsterdam, Dept of Gastroenterology[2], Radboud University Nijmegen Medical Centre, The Netherlands

16.30 Immunochemical fecal occult blood tests have the best performance in a screening population comparing four different screening strategies with intention to screen analysis. (p. 74)
L.G. van Rossum[1], A.F. van Rijn[2], R.J. Laheij[1], M.G. van Oijen[1], P. Fockens[2], A.L. Verbeek[3], J.B. Jansen[1], E. Dekker[2]. Depts of Gastro-enterology[1] and Epidemiology[3], University Medical Center St. Radboud Nijmegen, Nijmegen, Dept of Gastroenterology and Hepatology[2], Academic Medical Center, University of Amsterdam, The Netherlands

16.40 Self Expanding Metal Stents (SEMS) for colonic obstruction as bridge to surgery: A safe procedure? (p.75)
J.J. Driest[1], M. Ledeboer, H. Zwaving[2], E.H. Eddes[2], M. Eeftinck Schattenkerk[2], F. ter Borg[1]. Depts of Gastroenterology[1] and Gastro-intestinal surgery[2], Deventer ziekenhuis, Deventer, The Netherlands

16.50 Prevalence of adenomas in familial colorectal cancer (p. 76)
A.E. van der Meulen-de Jong[1], H.J. Wolters[3], A.M.C. Witte[3], J. Vecht[3], W.R. ten Hove[3], J.M.J.L. Salemans[3], F.M. Nagengast[3], J.H. Kleibeuker[3], G.F. Nelis[3], H.F.A. Vasen[1,2]. Dept of Gastroenterology[1], Leiden University Medical Center, Leiden, The Netherlands Foundation for the Detection of Hereditary Tumours[2], Leiden, The Netherlands, Member Collaborative Group FACT Study[3] .

17.00 Einde sessie met vrije voordrachten

President Select (plenaire sessie) **Brabantzaal**

Voorzitter: J.B.M.J. Jansen

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

17.00 Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial (p. 77)
M.G. Besselink[1], H.C. van Santvoort, E. Buskens, M.A. Boermeester, H. van Goor, H.M. Timmerman, V.B. Nieuwenhuijs, T.L. Bollen, B. van Ramshorst, B.J. Witteman, C. Rosman, R.J. Ploeg, M.A. Brink, A.F. Schaapherder, C.H. Dejong, P.J. Wahab, C.J. van Laarhoven, E. van der Harst, C.H. van Eijck, M.A. Cuesta, L.M. Akkermans, H.G. Gooszen and the members of the Dutch Acute Pancreatitis Study Group, University Medical Center Utrecht[1] and the centres participating in the Dutch Acute Pancreatitis Study Group.

17.15 Can RNA interference (RNAi) combine with interferon-alpha in anti-HCV treatment? (p. 78)
Q. Pan[1], Scot D. Henry[2], H.J. Metselaar[1], B. Scholte[3], J. Kwekkeboom[1], H.W. Tilanus[2], H.L.A. Janssen[1], L.J.W. van der Laan[2]. Depts of Gastro-enterology and Hepatology[1], Surgery[2] and Cell Biology[3], Erasmus MC-University Medical Center, Rotterdam, The Netherlands

17.30 Perioperative enteral arginine supplementation in head and neck cancer patients improves long term survival (p. 79)
N. Buijs[1], M.A.E. van Bokhorst-van der Schueren[2], J.A.E. Langius[2], C.R. Leemans[3], M.A.R. Vermeulen[1], P.A.M van Leeuwen[1]. Depts of Surgery[1], Nutrition and Dietetics[2] and Otolaryngology-Head and Neck Surgery[3], VU University Medical Center, Amsterdam, The Netherlands

17.45 Stress induced visceral hypersensitivity after maternal separation in rats is transferred across generations in a behavioral and mast cell dependent fashion. (p. 80)
R.M. van den Wijngaard[1], O. Welting[1], W.J. de Jonge[1], G.E.E. Boeckxstaens[1]. Dept of Gastroenterology and Hepatology[1], Academic Medical Center, Amsterdam, The Netherlands

18.00 Einde programma

Donderdag 13 maart 2008

Postersessie DEGH **Meierij Foyer**

11.30 Inschrijving, koffie

12.00 Begeleide posterrondes per thema geleid door koppels van invited speaker en bestuurslid, tevens lunchbuffet aanwezig, zie pagina: 43 – 53.

Voordrachten DEGH (metabolisme) **Baroniezaal**

Voorzitters: K.N. Faber en E.H.H.M. Rings

13.00 **Nuclear receptors in the enterohepatic circulation**
Prof. B. Staels, Lille, Frankrijk

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

13.30 The intestinal FXR-mediated Fgf-15 pathway contributes to the diurnal control of hepatic bile acid synthesis and bile formation in chow fed mice but its contribution is overruled during bile acid feeding and bile acid sequestration (p. 81)
J.H.M. Stroeve[1], G. Brufau[1], F. Stellaard[1], F.J. Gonzalez[2], B. Staels[3], F. Kuipers[1] [1]Center for Liver, Digestive and Metabolic Diseases, Laboratory of Pediatrics, University Medical Center Groningen, Groningen, The Netherlands, [2]Laboratory of Metabolism, National Cancer Institute, National Institutes of Health, Bethesda MD 20892, USA, [3]Institut Pasteur de Lille, Département d'Athérosclérose, Lille F-59019, France

13.45 Hepatic cytochrome p450 oxidoreductase knockout mice show altered bile salt, cholesterol and phospholipids excretion (p. 82)
C. Kunne, D.R. de Waart, C.C. Paulusma and R.P.J. Oude Elferink. Liver Center, Academic Medical Center, Amsterdam, The Netherlands

14.00 Calcium signalling of neuronal cell line SH-SY5Y triggered by sera of cholestatic patients suffering from pruritus (p.83)
A.E. Kremer, U.H.W. Beuers, R.P.J. Oude Elferink. AMC Liver Center, Amsterdam The Netherlands

14.15 Differential gene expression in Caco-2 ATP8B1 knock down cells unrelated to FXR activation (p. 84)

L.M. van der Velden[1], J.M. Stapelbroek[1,2], P.A.J. Muller[1], D.H.A. van Beurden[1], J. Koedam[1], R. Berger[1], R.H.J. Houwen[2], L.W.J. Klomp[1]. [1]Dept of Metabolic and Endocrine Diseases, Netherlands Metabolomics Centre, UMC Utrecht, [2]Dept of Pediatric Gastroenterology, University Medical Center Utrecht, The Netherlands

14.30 Differential effects of PFIC1 and BRIC1 mutations on protein stability and canalicular trafficking of ATP8B1 (p. 85)

D.E. Folmer, K.S. Ho-Mok, R.P.J. Oude Elferink, C.C. Paulusma. AMC Liver Center, Academic Medical Center, Amsterdam, The Netherlands

14.45 Fic1 deficiency results in hearing loss and degeneration of the cochlear hair cells (p.86)

J. Stapelbroek[1,2], T. Peters[4], D. an Beurden[2], J. Urfs[4], A. Beynon[4], L. Bull[5], R. Oude Elferink[6], B. van Zanten[3], L. Klomp[2], R. Houwen[1]. Depts of Paediatric Gastroenterology[1], Metabolic and Endocrine Diseases[2], ENT/Audiology[3], UMC Utrecht and Otorhinolaryngology[4], UMC St. Radboud; UCSF Liver Centre[5], San Francisco General Hospital; AMC Liver Centre[6], AMC, The Netherlands

15.00 Theepauze

Voordrachten DEGH (immunologie / IBD) **Baroniezaal**

Voorzitters: J. Kwekkeboom en E.A.F. van Tol

15.30 **Pathogenesis of IBD**
Prof. R. Xavier, Boston, USA

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

16.00 Cigarette smoke extract protects intestinal- and T-cells against death-recepor- and oxidative stress induced apoptosis: an explanation for dichoomal effects of smoking on ulcerative colitis and Crohn's disease? (p. 87)
E.M.J. van der Logt[1], K.N. Faber[1], T. Blokzijl[1], D.J. Slebos[2], M.P. Peppelenbosch[3], G. Dijkstra[1]. Dept of Gastroenterology and Hepatology[1], Dept of Pulmonary diseases[2], Dept of Cell Biology, Section Immunology[3], University Medical Center Groningen, The Netherlands

16.15 Adaptation of carnivore-colonizing Helicobacter species to the diet of their host (p. 88)
J. Stoof[1], S. Breijer[1], R.G.J. Pot[1], J.G. Kusters[1], A.H.M. Van Vliet[1,2], E.J. Kuipers[1]. [1]Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Institute of Food Research, Norwich, United Kingdom

16.30 Macrophage mannose receptor deficient mice are more susceptible to Helicobacter hepaticus induced colitis (p.89)
S.E.M. Heinsbroek [1,2], K. Maloy [2], P. Ahern [2], M. Asquith [2], S. Buonocore [2], F.J.W. ten Kate [1], W.J. de Jonge [1], G.E.E. Boeckxstaens [1], S. Gordon [2]. [1]Dept of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands, [2]Sir William Dunn School of Pathology, University of Oxford, United Kingdom

16.45 Tumor cell-fibroblast interaction generates myofibroblasts in colon cancer via Transforming Growth Factor-β activation (p. 90)
L.J.A.C. Hawinkels[1], H.W. Verspaget[1], E. Wiercinska[2], J.M. van der Zon[1], W. van Duijn[1], J.J. van der Reijden[1], A.A. Mulder-Stapel[3], D.W. Hommes[1], C.B.H.W. Lamers[1], C.F.M. Sier[1], Dept of Gastroenterology-Hepatology[1] and Molecular Cell Biology[2], Leiden University Medical Center, [3]TNO Quality of Life BioSciences, Leiden, The Netherlands

17.00 Einde programma in deze zaal (vervolg programma plenair in Brabantzaal)

Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit **Parkzaal**

12.30 Inschrijving, koffie

Voorzitters: R.J.F. Felt-Bersma en J.W. Straathof

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

13.00 The effect of Acute Tryptophan Depletion (ATD) on the activity and connectivity of an emotional arousal network during visceral pain (p. 91)
J.S. Labus[1], E.A. Mayer[1],T.O.C. Kilkens[2], E.A.T. Evers[3], R-J. M. Brummer[2], W.H. Backes[4], M.A. van Nieuwenhoven[2]. Depts of [1]Medicine and Psychiatry, Center for Neurobiology of Stress, UCLA, Los Angeles, CA, USA; Depts of [3]Neuropsychology and Psychiatry, [4]Radiology and [2]Gastroenterology, University Hospital Maastricht, The Netherlands

13.10 Famine in Early Life is Associated with an Increased Risk of Developing Irritable Bowel Syndrome, a Population Based Cohort Study (p. 92)
T. K. Klooker[1], B. Braak[1], R. C. Painter[2], S.R. de Rooij[2], R.M. van Elburg[3], R.M. van den Wijngaard[1], T.J.Roseboom[2], G.E. Boeckxstaens[1], [1]Gastro-enterology and Hepatology, Academic Medical Center, Amsterdam, Netherlands. [2]Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, Netherlands [3]Pediatrics, Division of Neonatology, VU University Medical Center, Amsterdam, The Netherlands

13.20 Role of serine protease signalling in dyspeptic symptom generation; a pilot study (p. 93)
O.S. van Boxel[1], J.J.M. ter Linde[1], N. van Lelyveld[1], P.D. Siersema[1], A.J.P.M. Smout[1], Dept of Gastroenterology and Hepatology[1], University Medical Center, Utrecht, The Netherlands

13.30 Effect of the GABAB receptor agonist AZD9343 on transient lower esophageal sphincter relaxations and acid reflux in healthy volunteers: a phase I trial (p. 94)
G.E.E. Boeckxstaens[1], H. Beaumont[1], H. Rydholm[2], M. Ruth[2], A. Lei[1], A. Lehmann[2], A. Smout[3]. [1]Gastroenetrology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]AstraZeneca R&D, Mölndal, Sweden, [3]Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands

Donderdag 13 maart 2008

13.40 Increased swallowing frequency in GERD is likely to be caused by perception of reflux episodes (p. 95)
G.J.M. Hemmink[1,2], B.L.A.M. Weusten[1], A.J. Bredenoord[1], R. Timmer[1], A.J.P.M. Smout[2]. [1]Dept of Gastroenterology, Sint Antonius Hospital, Nieuwegein, [2]Gastrointestinal Research Center, University Medical Center, Utrecht, The Netherlands

13.50 Differences in acidity of the refluxate during TLESRs between healthy subjects and gastroesophageal reflux disease patients (p. 96)
H. Beaumont[1], G.E.E. Boeckxstaens, [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

14.00 Scintigraphic imaging of the postprandial acid pocket in healthy subjects and gastroesophageal reflux disease patients (p. 97)
H. Beaumont[1], J.W. de Jong[2], R.J. Bennink[2], G.E.E. Boeckxstaens. [1]Dept of Gastroenterology and Hepatology, [2]Dept of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

14.10 Vagal nerve activity stimulates endo- and phagocytosis in intestinal and peritoneal macrophages via nicotinic acetylcholine receptor $\alpha 4/\beta 2$ in mice (p. 98)
W.J. de Jonge[1,2], S. Heinsbroek[1], E.P. van der Zanden[1], S.A. Snoek[1], C. Cailotto[1], G.E. Boeckxstaens[1], D.R. Greaves[2], S. Gordon[2].[1]Dept of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands, [2]Sir William Dunn School of Pathology, University of Oxford, United Kingdom

14.20 The safety of pneumatic balloon dilatation in achalasia patients: results from a large cohort study. (p.99)
J. Alderliesten, J.M. Conchillo, E.J. Kuipers. Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

14.30 No effect of gut-directed hypnotherapy on rectal sensitivity in children with functionnal abdominal pain and irritable bowel syndrome (p. 100)
M.M. van den Berg[1], A.M. Vlieger[2], C. Menko-Frankenhuis[1], M.E.J. Bongers[1], M.A. Benninga[1]. Emma Children's Hospital, Academic Medical Center, Amsterdam, [2]St. Antonius Hospital, Nieuwegein, The Netherlands

14.40 CT angiography and 24 hours tonometry: a novel and useful approach in the diagnosis of chronic gastrointestinal ischemia (p.101)
D. van Noord[1], P.B.F. Mensink[1], P.M.T. Pattynama[2], M.R.H.M. van Sambeek[3], E.J. Kuipers[1]. Depts of Gastroenterology and Hepatology[1], Interventional Radiology[2], Vascular Surgery[3], Erasmus Medical Center, Rotterdam, The Netherlands

14.50 Magnetic resonance imaging of the lumbosacral spine in children with chronic constipation and functional non-retentive fecal incontinence: a prospective study * (p. 102)
N. Bekkali[1], M.E.J. Bongers[1] , E.E. Hagebeuk[2] , R.R. van Rijn[3] , M.P. van Wijk[1], M.A. Benninga[1]. [1]Dept of Paediatric Gastroenterology and Nutrition, [2]Dept of Paediatric Neurology, Emma Children's Hospital, [3]Dept of Radiology, Academic Medical Center, Amsterdam, The Netherlands

15.00 Theepauze, einde programma

Voordrachten Netherlands Society of Parenteral and Enteral Nutrition — Parkzaal

Voorzitters: E.H.H.M. Rings en G. Wanten

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

15.30 Human intestinal ischemia-reperfusion induced cell damage is rapidly reversed by shedding of injured enterocytes (p. 103)
J.P.M. Derikx[1], R.A. Matthijsen[1], A.P. de Bruïne[2], A.A. van Bijnen[1], R.M. van Dam[1], E. Heineman[1], C.H.C. de Jong[1], W.A. Buurman[1]. [1]Dept of Surgery, University Hospital Maastricht and Nutrition and Toxicology Research Institute (NUTRIM), Maastricht University, [2]Dept of Pathology, University Hospital Maastricht and Cardiovascular Research Institute (CARIM), Maastricht University, The Netherlands

15.40 Mannose-binding lectin null alleles are associated with preserved epithelial cell integrity following intestinal ischemia reperfusion in man (p. 104)
R.A. Matthijsen[1], J.P.M. Derikx[1], R. Steffensen[2], R.M. van Dam[1], C.H.C. de Jong[1], W.A. Buurman[1]. [1]Dept of Surgery, Academic Hospital Maastricht and Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University, The Netherlands. [2]Regional Centre for Blood Transfusion and Clinical Immunology, Aalborg Hospital, Aalborg, Denmark

15.50 Non-invasive evaluation of intestinal damage in celiac disease using I-FABP and L-FABP * (p. 105
J. Grootjans[1], J.P.M. Derikx [1], A.C.E. Vreugdenhil [2], A.M. van den Neucker[2], A.A. van Bijnen[1], J.G.M.C. Damoiseaux[3], L.W.E. van Heurn[1], W.A. Buurman[1], E. Heineman[1]. [1]Dept of Surgery, University Hospital Maastricht and Nutrition and Toxicology Research Institute (NUTRIM), Maastricht University, [2]Dept of Paediatrics, [3]Dept of Internal Medicine, University Hospital Maastricht, The Netherlands

16.00 Intestinal permeability and inflammatory balance reflected by LPS binding protein and Angiopoietin 1 and 2, in brain dead and living donors (p. 106)
L.G. Koudstaal[1,2], W.N. Nijboer[1], J.J. Zwaagstra[1], V.B. Nieuwenhuijs[1], H. van Goor[2], R.J. Ploeg[1], H.G.D. Leuvenink[1]. [1]Surgery, [2]Pathology and Laboratory Medicine, University Medical Center, Groningen, The Netherlands

16.10 Mast cell induced bacterial translocation in the pathogenesis of post-operative ileus studied in a mouse model (p. 107)
S.A. Snoek[1], G.E. Boeckxstaens[1], O. Welting[1], O.I. Stanisor[1], C. Cailotto[1], R.M. van den Wijngaard[1], W.J. de Jonge[1,2]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Sir William Dunn School of Pathology, University of Oxford, United Kingdom

16.20 The composition of the dominant faecal microbiota in COPD patient receiving multispecies probiotics during and after antibiotic intake (p. 108)
C.J.M. Koning[1], D.M.A.E. Jonkers[1,2], H. Smidt[3], H.J. Pennings[4], E. Wouters[4], E.E. Stobberingh[2], R.W. Stockbrügger[1]. Div of [1]Gastro-enterology and Hepatology, [2]Medical Microbiology, University Hospital Maastricht, Maastricht. [3]Laboratory of Microbiology, Wageningen Univer-sity, Wageningen. [4]Dept of Respiratory Medicine, Centre for Integrated Rehabilitation of Organ failure (CIRO), Horn, The Netherlands

16.30 Mastocytic enterocolitis: a new identity in patients with chronic diarrhoea? (p. 109)
C. van Enckevort[1], M. Havenith[2], J. Vecht[1]. Dept of Gastroenterology[1], Dept of Pathology[2], Isala Clinics, Zwolle, The Netherlands

16.40 Pancreatic function after surgery for painful chronic pancreatitis (p.110)
N.A. van der Gaag[1], M.A. Boermeester[1],M. Schuiling[1], O.R.C. Busch[1], M.J. Bruno[2], T.M. van Gulik[1], D.J. Gouma[1]. Dept of Surgery[1], Dept of Gastro-enterology[2], Academic Medical Center, Amsterdam, The Netherlands

16.50 Complications after Endoscopic Retrograde Cholangiopancreatography: risk factors for pancreatitis, cholangitis and hemorrhage (p.111)
S.M. Jeurnink[1], E.W. Steyerberg[2], P.D. Siersema[1], J. Dees[1], J. Haringsma[1], J.W. Poley[1], E.J. Kuipers[1, 3]. Depts of Gastroenterology and Hepatology[1], Public Health[2], Internal Medicine[3], Erasmus Medical Center, Rotterdam, The Netherlands

17.00 Voor de plenaire sessie (President Select) kunt u zich begeven naar de Brabantzaal.

Nederlandse Vereniging voor Gastroenterologie **Genderzaal**

07.30 **Ledenvergadering NVGE**
Onbijtbuffet in de zaal

08.30 Sluiting

Casuïstiek **Brabantzaal**

Voorzitter: W. Hameeteman

08.30 Casuïstische Patiëntenbespreking

Vrije voordrachten Sectie Gastrointestinale Endoscopie **Brabantzaal**

Voorzitters: J.J.G.H.M. Bergman en B.L.A.M. Weusten

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

09.00 Feasibility of transgastric and transcolonic NOTES peritoneoscopy combined with intraperitoneal endoscopic ultrasonography (p.112)
R.P. Voermans[1, 2], M.I. van Berge Henegouwen[2], W.A. Bemelman[2], P. Fockens[1]. Dept Gastroenterology and Hepatology[1], Dept of Surgery[2], Academic Medical Center, Amsterdam, The Netherlands

09.10 Endoscopic ultrasonography is a valuable tool with high yield in screening of patients at high-risk patients for pancreatic cancer (p.113)
J.W. Poley[1], I. Kluyt[2], D.J. Gouma[3], A. Wagner[4], C. Aalfs[5], C.H.J. van Eijck[6], A. Cats[7], Y. Nio[8], P. Fockens[9], E.J. Kuipers[1], M.J. Bruno[9]. Depts of Gastroenterology and Hepatology[1], Clinical Genetics[4], Surgery[6], Erasmus Medical Center, Rotterdam, Depts of Clinical Genetics[2], Gastroenterology[7], Dutch Cancer Institute/Antonie van Leeuwenhoek Hospital, Amsterdam, Depts of Surgery[3], Clinical Genetics[5], Radiology[8], Gastroenterology and Hepatology[9], Academic Medical Center, Amsterdam, The Netherlands

09.20 The diagnostic value of Endoscopic Ultrasonography in patients with a clinical suspicion of malignant pancreatic disease and inconclusive or negative CT scan (p.114)
O.L.M. Meijer, R.K. Weersma, H.M. van Dullemen. Dept of Gastroenterology and Hepatology, University Medical Center, Groningen, The Netherlands

09.30 Endoscopic elastosonography is highly predictive of definite pathology (p.115)
J.W. Poley, E.J. Kuipers. Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

09.40 Contamination of the working channel during endoscopic ultrasonography guided fine needle aspiration of lymph nodes in staging of esophageal cancer results in false positive cytology (p. 116)
A. Lamprou[1], R.K. Weersma[1], B. Hemel[2] , A. ten Hoor-van 't Klooster[2], J.T.M. Plukker[3], H.M. van Dullemen[1] . [1]Dept of Gastroenterology and Hepatology, [2]Dept of Pathology, [3]Dept of Surgery, University Medical Center, Groningen, The Netherlands

09.50 A randomized prospective trial comparing the cap-technique and multiband mucosectomy technique for piecemeal endoscopic resection in Barrett's esophagus (p. 117)
R.E. Pouw[1], J.J. Gondrie[1], F.G. van Vilsteren[1], F.J. ten Kate[2], K.K. Krishnadath[1], P. Fockens[1], B.L. Weusten[3], J.J. Bergman[1]. Dept of Gastroenterology[1], Dept of Pathology[2], Academic Medical Center, Amsterdam, Dept of Gastroenterology[3], St. Antonius Hospital, Nieuwegein, The Netherlands

10.00 Einde sessie

Vrijdag 14 maart 2008

Symposium Richtlijn Sedatie **Brabantzaal**

Voorzitter: P. Fockens

10.00 Opening door prof. dr. P. Fockens

10.35 Wat is sedatie eigenlijk?
Prof. dr. J.T.A. Knape, hoogleraar anaesthesiologie, UMC Utrecht

10.50 Ervaringen met de sedatierichtlijn 2001 in een groot perifeer ziekenhuis
Dr. J.J. Kolkman, mdl-arts, Medisch Spectrum Twente, Enschede

11.05 Propofol administration by non-anaesthesiologists
Prof. Chr. Beglinger, hoogleraar gastroenterologie, Basel, Zwitserland

11.30 Nieuwe CBO richtlijn sedatie, een tipje van de sluier opgelicht
Dr. S.J. van den Hazel, mdl-arts, Slingeland Ziekenhuis, Doetinchem

11.45 Paneldiscussie

12.00 Sluiting

Meet the speakers breakfast DEGH **Zaal 20**

ZonMw

08.00 Meet the speakers breakfast
met Prof. R. Xavier en Prof. I.N. Crispe

09.00 Einde programma

Voor deze bijeenkomst dient u zich tevoren in te schrijven!

Voordrachten DEGH (immunologie) **Baroniezaal**

Voorzitters: G. Dijkstra en L. Klomp

09.00 **Immune-regulation in the Liver**
Prof. I.N. Crispe, Rochester, USA

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

09.30 Regulation of the T cell response to the hepatitis C virus (p. 118)
A. Boonstra[1], M. Claassen[1], D. Turgut[1], R.J. de Knegt[1], H.L.A. Janssen[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

09.45 Human plasmacytoid dendritic cells induce profound hyporesponsiveness and suppressive capacity in allogeneic T-cells (p. 119)
P.P.C Boor[1], H.J. Metselaar[1], S. de Jonge[1], L. van der Laan[1,2], J. Kwekkeboom[1]. [1]Dept of Gastroenterology and Hepatology, [2]Dept of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands

10.00 Koffiepauze, expositie

Voordrachten (immunologie/celbiologie) DEGH **Baroniezaal**

Voorzitters: G. Dijkstra en L. Klomp

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

10.30 Migration of donor myeloid dendritic cells after human liver- but not after kidney transplantation: implications for liver graft acceptance? (p. 120)
J. Kwekkeboom[1], B.M. Bosma[1], J.H. Gerrits[2], N.M. van Besouw[2], S. Mancham[1], Z.M.A. Groothuismink[1], L.W.J. van der Laan[3], H.W. Tilanus[3], E.J. Kuipers[1], H.J. Metselaar[1]. Dept of Gastroenterology and Hepatology[1], Dept of Internal Medicine[2], Dept of Surgery[3], Erasmus Medical Center, Rotterdam, The Netherlands

Vrijdag 14 maart 2008

10.45 The hydrophobic iminosugar AMP-DNM increases biliary lipid secretion in mice via FGF mediated regulation of CYP7A1 (p. 121)
N. Bijl, R. Ottenhoff, C.P.A.A. van Roomen, S. Scheij, J.M.F.G. Aerts, A.K. Groen. Dept of Medical Biochemistry, Academic Medical Center, Amsterdam, The Netherlands

11.00 Reactive oxygen species are not involved in bile acid induced apoptosis of hepatocytes (p. 122)
T.E. Vrenken, M. Buist-Homan, K.N. Faber, H. Moshage. Dept of Gastro-enterology and Hepatology, University Medical Center Groningen, The Netherlands

11.15 Pharmacological inhibition of ACC activity by Soraphen reverses high fat-induced obesity and insulin resistance in mice (p. 123)
M. Schreurs, T.H. van Dijk, R. Havinga, D.J. Reijngoud, F. Kuipers. Center for Liver, Digestive and Metabolic Diseases, Laboratory of Pediatrics, University Medical Center Groningen, The Netherlands

11.30 Noninvasive quantitative assessment of hepatic steatosis in the rat liver using 3.0 Tesla ^{1}H-Magnetic Resonance Spectroscopy (p.124)
H.A. Marsman[1], J.R. van Werven[2], A.J. Nederveen[2], F.J.W. ten Kate[3], J. Stoker[2], T.M. van Gulik[1]. Depts of Surgery[1], Radiology[2] and Pathology[3], Academic Medical Center, Amsterdam, The Netherlands

11.45 Functional cellular copper uptake requires oligomerization of the high affinity copper transporter 1 (hCTR1) (p. 125)
P.V.E van den Berghe[1], R. Berger[1], L.W.J. Klomp[1]. [1]Dept of Metabolic and Endocrine Diseases, University Medical Center, Utrecht, Netherlands Metabolomics Centre, The Netherlands

12.00 Lunchbuffet en uitreiking posterprijzen in Meierij Foyer

Voorzitter: A.A. van Bodegraven en D.J. de Jong

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

08.30 Confirmation of several genetic associations from the WTCCC study and identification of novel susceptibility loci in a large Dutch-Belgian Crohn's disease cohort (p. 126)
R.K. Weersma[1], P.C. Stokkers[2], I. Cleynen[3], S. Schreiber[4], L. Henckaerts[3], A. Franke[4], G. Dijkstra[1], P. Rutgeerts[3], C. Wijmenga[5], S. Vermeire[3]. [1]Gastroenterology and Hepatology, University Medical Center, Groningen, [2]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Institute for Clinical Molecular Biology, Christian-Albrechts University Kiel, Germany, [4]Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium

08.40 Wnt-pathway activation in early IBD-associated colorectal carcinogenesis: a biomarker for colonic surveillance (p. 127)
M.M.H. Claessen[1], F.P. Vleggaar[1], M.E.I. Schipper[2], B. Oldenburg[1], G.J.A. Offerhaus[2], P.D. Siersema[1]. Dept of Gastroenterology and Hepatology[1], Dept of Pathology[2], University Medical Center, Utrecht, The Netherlands

08.50 Genetic analysis of the innate immune system identifies CARD9 and the IL18 receptor locus as susceptibility genes for both Crohn's disease and ulcerative colitis (p. 128)
*A. Zhernakova[1], E.A. Festen[2,3], L. Franke[1], G. Trynka[3], A.J. Monsuur[1], M. Bevova[1], R.M. Nijmeijer[4], R. Heijmans[5], D.A. van Heel[6], A.A. van Bodegraven[7], P.C. Stokkers[8], C. Wijmenga[8], J.B. Crusius[5], R.K. Weersma[2]. Dept of Genetics, UMCU[1], UMCG[3], VUMC[5], Dept of Gastro-enterology and Hepatology, UMCG[2], VUMC[7], AMC[8], Dept of Surgery, UMCU[4], Institute of Cell & Molecular Science[6], Queen Mary's School of Medicine and Dentistry, London, United Kingdom, * Present address: Netherlands Vaccine Institute, Bilthoven, the Netherlands*

Vrijdag 14 maart 2008

09.00 The glucocorticoid receptor gene polymorphism BclI which modulates glucocorticoid sensitivity is associated with inflammatory bowel disease (p. 129))

M.J.M. van Oosten[1], C.J. van der Woude[3], R.K. Weersma[2], E.F.C. van Rossum[1], J.W. Koper[1], E.J. Kuipers[3], S.W.J. Lamberts[1], R.A. Feelders[1]. [1]Dept of Internal Medicine, Endocrine Section, Erasmus Medical Center, Rotterdam, [2]Dept of Hepatology and Gastroenterology, University Medical Center, Groningen, [3]Dept of Hepatology and Gastroenterology, Erasmus Medical Center, Rotterdam, The Netherlands

09.10 Crohn's associated genes ATG16L1 and IRGM are not associated with granuloma formation (p.130)

S.C.S. Wolfkamp[1,2], P.C.F. Stokkers[2], A.A. te Velde[1]. Dept of Experimental Internal Medicine[1], Dept of Gastroenterology and Hepatology [2], Academical Medical Center, Amsterdam, The Netherlands

09.20 Sex-related Inheritance and Transmission Pattern in Inflammatory Bowel Disease (p. 131)

Z. Zelinkova[1], P. Stokkers[2], K. van der Linde[3], E.J. Kuipers[1], C.J. van der Woude[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept of Gastroenterology and Hepatology, Medical Center Leeuwarden, The Netherlands

09.30 Colonoscopic Surveillance in Inflammatory Bowel Disease Improves Survival after Colorectal Cancer Diagnosis (p. 132)

*M.W.M.D. Lutgens[1], B. Oldenburg[1**], P.D. Siersema[1], F.P. Vleggaar[1]. [1]Dept of Gastroenterology and Hepatology, University Medical Center, Utrecht, The Netherlands, **On Behalf of the Initiative on Crohn and Colitis*

09.40 More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis (p. 133)

M.M.H. Claessen[1], M.W.M.D. Lutgens[1], H.R. van Buuren[2], B. Oldenburg[1], K.M.A.J. Tytgat[1], P.D. Siersema[1], F.P. Vleggaar[1]. [1]Dept of Gastroenterology and Hepatology, University Medical Centre, Utrecht, [2]Dept of Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands

09.50 The risk of colorectal carcinoma in IBD patients is limited in non-tertiary cohorts: results of a nation wide long-term survey (p. 134)
J.E. Baars[1], E.J. Kuipers[1], R.P.R. Adang[2], L.G.J.B. Engels[3], G.W. Erkelens[4], J.J. Nicolai[5], M.K. Casparie[6], C.J. van der Woude[1]. Dept of Gastroenterology and Hepatology, [1]Erasmus Medical Center, Rotterdam, [2]VieCuri Medical Center, Venlo, [3]Maaslandziekenhuis, Sittard, [4]Reinier de Graaf Gasthuis, Delft, [5]Hagaziekenhuis, Den Haag, [6]PALGA, Utrecht, The Netherlands

10.00 Koffiepauze, expositie

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

Voorzitters: B. Oldenburg en C.J. van der Woude

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

10.30 Magnetic Resonance Imaging for suspected IBD in a pediatric population * (p.135)
L. de Ridder[1,2], K. Horsthuis[3], A.M. Smets[3], R.A. Nievelstein[4], M.S. van Leeuwen[4], M.A. Benninga[2], R.H. Houwen[5], J. Stoker[3]. [1]Pediatric Gastroenterology, Erasmus Medical Center/Sophia Children's Hospital, Rotterdam, [2]Pediatric Gastroenterology, [3]Radiology, Academic Medical Center, Amsterdam, [4]Radiology, [5]Pediatric Gastroenterology, University Medical Center Utrecht, The Netherlands

10.40 Scintigraphic identification of pancolitis and distal ileitis using 99mTc-labeled interleukin-8 in inflammatory bowel disease (p. 136)
D.J. de Jong[1], J.P.H. Drenth[1], J. Tielen[1], F.H.M. Corstens[2], O.C. Boerman[2], W.J.G. Oyen[2]. Dept of Gastroenterology and Hepatology[1], Dept of Nuclear Medicine[2], Radboud University Medical Center, Nijmegen, The Netherlands

10.50 Maintenance therapy with once-daily 2 g mesalazine (Pentasa) treatment improves remission rates in subjects with ulcerative colitis compared to twice daily 1 g mesalazine: Data from a randomised controlled trial (p. 137)
M. Oudkerk-Pool[1], A.U. Dignass[2], T. Stijnen[3], H. Veerman[4]. [1]Gelre Ziekenhuizen, Apeldoorn, The Netherlands. [2]Dept of Medicine I, Markus-Krankenhaus, Frankfurt / Main, Germany, [3]University Leiden, [4]Ferring BV, Hoofddorp, The Netherlands

11.00 Treatment regimens of azathioprine or 6-mercaptopurine in inflammatory bowel disease in clinical practice (p. 138)

C.J. van Marrewijk[1], B. Franke[1], M.J.H. Coenen[1], L.J.J. Derrijks[4], H.J. Guchelaar[5], O.H. Klungel[6], M.E. v.d. Akker-v. Marle[7], A.L.M. Verbeek[2], H.H.M. Vermeulen[2], H. Scheffer[1], D.J. de Jong[3]. [1]Human Genetics, [2]Epidemiology and Biostatistics, [3]Gastroenterology and Hepatology, RUNMC, Nijmegen, [4]Clin. Pharmacy & Toxicology, MMC, Veldhoven, [5]Clin. Pharmacy and Toxicology, LUMC, Leiden, [6]Pharmacoepidemiology and Pharmacotherapy, UU, Utrecht, [7]Neth. Organization for Applied Scientific Research, Leiden, The Netherlands

11.10 Predictors for failing thiopurine therapy in IBD patients; treated at an academic or general district hospital (p. 139)

B. Jharap[1], M.L. Seinen[1], R.K. Linskens[2], J.C. Kneppelhout[2], C.J.J. Mulder[1], N.K. de Boer[1], A.A. van Bodegraven[1]. [1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Dept of Gastroenterology and Hepatology, St Anna Hospital, Geldrop

11.20 Thiopurine metabolite measurements during pregnancy in mother and child (p. 140)

B. Jharap[1], N.K.H. de Boer[1], C.J. van der Woude[2], D.W. Hommes[3], P. Stokkers[4], D.J. de Jong[5], B. Oldenburg[6], G. Dijkstra[7], R.M. van Elburg[8], A.A. van Bodegraven[1] for the Initiative on Crohn and Colitis. Dept of Gastroenterology and Hepatology[1], Amsterdam, Dept of Gastroenterology and Hepatology[2], Erasmus University Med.Center, Rotterdam, Dept of Gastroenterology and Hepatology[3], Leiden University Med. Center, Leiden, Dept of Gastroenterology and Hepatology[4], Academic Med.Center, Amsterdam, Dept of Gastroenterology and Hepatology[5], Radboud University Med. Center, Nijmegen, Dept of Gastroenterology and Hepatology[6], University Med. Center Utrecht, Dept of Gastroenterology and Hepatology[7], University Med. Center Groningen, Dept of paediatrics[8] VU Med. Center, Amsterdam,The Netherlands

11.30 Scheduled monitoring of vital signs during infusion with infliximab is not indicated (p. 141)

H.S. de Vries[1], M.G.H. van Oijen[1], C.E.J. van Hoven-van Loo[1], D.J. de Jong[1]. Dept of Gastroenterology and Hepatology[1], Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

11.40 Serious events during nine years single centre experience with infliximab (p. 142) *H.S. de Vries[1], M.G.H. van Oijen[1], C.E.J. van Hoven-van Loo[1], D.J. de Jong[1]. Dept of Gastroenterology and Hepatology[1], Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands*

11.50 Does immunogenicity play a role in adalimumab treatment for Crohn's disease? (p. 143)
R.L. West[1], Z. Zelinkova[1], G.J. Wolbink[2], E.J. Kuipers[1], P.C.F. Stokkers[3], C.J. van der Woude[1]. Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam[1] , Sanquin Research, Amsterdam[2] , Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam[3] , The Netherlands

12.00 Lunchbuffet in expositiehal

Sectie Gastrointestinale Endoscopie — Brabantzaal

Voorzitters: H. van Dullemen en W. Hameeteman

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

13.30 Stepwise radical endoscopic resection for complete removal of Barrett's esophagus with early neoplasia: an international multicenter study.
(p.144 + p. 145) *J.J. Gondrie[1], S. Seewald[2], R.E. Pouw[1], P.H. Deprez[3], H. Piessevaux[3], H. Pohl[4], T. Rösch[4], N. Soehendra[2], J.J. Bergman[1]. Dept of Gastroenterology[1], Academic Medical Center, Amsterdam, The Netherlands, Dept of Interdisciplinary Endoscopy[2], University Clinics Eppendorf, Hamburg, Germany, Dept of Gastroenterology[3], Cliniques Universitaires Saint-Luc, Brussel, Belgium, Dept of Gastroenterology[4], Charité, Berlin, Germany*

13.40 Stepwise circumferential and focal radiofrequency ablation of Barrett's esophagus preserves esophageal diameter, compliance and motility
(p. 146) *H. Beaumont[1], J.J. Gondrie[1], B.P. McMahon[2], H. Gregersen[3], W.D. Rosmolen[1], J.J. Bergman[1], G.E.E. Boeckxstaens. [1]Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [1]Medical Physics and Clinical Engineering, Adelaide & Meath Hospital, Dublin, Ireland, [3]Gastroenterology, Aalborg Hospital, Aalborg, Denmark*

Vrijdag 14 maart 2008

13.50 Endoscopic interobserver agreement for the Spigelman classification in patients with familial adenomatous polyposis (FAP) (p. 147)
J.W. Poley[1], E. Dekker[2], F.M. Nagengast[3], E.M.H. Mathus-Vliegen[2], J. Dees[1], E.J. Kuipers[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands

14.00 Validation of interobserver agreement and accuracy of the combined use of autofluorescence imaging and narrow band imaging for differentiation of adenomatous and non-neoplastic colonic polyps in a non-expert setting (p. 148)
F.J.C. van den Broek[1], E.J. van Soest[1], A.H. Naber[2], A.H.A.M. van Oijen[3], R.Ch. Mallant-Hent[4], C.J.M. Böhmer[5], L.C. Baak[6], P. Scholten[7], W.L. Curvers[1], J.J.G.H.M. Bergman[1], J.B. Reitsma[1], P. Fockens[1], E. Dekker[1]. [1]Academic Medical Center, Amsterdam, [2]Tergooiziekenhuizen, Hilversum, [3]Medisch Centrum Alkmaar, Alkmaar, [4]Flevoziekenhuis, Almere, [5]Spaarne ziekenhuis, Hoofddorp, [6]Onze Lieve Vrouwe Gasthuis, Amsterdam, [7]St. Lucas Andreas ziekenhuis, Amsterdam, The Netherlands

14.10 Diagnostic yield of colorectal neoplasia in daily clinical practice: consequences for future colorectal cancer screening? (p. 149)
J.S. Terhaar sive Droste[1], M.E. Craanen[1], R.W.M. van der Hulst[2], J.F. Bartelsman[3], P.D. Bezemer[4], K.R. Cappendijk[1], G.A. Meijer[5], L.M. Morsink[1], P. Snel[6], H.A.R.E. Tuynman[7], R.L.J. van Wanrooy[1], I.C.E. Wesdorp[8], C.J.J. Mulder[1]. Dept of Gastroenterology and Hepatology[1], Dept of Epidemiology and Biostatistics[4], Dept of Pathology[5], Dept of Gastroenterology and Hepatology[2], Kennemer Gasthuis, Haarlem, Dept of Gastroenterology and Hepatology[3], Academic Medical Centre, Amsterdam, Dept of Gastroenterology and Hepatology[6], Slotervaart Hospital, Amsterdam, Dept of Gastroenterology and Hepatology[7], Medical Centre Alkmaar, Dept of Gastroenterology and Hepatology[8], Sint Lucas Andreas Hospital, Amsterdam, The Netherlands

14.20 Screening for colorectal cancer in the Netherlands; randomized controlled trial comparing attendance and diagnostic yield of two different forms of fecal occult blood tests and sigmoidoscopy. (p.150 + p.151)
L. Hol[1], M.E. van Leerdam[1], M. van Ballegooijen[2], A.J. van Vuuren[1], J.C.I.Y. Reijerink[3], A.C.M. van der Togt[4], J.D.F. Habbema[2], E.J. Kuipers[1]. [1]Dept of Gastroenterology and Hepatology, [2]Dept of Public Health, Erasmus Medical Center, Rotterdam, [3]Association of population-based screening southwest of The Netherlands, Vlaardingen, [4]Comprehensive Cancer Center, Rotterdam, The Netherlands

14.30 High prevalence of small adenomas in a colorectal cancer screening population using primary colonoscopy (p.152)
C. Khalid-de Bakker[1], D. Jonkers[1], S. Sanduleanu[1], A. de Bruïne[2], W. Hameeteman[1], A. Masclee[1], R. Stockbrügger[1]. Dept of Gastroenterology and Hepatology[1], Dept of Pathology[2], University Hospital Maastricht, Maastricht, The Netherlands

14.40 Nurse endoscopy for colorectal screening? A survey of expectations, opinions and future perspectives (p. 153)
P.G. van Putten[1], M.E. van Leerdam[1], E.J. Kuipers[1]. Dept of Gastroenterology and Hepatology[1], Erasmus Medical Center, Rotterdam, The Netherlands

14.50 Adjusting cut-off values of immunological FOBT allows tuning of CRC screening programs to colonoscopy capacity (p. 154)
F.A. Oort[1], J.S. Terhaar sive Droste[1], M.E. Craanen[1], R.W.M. van der Hulst[2], H.A. van Heukelem[3], R.J.L.F. Loffeld[4], I.C.E. Wesdorp[5], G.A. Meijer[6], C.J.J. Mulder[1]. Dept of Gastroenterlogy and hepatology[1], Dept of Pathology[6], VU medical center, Amsterdam, Dept of Gastroenterlogy and Hepatology[2], Kennemer Gasthuis, Haarlem, Dept of Gastroenterlogy and Hepatology[3], Slotervaart Hospital, Amsterdam, Dept of Internal Medicine[4], Zaans Medical Center, Zaandam, Dept of Gastroenterlogy and Hepatology[5], St. Lucas and Andreas Hospital, Amsterdam, The Netherlands

15.00 Einde programma, koffie/thee expositiehal

Voordrachten DEGH (genetica / cancer / other) **Baroniezaal**

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

13.00 **Genetic basis of pancreatitis**
Prof. H. Witt, Berlin, Germany

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

13.30 Disturbed Hepatic Carbohydrate Management During High Metabolic Demand in Medium-Chain Acyl-CoA Dehydrogenase (MCAD)-Deficient Mice (p. 155)
H. Herrema[1,2], T.G.J. Derks[1*], T.H. van Dijk[1], V.W. Bloks[1], A. Gerding[1], R. Havinga[1], U.J.F. Tietge[1], M. Müller[2], G.P.A. Smit[1], F. Kuipers[1], D.J. Reijngoud[1]. [1]Laboratory of Pediatrics, University Medical Center, Groningen, [2]Nutrigenomics Consortium, TI Food & Nutrition, Wageningen, The Netherlands *These authors contributed equally*

13.45 The role of IGFBP5 in liver fibrosis (p. 156)
A. Sokolovic, P. Bosma, Liver Center, Academic Medical Center, Amsterdam, The Netherlands

14.00 Conditional inactivation of glutamine synthetase in the liver (p. 157)
Y. He[1], T.B.M. Hakvoort[1], S.E. Köhler[2], J.L.M. Vermeulen[1], R. de Waart[1], J.M. Ruijter[1], C. de Theije[2], G.A.M. ten Have[3], H. van Eijk[3], N.E.P. Deutz[3], W.H. Lamers[1,2]. [1]Liver Center and Dept of Anatomy & Embryology, Academic Medical Center, Amsterdam, [2]Dept of Anatomy & Embryology and [3]Metabolic Research Center, Maastricht University, Maastricht, The Netherlands

14.15 The Bone Morphogenetic Protein Pathway is inactivated in the majority of Sporadic Colorectal Cancers (p. 158)
L.L. Kodach[1], E. Wiercinska[2], N.F.C.C. de Miranda[3], S.A. Bleuming[4], M.P. Peppelenbosch[5], E. Dekker[6], G.R. van den Brink[1], C.J.M. van Noesel[7], H. Morreau[3], P. ten Dijke[2], G.J.A. Offerhaus[8], J.C.H. Hardwick[1]. Dept Gastroenterology[1], Mol. Biol.[2], Path.[3], LUMC, Dept Exp. Int. Med.[4], Gastro.[6], Path.[7], AMC, Dept Cell Biol.[5], UMCG, Dept Path.[8], UMC, The Netherlands

14.30 Diminished epithelial protection during post-natal development and suckling-weaning transition in Mucin 2 deficient mice (p. 159)
M. van der Sluis[1], N. Burger-van Paassen[1], A.M. Korteland- van Male[1,2], I. van Seuningen[3], J.B. van Goudoever[1], I.B. Renes[1]. Dept of Pediatrics, [1]Division of Neonatology, [2]Division of Gastroenterology, Erasmus Medical Center and Sophia Children's Hospital, Rotterdam, The Netherlands, [3]Inserm, U837, Centre de Recherche Jean-Pierre Aubert, Lille, France

14.45 **Prijsuitreiking beste voordrachten**

15.00 **Ledenvergadering SEG**

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

Voorzitter: P.D. Siersema en H.J. Verkade

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

13.30 Prospective multicenter study on the incidence of neoplastic progression in Barrett esophagus patients (p.160)
M. Sikkema[1], M. Kerkhof[1], E.W. Steyerberg[2], H. van Dekken[3], A.J. van Vuuren[1], W.A. Bode[4], H. van der Valk[5], D.J. Bac[6], R.Giard[7], W. Lesterhuis[8], R. Heinhuis[9], E.C. Klinkenberg[10], G.A. Meijer[11], F. ter Borg[12], J.W. Arends[13], J.J. Kolkman[14], J. van Baarlen[15], R.A. de Vries[16], A. Mulder[17], A.J.P. van Tilburg[18], G.J.A. Offerhaus[19], F.J.W. Ten Kate[19], J.G. Kusters[1], E.J. Kuipers[1], P.D. Siersema[1] for the CYBAR study group. Depts of Gastroenterology and Hepatology[1], Public Health[2] and Pathology[3], Erasmus MC, University Medical Center Rotterdam, Dept of Gastroenterology and Hepatology[4], IJsselland Hospital, Capelle a/d IJssel, Dept of Pathology[5], PATHAN, Rotterdam, Dept of Gastroenterology and Hepatology[6], Ikazia Hospital, Dept of Pathology[7], Medical Center Rijnmond Zuid, Rotterdam, Dept of Gastroenterology and Hepatology[8], Albert Schweitzer Hospital, Dept of Pathology[9], Laboratory for Pathology, Dordrecht, Depts of Gastroenterology and Hepatology[10]and Pathology[11], Free University Medical Center, Amsterdam, Depts of Gastroenterology and Hepatology[12] and Pathology[13], Deventer Hospital, Deventer, Dept of Gastroenterology and Hepatology[14], Medisch Spectrum Twente, Dept of Pathology[15], Laboratory Pathology Oost-Nederland, Enschede, Depts of Gastroenterology and Hepatology[16] and Pathology[17], Rijnstate Hospital, Arnhem,

Dept of Gastroenterology and Hepatology[18], Sint Franciscus Hospital, Rotterdam, Dept of Pathology[19], University Medical Center Utrecht, The Netherlands

13.40 Flow CYtometry in BARrett Esophagus (CYBAR study): a prospective cohort study (p. 161)

M. Sikkema[1], M. Kerkhof[1], E.W. Steyerberg[2], H. van Dekken[3], A.J. van Vuuren[1], H. Geldof[4], H. van der Valk[5], D.J. Bac[6], R. Giard[7], W. Lesterhuis[8], R. Heinhuis[9], E.C. Klinkenberg[10], G.A. Meijer[11], F. ter Borg[12], J.W. Arends[13], J.J. Kolkman[14], J. van Baarlen[15], R.A. de Vries[16], A. Mulder[17], A.J.P. van Tilburg[18], G.J.A. Offerhaus[19], F.J.W. Ten Kate[19], J.G. Kusters[1], E.J. Kuipers[1], P.D. Siersema[1] for the CYBAR study group. Depts of Gastroenterology and Hepatology[1], Public Health[2] and Pathology[3], Erasmus MC, University Medical Center Rotterdam, Dept of Gastroenterology and Hepatology[4], IJsselland Hospital, Capelle a/d IJssel, Dept of Pathology[5], PATHAN, Rotterdam, Dept of Gastroenterology and Hepatology[6], Ikazia Hospital, Dept of Pathology[7], Medical Center Rijnmond Zuid, Rotterdam, Dept of Gastroenterology and Hepatology[8], Albert Schweitzer Hospital, Dept of Pathology[9], Laboratory for Pathology, Dordrecht, Depts of Gastroenterology and Hepatology[10]and Pathology[11], Free University Medical Center, Amsterdam, Depts of Gastroenterology and Hepatology[12] and Pathology[13], Deventer Hospital, Deventer, Dept of Gastroenterology and Hepatology[14], Medisch Spectrum Twente, Dept of Pathology[15], Laboratory Pathology Oost-Nederland, Enschede, Depts of Gastroenterology and Hepatology[16] and Pathology[17], Rijnstate Hospital, Arnhem, Dept of Gastroenterology and Hepatology[18], Sint Franciscus Hospital, Rotterdam, Dept of Pathology[19], University Medical Center Utrecht, The Netherlands

13.50 Low-grade intra-epithelial in Barrett's esophagus: over-diagnosed but underestimated (p. 162)

W. Curvers[1], W. Rosmolen[1], B. Elzer[1], A. Schaap[1], A. van Oijen[2], A. Naber[3], K. Krishnadath[1], G. Meijer[4], F. ten Kate[1], J. Bergman[1]. [1]Academic Medical Center, Amsterdam, [2]Medical Center Alkmaar, Alkmaar, [3]Tergooi Hospitals, Hilversum, [4]Free University Hospital, Amsterdam.

14.00 Ursodeoxycholic acid treatment for unconjugated hyperbilirubinemia: promising results in Gunn rats * (p. 163)

F.J.C. Cuperus[1], A.M. Hafkamp[1], R. Havinga[1], J. Zelenka[2], M. Jirsa[2], C. Tiribelli[3], J.D. Ostrow[4], H.J. Verkade[1]. [1]Pediatric Gastroenterology, UMCG, Groningen, The Netherlands; [2]Charles Univ., Prague, Czech Republic; [3]Univ. Trieste, Italy and [4]Univ. Washington, Seattle, United States

14.10 (Non)toxigenic Clostridium difficile colonization and the risk of atopic manifestations in infancy (p. 164)
J. Penders[1,2], E.E. Stobberingh[2], P.A. van den Brandt[1], R. van Ree[3], C. Thijs[1]. [1]Dept of Epidemiolgy, Maastricht University, [2]Dept of Medical Microbiology, Academic Hospital Maastricht, [3]Dept of Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands

14.20 Long-term follow-up and outcome of a cohort of pediatric patients with functional constipation, **(MLDS-project SWO 03-13**). (p. 165)
M.E.J. Bongers, M.P. van Wijk, M.A. Benninga. Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Center, The Netherlands

14.30 Association of catechol-O-methyltransferase gene variants with chronic pancreatitis in 2 independent Dutch and Hungarian cohorts (p. 166))
A.A.J. van Esch[1], E. de Vries[1], R.H.M. ter Morsche[1], A. Pap[2], Z. Nemoda[3], J.B.M.J. Jansen[1], J.P.H. Drenth[1]. [1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, [2]Dept of Gastroenterology, MÁV Hospital, Budapest, Hungary, [3]Dept of Medical Chemistry, Semmelweis University, Budapest, Hungary

14.40 Genome-wide association study in coeliac disease: identification of novel genetic risk loci (p. 167)
A. Zhernakova[1], K.A. Hunt[2], L. Franke[1], G. Trynka[3], G. Heap[2], J. Romanos[3], G. Turner[5], R. McGinnis[4], R. McManus[5], D.A. van Heel[2], C. Wijmenga[1,3]. [1]Complex Genetics Sect, DBG, UMCU, The Netherlands, [2]Inst of Cell and Mol Science, Queen Mary University of London, United Kingdom, [3]Genetics Dept, UMCG, The Netherlands; [4]Wellcome Trust Sanger Inst, United Kingdom, [5]Dept Clinical Medicine, Immunology, Trinity College, Ireland

14.50 Endoscopic treatment of duodenal polyposis in familial adenomatous polyposis (FAP) * (p. 168)
K.S. Boparai, E.M.H. Mathus-Vliegen, P. Fockens, E. Dekker. Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

Vrijdag 14 maart 2008

15.00 Sulindac potentiates rhTRAIL-induced apoptosis in colon adenoma cells (p. 169)
D.M. Heijink[1,2], M. Jalving[1,2], D. Oosterhuis[1], I.A. Sloots[1], J.J. Koornstra[2], E.G.E. de Vries[1], S. de Jong[1], J.H. Kleibeuker[2]. Departments of Medical Oncology1 and Gastroenterology & Hepatology[2]. University Medical Center Groningen, Groningen, The Netherlands.

15.10 Einde programma, koffie/thee in expositiehal

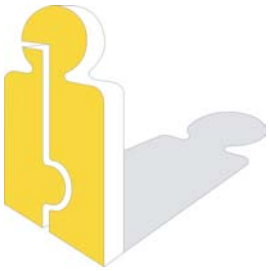
Sectie Endoscopie Verpleegkundigen en Assistenten **Diezezaal**

09.30	*Ontvangst met koffie en thee*
10.00	Opening en welkom, Suzanne Swartz
10.10	Free-paper sessie, Marjon de Pater *SEVA-leden geven een presentatie van 10 minuten, deze zullen door de jury beoordeeld worden en de beste free paper verdient een reisbeurs voor het UEGW in Parijs.*
11.05	Acute pancreatitis,
11.30	Vernieuwde sedatie richtlijn
12.00	*Lunch*
13.15	Ledenvergadering
14.00	Stralingshygiëne
14.20	Kinder-endoscopie
14.40	Dilataties
15:05	*Sluiting* *Koffie/thee, einde programma*

Symposium Coloncare

09.30	Ontvangst met koffie en thee
09.45	Welkomstwoord *W. Goverde, voorzitter VMDLV*
10.00	Landelijke screening op coloncarcinoom *Prof. dr. J.B.M.J. Jansen, mdl-arts, UMC St. Radboud Nijmegen*
10.30	Aanleiding en opzet van ketenzorg rondom coloncarcinoom *W. Goverde, UMC St Radboud, Nijmegen*
10.50	De rol van de coloncare verpleegkundige in de keten *mw. K. van Meerten en de heer J. Peters, coloncareverpleegkundigen, UMC St Radboud, Nijmegen*
11.30	Ledenvergadering
12. 00	Lunch in de expositiehal
13.30	Coecostomie spoeling als oplossing voor chronische obstipatie *Mevr. E. Geerards, nurse practitioner, UMC St Radboud, Nijmegen* *Mevr. Fasen-Wolf, ervaringsdeskundige*
14.15	Diagnostiek van de dunne darm door dubbelballontherapie bij o.a. verdenking Coeliakie *Dr. P.H.G.M. Stadhouders, MDL-arts, St. Antonius Ziekenhuis, Nieuwegein*
14.35	Verschillende vormen van obstipatie en voedingstherapie bij chronische obstipatie *spreker bij het ter perse gaan nog niet bekend, Medisch Centrum Alkmaar*
15.00	Afsluiting met daarna mogelijkheid tot borrelen en netwerken *W. Goverde*

Dutch Experimental Gastroenterology and Hepatology Meeting



Poster session

Meierij Foyer

ZonMw

Poster rounds DEGH meeting March 13, 2008 from 12:00 to 13:00.

Theme 1. *Cell biology*. Chaired by C.C.Paulusma and E.A.F. van Tol

Time	#	*Abstract*	*Title*
12:00	**1**	3179	Influence of extracellular acidosis on apical plasma membrane dynamics in epithelial cells *M. Golachowska[1], T. Visser[1], D. Hoekstra[1], E. Rings[2], S. van IJzendoorn[1]. [1]Dept of Cell Biology and [2]Dept of Gastroenterology, University Medical Center Groningen, Groningen, The Netherlands*
12:08	**2**	3038	Effects of butyrate on the colonic mucus layer in healthy humans *H. Hamer[1,2], D. Jonkers[1,2], S. Vanhoutvin[1,2], F. Troost[1,2], A. Kodde[1,2], K. Venema[1,3], G. Koek[2], R.-J. Brummer[1,2].TI Food and Nutrition, Wageningen[1], Dept of Internal Medicine, Division of Gastroenterology-Hepatology, Nutrim, Maastricht University[2], TNO Quality of Life, Zeist[3]*
12:15	**3**	3206	Release of CD105 from colon cancer associated endothelial cells is mediated by MMP activity *P. Kuiper[1], L.J.A.C. Hawinkels[1], H.W. Verspaget[1], E.S.M. de Jonge-Muller[1], W. van Duijn[1], D.W. Hommes[1], C.F.M. Sier[1],[1]Leiden University Medical Center, Dept of Gastroenterology-Hepatology, Leiden, The Netherlands*
12:23	**4**	3064	Conclusive evidence for the importance of intrahepatic regulatory T cells in chronic hepatitis C patients. *M. Claassen[1], R.J. de Knegt[1], H.L.A. Janssen[1], A. Boonstra[1] , [1]Dept of Gastroenterology and Hepatology, Erasmus MC - University Medical Center Rotterdam*
12:30	**5**	3189	Characterization of the micro-environment of canine liver progenitor cells during health and disease. *B.A.Schotanus[1], B.Spee[1,2], B.Arends[1], R.P.Favier[1], L.C.Penning[1], T.S.G.A.M.van den Ingh[3], T.A.Roskams[2], J.Rothuizen[1]. [1]Dept of Clinical Sciences of Companion Animals, Faculty of Veterinary medicine, Utrecht University, The Netherlands[2], Dept of Morphology and Molecular Pathology, University of Leuven, Leuven, Belgium[3]*

12:38 **6** 3090 Translocation of the Breast Cancer Resistance Protein (BCRP/ABCG2) in Inflammatory Bowel Disease related colorectal cancer

C.L. Koelewijn[1], M.M. Gerrits[1], H.J. Verhoog[1], H. van Dekken[2], H. Moshage[3], E.J. Kuipers[1], C.J. van der Woude[1]Erasmus MC – University Medical Centre Rotterdam, Depts [1] Gastroenterology and Hepatology, [2] Pathology, Rotterdam, The Netherlands[3] University Medical Center Groningen, Dept of Gastroenterology and Hepatology, Groningen, The Netherlands

12:45 **7** 3106 Functional analysis of Wilson disease mutations in the copper-transporting ATPase ATP7B

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

12:53 **8** 3139 Lactobacillus plantarum WCFS1 modulates intestinal epithelial tight junctions in vivo in healthy subjects

F.J Troost[1,3], J. Karczewski[2,3], R.M. Brummer[1,3], J. Wells[2,3]. [1]Dept of Internal Medicine, div. of Gastroenterology and Hepatology, Maastricht University; [2]Host-Microbe-Interactomics Group, University of Wageningen and TNO Quality of Life and [3]Top Institute for Food and Nutrition, Wageningen, The Netherlands

Theme 2. *Cell biological markers*. Chaired by L. Klomp and G. Douma

Time *#* *Abstract* *Title*

12:00 **9** 3015 Adiponectin and adiponectin receptor expression in primary colon epithelial cells.

J.W.P.M. van Baal[1, 2], M. Pini[1], M.E. Gove[1], R. Fayad[1], G. Fantuzzi[1] . Dept of Human Nutrition[1], University of Illinois at Chicago, Chicago, U.S.A., Dept of Gastroenterology and Hepatology[2], UMC Utrecht, The Netherlands

12:08 **10** 3223 Large induction of type III deiodinase (D3) expression during liver regeneration

M.H.A. Kester[1], A.C. Punt[2], M.J.M. Toussaint[2], M.E. Everts[2], V. Darras[3], A. de Bruin[2], T.J. Visser[1]. [1]Dept Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands[2] Dept Pathobiology, Utrecht University, Utrecht, The Netherlands[3] Laboratory *of Comparative Endocrinology, Catholic University Leuven, Belgium*

12:15 **11** 3191 Caspase-3 activity as a prognostic factor in colorectal cancer
P.J. Koelink, Cornelis F.M. Sier, D.W. Hommes and H.W. Verspaget. Dept of Gastroenterology-Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

12:23 **12** 3099 Local Reduction of CIS Protein Activity is Associated with Increased Neoplasia Risk in Barrett's Esophagus
M. Chen[1,3], H. van Dekken[2], L.G Capelle[1], B. Xia[3], J.G. Kusters[1], C.J. van der Woude[1], E.J. Kuipers[1], M.M. Gerrits[1]Depts of [1] Gastroenterology and Hepatology and [2] Pathology, Erasmus MC - University Medical Center Rotterdam, Rotterdam, The Netherlands; [3] Dept of Research Center of Digestive Diseases, Zhongnan Hospital, Wuhan University, Wuhan, China

12:30 **13** 3160 Suppressor of Cytokine Signaling-2 activity is diminished in Barrett's esophagus related neoplasia
M. Chen[1,3], C.J. van der Woude[1], A. van der Winkel[1], H. van Dekken[2], B. Xia[3], J.G. Kusters[1], E.J. Kuipers[1], M.M. Gerrits[1]. Depts of [1] Gastroenterology and Hepatology and [2] Pathology, Erasmus MC - University Medical Center Rotterdam, Rotterdam, The Netherlands; [3]Dept of Research Center of Digestive Diseases, Zhongnan Hospital, Wuhan University, Wuhan, China

12:38 **14** 3110 CA19-9 is a novel biomarker for polycystic liver disease
E. Waanders[1], L. van Keimpema[1], F. Nevens[2], R. Aerts[3], F.C.G.J. Sweep[4], J.P.H. Drenth[1],[1]Dept of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands[2]Dept of Hepatology, University Hospital Leuven, Leuven, Belgium[3] Dept of Abdominal Surgery, University Hospital Leuven, Leuven, Belgium[4]Dept of Chemical Endocrinology, Radboud University Nijmegen Medical Center

12:45 **15** 3013 Identification of cell surface proteins as biomarkers for Colorectal Cancer
M. de Wit[1], C.R. Jimenez[2], B. Carvalho[1], S. Piersma[2], R. Lamerichs[3], G.A. Meijer[1], R.J.A. Fijneman[1]. Depts of Pathology[1] and Medical Oncology[2], VU University Medical Centre, Amsterdam, Philips Research[3], Eindhoven, The Netherlands

12:53 **16** 3211 Etiology of Barrett's esophagus: Expression of HOX genes in the human esophagus
A. van de Winkel[1], K.B. Ackema[2], K.P.M van Zoest[1], E.J. Kuipers[1], J. Charité[2], Dept of Gastroenterology & Hepatology[1] and Cell biology[2], Erasmus MC University Medical Center, Rotterdam, The Netherlands

Theme 3. *Genetics and -omics*. Chaired by H. Witt and J.P.H. Drenth

Time	*#*	*Abstract*	*Title*
12:00	**17**	3142	Characterization of the role of the oncomir hsa-mir-17-92 cluster located in 13q during colorectal cancer progression *B. Diosdado[1], M. van de Wiel[1,2], S. Mongera[1], C. Postma[1], B. Carvalho[1], G.A. Meijer[1]. [1]Tumour profiling Unit, Dept of Pathology and [2]Dept of Mathematics, VUmc, Amsterdam, The Netherlands*
12:08	**18**	3045	Eotaxin-3 expression and increased Eosinophil number in Barrett's esophagus compared to reflux esophagitis *W.L. Hazen, R.C.M. Kiekens, P.D. Siersema. Dept of Gastro-enterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands*
12:15	**19**	3164	Cellular and secretion proteome of human hepatic stellate cells *J. van Tilburg, F. Bouwman, E. Mariman. Maastricht University, Dept of Human Biology NUTRIM*
12:23	**20**	3216	Vitamin D Receptor gene polymorphisms and the risk of esophageal disease *A. van de Winkel[1], L.M.G. Moons[1], P. Arp[2], J. van Meurs[2], R.G.J. Pot[1], A. Uitterlinden[2], E.J. Kuipers[1,2], Dept of Gastroenterology & Hepatology[1] and Internal Medicine[2], Erasmus MC University Medical Center, Rotterdam, The Netherlands*
12:30	**21**	3067	Novel insights into the pathophysiology of Wilson disease and hereditary hemochromatosis from a transcriptomics meta-analysis *P.A.J. Muller[1, 2], P. de Bie[1, 2], C. Wijmenga[2, 3], L.W. Klomp[1], Laboratory for Metabolic and Endocrine Diseases, UMC Utrecht, and Netherlands Metabolomics Centre, The Netherlands[1], Complex Genetics Section, DBG-Dept of Medical Genetics, UMC Utrecht, The Netherlands[2], Dept of Genetics, UMC Groningen, University of Groningen, The Netherlands[3]*

12:38 **22** 2986 Large genomic deletions of SMAD4, BMPR1A and PTEN in Juvenile Polyposis
L.A.A. Brosens[1], W.A. van Hattem[1]*, W.W.J. de Leng[1], F.H. Morsink[1], S. Lens[2], R. Carvalho[2], F.M. Giardiello[3], G.J.A. Offerhaus[1]. Dept of Pathology[1], University Medical Center Utrecht, Utrecht, MRC-Holland B.V.[2], Amsterdam, The Netherlands, Dept of Medicine[3], Division of Gastroenterology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA *These authors contributed equally to this work*

12:45 **23** 3036 Methylation pattern of high risk flat adenomas in CRC
Q.J.M. Voorham[1], B. Carvalho[1], A.J. Spiertz[2], S. Derks[2], H. Grabsch[3], B. Rembacken[4], A. de Bruïne[2], M. van Engeland[2], G.A. Meijer[1]. Dept of Pathology[1], VUmc, Amsterdam, Dept of Pathology[2], University Maastricht, Maastricht, The Netherlands, Dept of Pathology and Tumour Biology[3], Leeds Institute of Molecular Medicine, University of Leeds, Leeds, Centre for Digestive Disease[2], Leeds General Infirmary, Leeds, United Kingdom

12:53 **24** 3074 Butyrate induces transcriptional changes in human colonic mucosa
H. Hamer[1,2], D. Jonkers[1,2], S. Vanhoutvin[1,2], F. Troost[1,2], A. Kodde[1,2], K. Venema[1,3], G. Koek[2], R.-J. Brummer[1,2].TI Food and Nutrition, Wageningen[1], Dept of Internal Medicine, Division of Gastroenterology-Hepatology, Nutrim, Maastricht University[2], TNO Quality of Life, Zeist[3]

Theme 4. *Immunology*. Chaired by I.N. Crispe and J. Kwekkeboom

Time # Abstract Title

12:00 **25** 3207 Human liver graft contains hematopoietic stem cells which are mobilized during liver transplantation: contribution to chimerism?
Q. Pan[1], Fatima SF A. Kaya[2], J. Kwekkeboom[1], H.J. Metselaar[1], H.W Tilanus[3], Harry LA Janssen[1], Gerard Wagemaker[2] and L.JW van der Laan. [3]Depts of 1Gastroenterology & Hepatology; [2]Hematology and [3]Surgery, Erasmus MC, University Medical Center Rotterdam

12:08 **26** 3218 Low IL-10 espression in liver and blood during acute rejection after liver transplantation

A. Demirkiran1, H.J. Metselaar[2], A. van der Sloot[1], J. Kwekkeboom[2], J. Francke[2], C.C. Baan[3], A.J. van Vuuren[2], H.W. Tilanus[1] and L.J.W. van der Laan[1]. Depts of [1]Surgery, [2]Gastroenterology and Hepatology, and [3]Internal Medicine, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

12:15 **27** 3169 Dexamethasone transforms lps-stimulated human blood dendritic cells (DC) into DC that prime IL-10 production in T-cells

B.M. Bosma[1], H.J. Metselaar[1], N.M.A. Nagtzaam[1], R. de Haan[1], S. Mancham[1], L.J.W. van der Laan[2], E.J. Kuipers[1], and J. Kwekkeboom[1]. [1]Gastroenterology and Hepatology and [2]Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands

12:23 **28** 3193 Internalization route of hepatitis B surface antigen by myeloid dendritic cells is dependent on HBV vaccination status

M.L. Op den Brouw[1], T.B.H. Geijtenbeek[2], H.L.A. Janssen[1] and A.M. Woltman[11] Dept of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, [2]Dept of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

12:30 **29** 3182 Hepatitis B virus directly interferes with plasmacytoid dendritic cell function

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

12:38 **30** 3170 Viral load reduction in chronic hepatitis B infection ameliorates the interaction of natural killer cells with dendritic cells: a key step in achieving anti-viral immunity ?

E.T.T.L. Tjwa, P.J. Biesta, R.S. Binda, H.L.A. Janssen and A.M. Woltman. Dept of Gastroenterology and Hepatology, Erasmus Medical Center Rotterdam, The Netherlands

12:45 **31** 3186 PEG-IFNα-2a therapy of chronic HBV patients alters the endogenous TLR-induced IFNα production by plasmacytoid dendritic cells

M.L. op den Brouw, R.S. Binda, P.J. Biesta, D. Turgut, H.L.A. Janssen and A.M. Woltman, Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands

12:53 **32** 3039 Assessment of liver fibrosis by non-invasive methods: comparison of breath tests, serum markers and FibroScan

K.J.M. Stibbe[1], C. Verveer[1], J. Francke[1], B. Hansen[2], P.E. Zondervan[3], E.J. Kuipers[1], R.J. de Knegt[1], A.J. van Vuuren[1], Dept of Gastroenterology and Hepatology[1], and Biostatistics[2], and Pathology[3], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Theme 5. *Immunology & colitis*. Chaired by R. Xavier and G. Dijkstra

Time # Abstract Title

12:00 **33** 3089 Breast Cancer Resistance Protein (BCRP/ABCG2) is equally distributed throughout the colon of patients with ulcerative colitis and its expression is decreased in active inflammation

C.L. Koelewijn[1], M.M. Gerrits[1], H.J. Verhoog[1], H. van Dekken[2], H. Moshage[3], E.J. Kuipers[1], C.J. van der Woude[1]. Erasmus MC - University Medical Center Rotterdam, Depts [1] Gastroenterology and Hepatology, [2] Pathology, Rotterdam, The Netherlands[3] University Medical Center Groningen, Dept of Gastroenterology and Hepatology, Groningen, The Netherlands

12:08 **34** 3123 The absence of functional PI3Kγ has a protective effect on DSS-induced colitis in mice

W.A. van Dop[1], S. Marengo[2], A.A. te Velde[1], F.J. ten Kate[3], D.W. Hommes[4], G.E. Boeckxstaens[1,5], E. Hirsch[2], G.R. van den Brink[4] CEMM[1], Dept of Pathology[3] and Dept of Gastroenterology[5], AMC, Amsterdam, The Netherlands, Dept of Genetics, Biology and Biochemistry[2], MBC, Turin, Italy, Dept of Gastroenteroly[4], LUMC, Leiden, The Netherlands

12:15 **35** 3005 Colitis in the zebrafish; a new model to study early disease pathogenesis

S. Brugman[1], L.A van Berkel[1], D. Lindenbergh-Kortleve[1], H. Hammad[4], S.A. Renshaw[2], B.N. Lambrecht[4], J.N. Samsom[1], R. Willemsen[3], E.E.S. Nieuwenhuis[1]. Depts of Pediatric Gastroenterology[1], Clinical Genetics[3] and Pulmonary Medicine[4], Erasmus MC, Rotterdam, The Netherlands, Centre for Developmental and Biomedical Science[2], University of Sheffield, Sheffield, United Kingdom

12:23 **36** 3051 Dendritic cell subtypes in the colon and their role in TNBS colitis
C. de Haar[1,2], P.P.E. van Lierop[1,2], M. Kool[3], L. van Rijt[3], B.N. Lambrecht[3], E.E.S. Nieuwenhuis[1,4], J.N. Samsom[1,4]. [1]Dept of Pediatrics, Erasmus MC – Sophia Children's Hospital, Rotterdam [3]Dept of Pulmonary Medicine, Erasmus MC, Rotterdam[2] Authors have contributed equally.[4]

12:30 **37** 3022 β-Glucans increase the Th1 activity of PHA stimulated PBMCs via inhibition of enterocyte derived TSLP production
J.J. Volman[1], R.P. Mensink[1], W.A. Buurman[2], G. Önning[3], J. Plat[1]. Depts of Human Biology[1] and General Surgery[2], Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University, Maastricht, The Netherlands, Biomedical Nutrition[3], Center for Chemistry and Chemical Engineering, Lund University Lund, Sweden

12:38 **38** 3092 The role of the innate immune system at the earliest stages of a mucosal inflammation model
P.P.E. van Lierop[1,3], C. de Haar[1,3], D. Lindenbergh-Kortleve[1], L. van Rijt[2], B.N. Lambrecht[2], J.N. Samsom[1,4], E.E.S. Nieuwenhuis[1,41]. Dept of Pediatrics, Erasmus MC – Sophia Children's Hospital, Rotterdam [2] Dept of Pulmonary Medicine, Erasmus MC, Rotterdam[3] Authors have contributed equally.[4]

12:45 **39** 3073 Dietary calcium inhibits colitis development in HLA-B27 transgenic rats
M.A.A. Schepens[1,2], A.J. Schonewille[1,2], C. Vink[1,2], E.M. van Schothorst[1,3], E. Kramer[1,3], J. Keijer[3], R-J. Brummer[1], R. van der Meer[1,2], I.M.J. Bovee-Oudenhoven[1,2] TI Food and Nutrition[1], Wageningen, NIZO food research[2], Ede, and RIKILT - Institute of Food Safety[3], Wageningen, The Netherlands

12:53 **40** 3075 Supplemental calcium, but not antioxidants, inhibits colitis progression in HLA-B27 transgenic rats
M.A.A. Schepens[1,2], C. Vink[1,2], A.J. Schonewille[1,2], R-J. Brummer[1], R. van der Meer[1,2], I.M.J. Bovee-Oudenhoven[1,2] TI Food and Nutrition[1], Wageningen and NIZO food research[2], Ede, The Netherlands

Theme 6. *Metabolism*. Chaired by B. Staels and E.H.H.M. Rings

Time	#	*Abstract*	*Title*
12:00	**41**	3094	FXR activation reduces TNFα-induced inflammatory signaling. *R.M. Gadaleta[1,2,3], A. Moschetta[3], B. Oldenburg[1], Leo W.J. Klomp[2], P.D. Siersema[1], K. van Erpecum[1], S.W.C. van Mil[2]. Dept of Gastroenterology and Hepatology[1], Laboratory of Metabolic and Endocrine Diseases and Netherlands Metabolomics Centre[2], UMC Utrecht, The Netherlands and Laboratory of Lipid Metabolism and Cancer, Consorzio Mario Negri Sud, S.ta Maria Imbaro (Ch), Italy[3]*
12:08	**42**	3217	High fat diet-induced FGF19 resistance in livers of C57bl6 mice *P.J. Jansen[1], V. Triantis[1], K. van den Oever[1], C. Kunne[1], P.L.M. Jansen[1], F. Schaap[11]AMC Liver center, Amsterdam, The Netherlands*
12:15	**43**	3115	Absence of farnesoid X receptor improves fat absorption in essential fatty acid (EFA)-deficient mice *S. Lukovac, E.L. Los, G. Brufau, F. Stellaard, E.H.H.M. Rings, H.J. Verkade. Pediatric Gastroenterology, Beatrix Children's Hospital, Groningen University Institute for Drug Exploration (GUIDE), University Medical Center Groningen, The Netherlands*
12:23	**44**	3222	Prebiotic diet and the enterohepatic circulation of bile salts in rats *H. van Meer[1], G. Boehm[2], F. Stellaard[1], A. Vriesema[3], J. Knol[3], R. Havinga[1], P.J. Sauer[1], H.J.Verkade[1]. [1] Pediatric Gastroenterology/Research laboratory, University Medical Center Groningen, The Netherlands[2] Dept Pediatrics, University Medical Center Rotterdam, The Netherlands[3] Numico Research, Wageningen, The Netherlands*
12:30	**45**	3117	The enterohepatic circulation of bile salts in mice in vivo: effects of essential fatty acid (EFA) deficiency *S. Lukovac, F. Stellaard, E.H.H.M. Rings, H.J. Verkade. Pediatric Gastroenterology, Beatrix Children's Hospital, Groningen University Institute for Drug Exploration (GUIDE), University Medical Center Groningen, University of Groningen, 9700 RB Groningen, The Netherlands*

12:38 **46** 3208 The calorically overfed mouse subsequently displays steatosis, insulin resistance and steatohepatitis and is thus a highly physiological model for non-alcoholic fatty liver disease.
I.C. Gaemers, J.M. Stallen, C. Kunne, K. van den Oever and W.H. Lamers.AMC Liver Center, Amsterdam, The Netherlands

12:45 **47** 3023 Dietary proteins and serine proteases stimulate secretion of satiety hormones by the STC-1 cell line
M.C.P. Geraedts[1], F.J. Troost[2], W.H.M. Saris[1]. Depts of Human Biology[1] and Internal medicine, div. of Gastroenterology and Hepatology[2], Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University, The Netherlands

12:53 **48** 3173 Glutamine synthetase deficiency in murine astrocytes results in neonatal death
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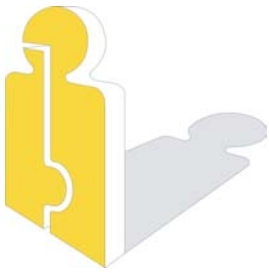
Abstracts

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Rectocele Repair by Anterolateral Rectopexy; Long-term Functional Outcome

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Rectoceles are frequently associated with feelings of pelvic discomfort and symptoms of obstructed defaecation. Repair by a transvaginal or transanal approach might result in de novo dyspareunia in up to approximately 40 percent of the cases. This study was designed to investigate whether abdominal anterolateral rectopexy provides an adequate rectocele repair without dyspareunia as a side effect. A consecutive series of 33 women (median age 55 years; range: 37-73 years) with a symptomatic rectocele (depth > 3 centimeters) underwent anterolateral rectopexy. Before the operation all patients underwent evacuation proctography, which was repeated 6 months after the repair in all but 3 patients. A standardized questionnaire concerning pelvic discomfort, obstructed defaecation and dyspareunia was used to assess the long-term effect of rectocele repair. The response rate was 91 percent. Six months after the procedure evacuation proctography revealed a recurrent or persistent rectocele in 6 patients (20 percent). However in 4 of these 6 patients the depth of the rectocele was less than 3 centimeters. The median duration of follow-up was 74 months (range 2 – 96 months). Among the patients with an adequate repair signs of obstructed defaecation persisted in 55 percent. Feelings of pelvic discomfort were dissolved in 79 percent of the patients. None of the patients encountered de novo dyspareunia after the procedure.
Conclusions: Anterolateral rectopexy provides an effective tool for anatomical correction of rectoceles and does not result in dyspareunia as a side effect. However, despite adequate repair, obstructed defaecation persist in 2 out of 3 patients.

Fibrin glue and transanal rectal advancement flap for high transsphincteric perianal fistulas; Is there any advantage?

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Perianal fistulas of cryptoglandular origin cause considerable discomfort and arise from infections in anal glands lying in the intersphincteric space. In recent decades fibrin glue has appeared as an alternative treatment for high perianal fistulas. Early reporting seemed promising, with high success rates being reported. However with increasing follow-up the enthusiasm was tempered, because of disappointing results. The aim of this study was to assess the additional value of fibrin glue to the transanal rectal advancement flap in a well defined group of patients with high transsphincteric fistulas of cryptoglandular origin. Between January 1995 and January 2006, 127 patients were operated for high perianal fistulas with an advancement flap. After exclusion of patients with inflammatory bowel disease or HIV, 80 patients remained. A consecutive series of 26 patients had advancement flap combined with obliteration of the fistula tract with fibrin glue. Patients were matched for prior fistula surgery. The advancement was performed identically in all patients. In the fibrin glue group, glue was installed retrogradely in the fistula tract after the advancement was completed and the fistula tract had been curetted. The minimal follow-up after surgery was 13 months with a median of 67 months (range 13-127). The overall recurrence rate was 26 percent (n=21). In 17 percent of the patients the fistula persisted in the AF group compared to 46 percent in the AF+G group (p=0.05). In the matched group without previous fistula surgery the result was significantly worse for the AF+G group compare to the AF group (p=0.014). The recurrence rates were 56 percent (n=5) and 13 percent (n=4) respectively. In the group with a history of fistula surgery the recurrence rate was 23 percent (n=5) compared to 41 percent (n=7) in the AF and the AF+G group respectively (p=0.216).
Conclusion: The rectal advancement flap combined with fibrin glue installation was associated with a significantly higher recurrence rate, compared to the advancement flap treatment alone in patients without previous fistula surgery. Since the costs of the fibrin glue are considerable and the therapeutic effect very doubtful, it cannot be recommended routinely in the adjunct of transanal rectal advancement flap treating high perianal fistulas.

Accuracy of the clinical diagnosis, a clinical prediction model, or imaging for the diagnosis of acute diverticulitis in patients with abdominal pain.

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Purpose: to asses the accuracy of the clinical diagnosis of acute diverticulitis and to compare this with the performance of a prediction model, based on diagnostic value of clinical findings and laboratory test results. MethodsConsecutive adults (>18 years) patients presenting at the Emergency Department (ED) with non-traumatic acute abdominal pain for >2 hours and <5 days were included and evaluated by residents from the surgical and emergency medicine department as in standard daily practice. The reference diagnosis was defined by an expert panel. Findings at medical history taking and physical examination, and a differential diagnosis were recorded prospectively. Sensitivity and specificity of the most likely clinical diagnosis was calculated. A prediction model, based on variables with known clinical value, was built and sensitivity and specificity of the model were calculated for different probability cut-off values. The accuracy of the model was compared with that of the clinical diagnosis and to accuracy of US and CT imaging.
Results: this study included 1021 patients, 55% female, with a mean age of 47 years (19-94). Acute diverticulitis was present in 119 patients (prevalence: 12%). The most likely diagnosis after clinical assessment was acute diverticulitis in 126 patients, yielding a sensitivity of 67% (95%CI: 59-76%, 33% of acute diverticulitis was missed) and a specificity of 95% (95%CI: 93-96%). The final prediction model contained 9 predictors, with age >40 years (odds ratio (OR): 6.6 (95%CI: 3.0-14.7)), no history of vomiting (OR: 13.1 (95%CI: 5.1-33.7)), direct tenderness in the left lower quadrant (OR: 6.5 (95%CI: 3.0-14.1)), and an elevated CRP (OR: 12.6 (95%CI: 4.2-37.8)) as strongest predictors. The most optimal probability cut-off for the model yielded a sensitivity of 76% (95%CI: 68-83%, 24% of acute diverticulitis was missed) and a specificity of 89% (95%CI:87-91%). Only a limited group of patients (25/119) could be marked as 'high probability cases' using the model. US in all patients gave a 36% missed rate, whereas this proportion was 7% for CT with less false positives than clinical assessment only.ConclusionThe diagnostic performance of the clinical diagnosis of acute diverticulitis is moderate but a clinical prediction model does not improve this performance significantly. Therefore, CT imaging is warranted when acute diverticulitis is considered as a clinical diagnosis.

Isolated segmental bile duct injury after laparoscopic cholecystectomy. Clinical presentation, diagnosis, and long-term outcome after multidisciplinary treatment

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Background & aim. Isolated segmental bile duct injury (ISBDI) is a distinct type of bile duct injury seen after laparoscopic cholecystectomy. Several small series only described the surgical approach of this severe complication. The aim of this study was to determine the prevalence, clinical characteristics, diagnostic modalities and multidisciplinary treatment outcome in ISBDI patients.Design, setting, patients. ISBDI patient data, obtained from a consecutive series of 500 bile duct injury patients referred to a tertiary centre, were analysed. Patient characteristics, diagnostic modalities, and treatment outcome by surgeons, gastroenterologists and intervention radiologists were determined. Results. Forty-two patients (8%) were identified among 500 bile duct injury patients having ISBDI. ISBDI was diagnosed in only 5 patients (12%) before referral to a tertiary centre. Post-operative symptoms in ISBDI patients are no different from overall bile duct injury patients. The mean interval between referral and accurate diagnosis was 126±361 days. Eighteen patients (43%) underwent surgery, 16 patients underwent endoscopy (38%) and 6 patients (14%) were treated by percutaneous radiological intervention. Surgical and endoscopic therapy of ISBDI patients is associated with higher morbidity compared to bile duct injury patients (post-operative abscesses 22% vs. 8%, p=0.044; endoscopic failure 25% vs. 4%, p=0.057).
Conclusions. ISBDI is a rare complication, difficult to diagnose, and associated with more treatment-related morbidity compared to general bile duct injury patients.

Intestinal barrier dysfunction in a randomised placebo-controlled trial of probiotic prophylaxis in acute pancreatitis

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Intestinal barrier dysfunction is thought to be associated with infectious complications, organ failure and mortality in acute pancreatitis. Several experimental studies have demonstrated that pre-treatment with probiotics abolishes barrier dysfunction. To date, no clinical study has reported a) a relationship between barrier dysfunction and the risk of infectious complications and b) a beneficial effect of probiotics on barrier dysfunction.During a randomised, double-blind, placebo-controlled trial on probiotic prophylaxis in patients with acute pancreatitis, intestinal permeability was assessed in 101 patients within 72 hours after admission and seven days thereafter by enteral administration of four polyethylene glycols (PEGs) with varying molecular weights (400, 1500, 4000 and 10000 kDa). PEG-recovery was determined by high performance liquid chromatography in 24-hour urine. Intestinal ischemia was assessed in 141 patients by measuring intestinal fatty binding acid protein (IFABP) concentration in urine collected 24-48 hrs after onset of probiotic or placebo treatment.PEG-recovery was higher in patients that died (PEG 4000, p=0.009), developed organ failure (PEG 4000, p<0.0001) or developed bacteremia (PEG 4000, p=0.001) than in patients without these events. Probiotic prophylaxis had no detectable influence on intestinal permeability but IFABP concentrations were higher in patients who received probiotics (median 362 vs 199 pg/ml; p= 0.02). This effect was only seen in patients with organ failure. IFABP concentrations were higher in patients that developed organ failure (p=0.008), pancreatic necrosis (p=0.001), bacteremia (p=0.03) and infected necrosis (p=0.01).
Conclusions: Intestinal barrier dysfunction occurs early in the course of acute pancreatitis and is associated with mortality, organ failure, infected necrosis and bacteremia. Probiotic prophylaxis does not improve intestinal permeability but is associated with intestinal ischemia.

Transgastric Peritoneoscopy versus Laparoscopy for the Detection of Peritoneal Metastases

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The presence of peritoneal metastases is a frequent cause of unresectability for GI malignancies such as pancreatic cancer. Preoperative detection is difficult and laparoscopy (LAP) is frequently required to exclude metastatic disease prior to resection. Transgastric peritoneoscopy (TGP) may be an alternative to LAP, which could be performed at the time of a staging EUS. Aim was to create a model of peritoneal metastases for use in the development of TGP and to employ this model to compare TGP to LAP.This investigator-initiated protocol was performed in a live anesthetized porcine model. 2.5 mm color-coded beads were stapled via LAP to the peritoneum to simulate metastases. Using a non-inferiority design a sample size of 64 beads was determined. Three to 7 beads were placed in each of 12 animals. Randomization was performed for number and location of beads. Locations included: abdominal peritoneum (14 beads), diaphragm (11), surface of liver (32), and miscellaneous sites (7): hepatoduodenal ligament, visceral peritoneum, omentum, anterior stomach and pelvis. 3-port LAP was performed by one of 2 surgeons blinded as to the location and number of beads. TGP was then performed with a 2 channel therapeutic upper endoscope using either standard accessories (forceps, cap)(TGP-S) or with a specially designed toolkit (bendable overtube, articulating retractors and graspers)(TGP-T) in randomized order by one of 2 endoscopists also blinded to bead placement. A 30 min time limit per examination was used. Fisher's exact test with Bonferroni's correction for multiple testing was used to calculate p-values.A total of 64 beads were placed into 12 pigs. LAP found 61 beads (yield=95%, 95% CI: 89-100%), TGP-S 39 beads (61%, CI: 49-73%, $p<0.0002$ vs. LAP), TGP-T 40 beads (63%, CI: 51-74%, $p<0.0002$ vs. LAP). TGP-S and TGP-T were similar in the number, distribution and time to detect beads. TGP was superior for detecting beads on the abdominal and diaphragmatic peritoneum (n=25) than for the other sites (n=39): TGP-S 92% vs. 55% ($p=0.002$), TGP-T 100% vs. 52% ($p=0.0002$). Conclusions: In this first prospective, blinded, comparative trial TGP was inferior to LAP for the detection of simulated metastases. We successfully created a model for peritoneal metastases and established the benchmark for LAP detection. This model will be useful for future device development, which should focus on improved access to the region of the liver and enhanced endoscope optics and performance.

Is there a role for post-imatinib surgery in advanced gastrointestinal stromal tumours?

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Imatinib (Glivec®) has established its role in the treatment of gastrointestinal stromal tumours (GIST). In advanced GIST-patients it prolongs both progression-free and overall survival. Moreover, it can result in a dramatic tumour response, creating surgical opportunities in previously non-resectable locally advanced or metastatic GIST. This study investigates the efficacy of post-imatinib surgery in the treatment of our patients with advanced GIST.Between 2001 and 2007, 37 consecutive patients underwent surgery for advanced or metastatic GIST after imatinib treatment. Of these 37 patients, 21 underwent surgery with a neoadjuvant intention; 13 for locally advanced and 8 for limited metastatic disease. Sixteen patients underwent surgical treatment for other reasons in the course of their Imatinib treatment; 5 as debulking procedure at maximal response, 7 for progressive disease, and 4 for complications. Patient data were evaluated from the prospective GIST database. In the neoadjuvant setting, only 2 of 21 patients died during follow-up (median follow-up 14 months, range 5-53 months). Both had locally advanced disease and eventually died of recurrent disease 14 and 17 months after surgery. Five of the 7 patients operated for disease progression under imatinib died (estimated median survival of 14 months). One of the five patients who underwent surgery at maximal Imatinib response died 26 months after surgery due to recurrence.
In conclusion: There is a definitive role for surgery after Imatinib treatment for advanced GIST. A substantial survival benefit is achieved in the neoadjuvant setting for locally advanced and limited metastatic disease. The role in progressive disease under Imatinib seems limited.

In vitro comparison of seven gastric closure modalities for Natural Orifice Transluminal Endoscopic Surgery (NOTES)

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Secure transluminal closure is one of the fundamental prerequisites for safe introduction of NOTES in humans. Various endoscopic closure modalities have been described in literature. Up till now, no complete and adequately powered comparison of different gastric closure modalities has been reported. Aim was to evaluate the acute strength of various gastrotomy closure techniques in an ex vivo porcine stomach model by assessing air leak pressures.Stomachs were harvested from freshly slaughtered adult pigs. Standardized gastrostomies were created by a small surgical incision followed by dilation with an 18 mm balloon. After closure, each specimen was fixed on the benchtest pot with the mucosa down, creating an airtight space within the pot. Subsequently, pressure within this airtight space was gradually raised. A standardized water film was positioned upon the specimen to visualize air-bubbles in case of leakage. By connecting the pressure gauge with two cameras, leak location and pressure could be determined in great detail. We started collecting gold standard values by means of testing 15 gastrostomies, closed with interrupted surgical suture with 3-0 Prolene. This resulted in a mean leak pressure of 206 mmHg (SD 59). Using a non-inferiority design a sample size of 11 specimens for each closure technique was determined. Seven different closure techniques were studied: 1) T-Tags (Ethicon); 2) Purse string modified T-tag (Cook); 3) Eagle claw VII (Olympus); 4) Endoclips (Boston-Scientific); 5) Flexible endoscopic stapler (Power Medical); 6) Purse string suturing device (LSI) and 7) Flexible endostitch (Covidien). Mean gastrotomy leak pressures in mm Hg were: 1) 138 (SD 68); 2) 73 (SD 14); 3) 187 (SD 56); 4) 202 (SD 68); 5) 244 (SD 55); 6) 102 (SD 32); 7) 231 (SD 71). One-tailed independent sample t-test showed inferiority of gastrotomy closure using T-tags ($p=0,6775$), running suture ($p>0,999$) and purse string suturing device ($p<0,9875$) in comparison with hand-sewn closure and non-inferiority closure with Eagle Claw ($p=0,0325$), endoclips ($p=0,0285$), endostitch ($p=0,002$) and stapler ($p<0,001$).
In conclusion, Eagle Claw VII, endoclips, endostitch and endoscopic stapler produced non inferior closures in comparison with hand-sewn closure when ideally placed in this ex vivo model. The stapler device yielded the strongest closures. In vivo survival experiments will need to be performed to further evaluate the most secure gastric closure techniques in real life.

A promising new combined treatment modality for Barrett's esophagus containing early neoplasia: endoscopic resection followed by step-wise circumferential and focal radiofrequency energy ablation

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Endoscopic resection (ER) allows for removal of high-grade dysplasia (HGD) and intramucosal cancer (IMC) in Barrett's esophagus (BE). Focal ER, however, does not remove residual "at-risk" BE tissue, while radical ER often results in stenosis. PDT or APC allow for treatment of residual BE after ER, but are associated with residual intestinal metaplasia (IM) +/-dysplasia, buried Barrett's (BB), and stenosis. Aim was to assess safety and efficacy of focal ER followed by radiofrequency ablation in patients with BE-HGD/IMC.Eligible patients had BE <10cm, HGD/IMC confirmed by an expert GI pathologist, and no submucosal or lymph node involvement on EUS. The cap- or multi-band mucosectomy (MBM) technique was used for ER. Circumferential ablation (CA) was performed with a balloon-based electrode, while focal ablation (FA) was performed with an endoscope-based electrode. 6 weeks after ER, CA was performed, then CA or FA every 2 months until complete BE eradication. Two months after the last ablation, EGD (NBI) with biopsies (4Q/1cm) was performed.In 31pts (25 M, mean age 62yrs, median Prague C5M7) a total of 35 ER sessions were performed (19cap, 16MBM; 15 en-bloc, 20 piecemeal). ER complications: 4 bleedings and 1 perforation, treated conservatively. Worst ER-histology per patient: 16 IMC, 12 HGD, 3 LGD. Post-ER/pre-RFA histology: 21 HGD, 8 LGD, 2 IM. Complete eradication of all IM and dysplasia was achieved in 30 pts (97%) after 1(1-2) CA and 2(2-3) FA sessions, and 1 additional focal MBM in 1pt. In one patient, a 5mm isle with dysplasia persisted (protocol failure). In 3 pts, a non-transmural laceration occurred at the level of the prior ER during CA, likely due to overstretching with the balloon. None required intervention or caused symptoms. 4 pts developed dysphagia, resolved with dilation; all had widespread ER or narrow esophagus prior to ablation. After median FU of 12 (6-18) months, no dysplasia recurred. In 1pt with C9M10 BE, a 1mm isle was observed at the upper end of the initial BE at 16 months FU. Only 1/1054 neosquamous biopsies showed BB. This biopsy was obtained at the same location where a 1mm isle was observed at a following FU-EGD in the patient mentioned above.
Conclusion: For BE with HGD and/or IMC, focal ER of visible lesions followed by stepwise CA and FA for residual BE +/- dysplasia is safe and effective. Serious complications can be avoided if the extent of ER is limited and the size of the ablation balloon is chosen conservatively.

Neo-adjuvant radiochemotherapy in esophageal cancer patients results in increased MMP-activity in surrounding healthy esophageal tissue at the time of surgery

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Neoadjuvant treatment strategies have shown promising results in the treatment of various malignancies and several clinical trials are currently exploring the possibilities to further intensify the neoadjuvant component. A major limitation in this respect may be the damage that such therapies cause to surrounding healthy tissues which may complicate the postoperative healing process.In this study, the effect of neoadjuvant radiochemotherapy (RCT) on the activity of Matrix Metalloproteinase (MMP) 2 and 9 in surrounding healthy esophageal tissue at the time of surgery was investigated since it is known that increased MMP-activity is associated with adverse side-effects such as anastomotic leakage.In total 28 patients participating in the CROSS-II-trial were randomised to either the control (n=16) or the neo-adjuvant radiochemotherapy group (n=12). In the latter group, surgery was performed 5 weeks after the last course of RCT. During surgery full thickness biopsies were taken from the esophagus both close to the tumor and at the most proximal border of the resection specimen. MMP-2 and MMP-9 activity in the samples was assessed by performing gelatin zymography.Total MMP-9 activity appeared to be significantly higher in esophageal biopsies taken from patients after RCT as compared to the control group both in the proximal (36.1 vs 5.5 $p<0.05$) and distal (36.8 vs 9.5 $p<0.05$) biopsy. A similar but not statistically significant pattern was seen for MMP-2 in the proximal (16.1 vs 9.3) and distal (18.7 vs 9.2) biopsy. This study shows that neoadjuvant radiochemotherapy results in an increased MMP-activity in the esophagus distant from the tumor at the time of surgery. Since increased levels of MMP-activity are associated with adverse side-effects such as anastomotic leakage this finding has to be taken into account when considering neoadjuvant treatment strategies.

Good results of surgery after Self-Expanding Metal Stent (SEMS) placement for acute malignant colonic obstruction

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Since 2003 patients with an acute colonic malignant obstruction has been treated with placement of a SEMS as first line treatment in our hospital. After decompression of the colon, patients were analysed for metastatic disease. For patients with evidence of diffuse metastatic disease or severe co-morbidity SEMS was decided to be the definitive treatment. All other patients were scheduled for curative resection of the colon within days or weeks after SEMS. From 2003-2007, in 35 patients (15 men, 20 women, median age 74 years, range 37-90) colonic resection was performed. Twenty SEMS were placed in the left, seven in the transverse and eight in the right hemicolon. The median time between successful SEMS placement and operation was 26 days (range 5-89). One patient had a non-functioning SEMS and was operated the next day because of persisting ileus. Resection types were right hemicolectomy (8) , transverse colectomy (7), left hemicolectomy (8), sigmoid resection (9), low anterior resection (1) and a Hartmann procedure (2). In one patient a temporarily diverting colostomy was performed. No stent-related perforation or tumour spill was encountered during operation. One patient died 3 days after operation from myocardial infarction (30-day mortality-rate of 2,6 %). Median hospital stay after operation was 9 days (4-20 days). Sixty-one percent of the patients had no complications. Nine patients suffered from wound infection, pneumonia and urinary tract infections. Pathology results showed that 1 patient had stage I, 11 stage II, 16 stage III and 7 stage IV malignant disease. Patients with stages III and IV received adjuvant chemotherapy. After a median follow-up of 19 months (1-51 months) 22 patients are still alive. Local recurrence occurred in one patient, three patients developed a second colonic malignancy. Of this three patients, one patient was operated curatively and two received a stent as definitive palliation.
Conclusion: mortality and morbidity of colonic resection after SEMS placement for colonic malignant obstruction is very low, comparing literature of acute colonic resections.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal origin shows acceptable morbidity and high survival.

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Patients with peritoneal carcinomatosis from colorectal origin have a poor prognosis. Recent clinical studies show that cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) improves survival of selected patients with a colorectal carcinoma and isolated peritoneal carcinomatosis in the absence of extra-abdominal metastases. Here, we retrospectively assess the clinical outcomes and survival after cytoreductive surgery and HIPEC of the first cohort of patients that were treated at our institution.Sixty-nine patients were operated between March 2005 and December 2007. The group consisted of 32 men and 37 women, with an average age of 55 years. All had a primary colorectal carcinoma. The majority was referred to our hospital after previous laparotomy at another institution, which had usually included resection of the primary tumor. Upon laparotomy, 17 patients showed tumor dissemination that was deemed irresectable and underwent no resection or HIPEC. In 52 patients, a macroscopically complete cytoreduction was achieved and all these resections were combined with HIPEC. Most patients underwent conventional adjuvant chemotherapy in the postoperative phase. After HIPEC, the median hospital stay was 13 days (range 6-140). The overall morbidity was 32%, including anastomotic leakage (14%) and intra-abdominal abcess (11%). The overall 1-year survival rate was 85%. The 2-year survival rate was 57% (8 out of 14 patients).
Conclusions: In selected patients referred to a specialised institution, cytoreductive surgery combined with HIPEC has an acceptable morbidity and high survival rate.

A high incidence of MSH6 mutations in Amsterdam Criteria II negative families tested in a clinical setting

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The clinical phenotype in MSH6 mutation families is slightly different from that of MLH1 and MSH2 families, with a later age of onset of colorectal cancer (CRC) and endometrial cancer (EC). A possible consequence is that MSH6 mutation families are less likely to fulfill the stringent Amsterdam II criteria (AC II) and thus will not be identified as a family affected by Lynch syndrome. The aim of the present study therefore was to evaluate the contribution of different mismatch repair gene mutations in families that were analyzed for Lynch syndrome in a clinical setting.Data were collected from medical records and family pedigrees of families who visited the department of Clinical Genetics of the Erasmus Medical Center between 2000 and 2006. Data collection included tumor characteristics, results of microsatellite instability (MSI) and immunohistochemical (IHC) analysis, and results of germline mutation analysis. Only families with familial clustering of Lynch associated tumors were included in this study. A total of 109 families were included in this study. MSI and IHC analysis was performed in tumor tissue of 98 (90%) families. A MSI high phenotype with an absence of protein expression was found in 40 (41%) of the families. An absent expression for MLH1 was found in 23 families, including 6 with a BRAF mutation. An absent expression for MSH2 and MSH6 was seen in 5 and 12 families respectively.Mutation analysis was performed in all the 109 families and a mutation was detected in 23 families (7 MLH1, 4 MSH2 and 12 MSH6), including 17 families with a MSI high phenotype and absent protein expression. Of the 12 families with a MSH6 mutation, only three (25%) fulfilled the AC II . This was significantly lower compared to the MLH1 (43%, $p < 0.01$) and MSH2 families (75%, $p < 0.01$). The mean age of CRC and EC onset were 60 ± 14 years and 55 ± 10 years respectively in the MSH6 positive families. A MSI high phenotype with absent protein expression was detected in all the MSH6 mutation families that did not fulfill the AC II (n=9).
Conclusions: There is a high incidence of MSH6 mutations in Amsterdam II criteria negative families tested in a clinical setting. These MSH6 families can be identified with targeted MSI and IHC analysis. Therefore, liberal MSI and IHC testing should be performed in families with a clustering of Lynch sydrome associated cancer at an older age.

Poor compliance with MSI-analysis in patients with colorectal cancer at high risk for Lynch Syndrome

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Lynch syndrome (LS) accounts for approximately 3-5% of all colorectal carcinomas (CRC). Microsatellite instability (MSI) is the molecular hallmark of LS. In 2004 the revised Bethesda criteria were published to improve the efficiency of recognizing LS by identifying LS-related malignancies that should be analyzed for MSI. The aim of this study was to evaluate whether MSI-analysis was performed in CRC patients at high risk for LS according to the Bethesda guidelines. All patients diagnosed with invasive CRC in 15 Dutch hospitals between January 2005 and January 2007 were selected from the regional Comprehensive Cancer Center. Data concerning all MSI-analyses between January 2005 and August 2007 were available. Patients were included if they met any of the following criteria derived from the Bethesda guidelines: (1) patients diagnosed with CRC < 50 years, (2) patients < 60 years with CRC displaying mucinous or signet-ring differentiation or medullary growth pattern, and (3) patients diagnosed with a second LS-associated tumor prior to the diagnosis of CRC in 2005/2006. Patients were excluded when they had previously been identified as LS mutation carrier. MSI performance rates were analyzed using chi square statistics and multivariate logistic regression. Family history and presence of tumor-infiltrating lymphocytes or Crohn's-like lymphocytic reaction in the tumor were not taken into account since these data were missing. Of the 1882 patients diagnosed with CRC, 173 (9%) met any of the inclusion criteria. One known LS mutation carrier was excluded. MSI-analysis had been performed in 23 (13%) of the remaining 172 patients. MSI was performed in 18 (23%) of the 79 included patients < 50 years of age, and in one (5%) of the 21 patients between 50-60 years with high-risk pathology markers. Of the 72 patients with a second LS-related tumor, 4 (5,5%) were referred for MSI-analysis. In patients with CRC < 50 years MSI-analysis was significantly more often performed than in patients fulfilling one of the other 2 inclusion criteria ($p < 0,01$). Gender and tumor localization were not associated with performance of MSI-analysis.

We conclude that despite multidisciplinary approach of oncology and easy access to a tertiary referral center and clinical genetics facilities, there is marked underutilization of MSI-analysis in patients at high risk for LS. As a result LS might be underdiagnosed in patients with CRC and their relatives.

Individualized prediction of MLH1 and MSH2 Mutations in Lynch Syndrome

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Lynch syndrome is a common cause of hereditary colorectal cancer. This syndrome is caused by mutations in the mismatch repair genes (MLH1, MSH2, MSH6). Mutations in the MLH1 and MSH2 genes accounts for almost 90 percent of cases, while mutations in the MSH6 gene accounts for approximately 10 percent of cases. The aim of the present study was to predict the probability of a MLH1 and MSH2 mutation separately rather than combined in a large cohort of patients undergoing genetic testing. Personal and family histories were collected for 1914 unrelated patients who submitted blood samples between 2000 and 2004 for full gene sequencing of MLH1/MSH2. A polytomous logistic model was used to perform univariable and multivariable analyses taking several aspects into account: the presence and the number of CRC, endometrial cancer, and other Lynch synmdrome associated cancers in the patient and relatives, the presence of adenomas, and the age when the cancer was diagnosed. The logistic regression coefficients were significantly different ($p<0.001$) for presence of a mutation in MLH1 (n=112) versus MSH2 (n=173). The presence CRC in the proband or relatives was stronger associated with an MLH1 mutation whereas the presence of other HNPCC-associated cancers was stronger associated with an MSH2 mutation. Similar associations were found for the presence of endometrial cancer in the proband (Odds ratios 3.9 and 4.3) or relatives (Odds ratios 2.7 and 2.8) with MLH1 and MSH2 mutations respectively.
Conclusions: the probabilities of having a MLH1 or MSH2 mutation are very different according to the personal and family history of CRC, endometrial and other Lynch syndrome related cancers, and the age at diagnosis. Accordingly, some patients are more readily candidates for MLH1 testing while others more for MSH2.

Prognostic impact of MMP-2 and MMP-9 gene promoter polymorphisms and their corresponding protein levels in colorectal cancer

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High tumor levels of the gelatinase-type of matrix metalloproteinases MMP-2 and MMP-9 are associated with angiogenesis, invasion, and metastasis. In this study we evaluated the prognostic value of the protein levels of MMP-2 and MMP-9, as determined by ELISA, in a cohort of 215 colorectal cancer patients in association with their single nucleotide polymorphisms (SNP). The SNPs for MMP-2 (-1306C>T, promoter) and MMP-9 (-1562C>T, promoter), previously associated with tumor occurrence and clinical outcome for various cancer types, were genotyped using ARMS-RFLP-PCR-based techniques. Carcinoma MMP-2 levels showed a stepwise increase with TNM stage, but with no statistical significant differences between subclasses. For all other clinico-pathological parameters no correlation with tumor MMP-2 or MMP-9 protein levels was found. An optimized cut off point, dividing the patients in 2 groups, showed an association of MMP-2 with overall survival (18.5 ng/mg protein, LR 5.07, P=0.024). The same approach for MMP-9 resulted in 2 differently oriented cut off points; a low MMP-9 value (11.2 ng/mg protein, LR 9.18, P=0.010) and a high value (125.0 ng/mg protein, LR 5.31, P=0.021), both associated with a poor prognosis. The MMP-2 and MMP-9 protein levels in homogenates from cancer tissues were not associated with their respective SNP genotypes. Evaluation of the association of the SNPs with the clinico-pathological parameters revealed for MMP-2 SNP -1306C>T a significant correlation with the TNM stage (P=0.03) and with 10 year survival (P=0.01) according to the Log-rank test. Univariate Cox survival analysis confirmed the association of the MMP-2 SNP and the tumor protein levels of MMP-2 and MMP-9 with survival. Multivariate Cox analysis against the prognosis-associated clinico-pathological parameters gender, age and TNM classification validated MMP-2 SNP -1306C>T as an significant independent marker for survival of colonic cancer patients (HR 1.40, P=0.038), but MMP-2 and MMP-9 protein levels in cancer tissue lost their significance. In conclusion, this study shows that SNP -1306C>T, located in the promoter region of the MMP-2 gene, is significantly associated with worse survival of colorectal cancer patients. Although enhanced MMP-2 protein levels in the tumors were also associated with worse survival, these levels were not correlated with the MMP-2 genotype. These observations underline the importance of MMP gene expression in the clinical outcome of colorectal cancer.

Usefulness of genetically engineered bacteria for the treatment and prevention of colorectal cancer

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Aim : theoretically targeted delivery of anti-cancer proteins to colon cancer lesions would be a powerful anti-cancer strategy. We have shown and reported earlier that both BMP and Hedgehog have anti-colon cancer properties and that Hedgehog release by bacteria is beneficial in preventing polyp formation in the APC min mouse model. Such strategies would be markedly improved if genetically modified bacteria could be targeted to the actual site of cancer formation. Methods: Antibodies are effective targeting agents. Here we report a novel recombinant scFvSIgA1 protein produced by Lactococcus lactis, anchored to the bacterial membrane, which retains its full immuno-recognizing potential. The scFv fragment employed was a sequence targeted to a colon cancer epitope, epithelial glycoprotein protein-2 (EGP-2). Furthermore we cloned A cDNA encoding mature human BMP-2 and tested these bacteria for colon cancer killing potential.Results: L. lactis expressing this chimeric protein was capable of binding cells expressing this epitope. E. coli. Coli expressed BMP-2 fusion proteins, which was functionally active as demonstrated by the induction of apoptotic activity in the DLD-1 cell line.
Conclusions: Expression of specific antibodies on bacteria may allow local delivery of anti-cancer agents produced by such bacteria in conjunction with the antibody and provides a new avenue in the quest for targeted mucosal drug delivery.

Accept or decline fecal occult blood test screening for colorectal cancer: the participants view

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Fecal occult blood test (FOBT) screening for colorectal cancer (CRC) is associated with relatively lower participation levels than other screening programs, e.g. breast cancer screening, 30-60% versus 70-80%. Evaluation of participation in this screening program can provide valuable information on CRC why individuals decide to either accept or decline participation. The aim of this study was to evaluate possible factors involved with this decision.A total of 20653 individuals, 50-75 yrs, were invited to the first Dutch CRC screening using FOBT from May 2006 to Jan 2007. A survey was developed, to evaluate this program, sent two weeks after initial invitation, containing 22 statements on: (1) the manner of invitation, (2) knowledge of screening and CRC; (3) test related behavior; (4) personal health; (5) fear; and (6) influences of friends and family. The survey was completed by 9594 invitees (response rate 46%). Of these invitees 94% also returned the FOBT (participants,n=8989) and 6% only returned the survey without the FOBT (non-participants,n=605). Participants to the screening program were more likely to have found the FOBT easy to use (OR 16,4 :95%CI 12,3-22,1), to interpret the manner of invitation as clear and readable (OR 14,8 :95%CI 9,2-23,9), to know that early detection of cancer can lead to better treatment (OR 3,5 :95%CI 1,9-6,5), and to know other individuals that also participated in the screening program (OR 2,5 :95%CI 2,1-3,1). Women were more likely to participate if they had also participated in other screening programs (OR 3,2 :95%CI 2,2-4,6). Participants were less likely to participate if they found the test shameful to perform (OR 0,1 :95%CI 0,0-0,1), disgusting (OR 0,1 :95%CI 0,1-0,2) and if they were frightened of a positive test (OR 0,6 :95%CI 0,5-0,9).
In conclusion, our study shows that the decision to either accept or decline FOBT screening is a complex process due to the fact that there are many different factors involved. This decision is strongly associated with the manner of invitation and with test-related issues. Furthermore, health related issues, fear and risk perception are also related to declining FOBT screening. These associations may be influenced by low levels of knowledge and awareness of CRC in The Netherlands. Providing the study population with adequate information may facilitate an informed choice and will hopefully raise participation levels.

Immunochemical fecal occult blood tests have the best performance in a screening population comparing four different screening strategies with intention to screen analysis.

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In the Netherlands four screening strategies are evaluated: fecal occult blood testing with the guaiac-based Hemoccult-II®(G-FOBT) and the immunochemical OC-Sensor®(I-FOBT) and endoscopy based screening with colonoscopy and sigmoidoscopy. Determining the best strategy is complex, because the outcome of different screening tests is dependent on both different detection and participation rates. Combining detection and participation rates in one overall outcome measure with intention to screen analysis, enables generalizing comparison of different screening tests on a population level. We aimed to compare four screening strategies (G-FOBT, I-FOBT, colonoscopy and sigmoidoscopy) with intention to screen analysis for the Netherlands. We used data from a large Dutch population-based study with a random sample of 20,623 individuals 50-75 years of age, randomized to either G-FOBT or I-FOBT and literature data from a recent study in Italy of 12,039 individuals 55 and 65 years of age randomized to either colonoscopy or sigmoidoscopy screening(Segnan, Gastroenterology 2007). For the I-FOBT(OC-Sensor®) a cut-off value of 50ng/ml was used. No dietary instructions were given for the G-FOBT(Hemoccult-II®). Prevalence of colorectal cancer was considered to be identical in Italy and the Netherlands. Data were converted to the Dutch population 50-75 years of age(4.5 million) and ±410,000 endscopies yearly. Numbers needed to screen(NNScreen) and numbers needed to scope(NNScope) per detected cancer patient are presented according to intention to screen analysis.In total 4,836(47%) of G-FOBTs and 6,157(60%) of I-FOBTs were returned and 1597(27%) and 1944(32%) respectively participated in colonoscopy and sigmoidoscopy based screening. NNScreen for cancer were 990 for G-FOBT, 363 for I-FOBT, 463 for colonoscopy, 595 for sigmoidoscopy. NNScope for cancer were 9 for G-FOBT, 10 for I-FOBT, 123 for colonoscopy, 192 for sigmoidoscopy. For the Netherlands in one screening round 1,300,000 additional colonoscopies have to be performed with colonoscopy screening compared with 123,000 additional colonoscopies with I-FOBT screening.
We conclude, that I-FOBT has the best outcome in a screening population according to intention to screen analysis, comparing G-FOBT, I-FOBT, sigmoidoscopy and colonoscoy based screening. Per cancer patient detected, with I-FOBT screening less people need to be screened and many times less people need to be scoped compared with colonoscopy based screening.

Self Expanding Metal Stents (SEMS) for colonic obstruction as bridge to surgery: A safe procedure?

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Colorectal stenting is nowadays used as “bridge to surgery” in patients presenting with colonic obstruction in specialised high volume centres. Reported rates of success are 95% with a serious complication rate of 5 %. Recently a randomised controlled trial investigating the safety and efficacy of colonic stenting was terminated because of an unexpected high rate of perforation. In our centre, however, emergency surgery for colonic obstruction as first line treatment has been abandoned since 2003. The aim of this study was to review our single centre experience with placing self-expandable metallic stents (SEMS) in patients with a malignant colonic obstruction and who were eligible for curative resection. Stents were placed under endoscopic and fluoroscopic control within 24 hours after admission. After decompression of the bowel patients were analysed for metastatic disease. During a period of 3,5 years 38 stents were placed in 37 patients (mean age 69,9 years range 35-91 years) prior to surgery, all of them having a malignant obstruction without evidence of metastatic disease. Thirty-five (92,5%) patients presented with an ileus. Obstruction was located in the right colon eight times, in the transverse colon five times, in the descending colon five times and nineteen times in the recto-sigmoid. The procedure was initially technical successful in 36 patients (97,5 %), clinical success was achieved in 35 patients: one patient had to be operated the next day because of persisting ileus. Serious complications after stentplacement occurred in 2 patients (5,4 %). One patient had a cecal perforation after placement of a stent in the sigmoid. One patient experienced a stent dislocation after five days but decompression was achieved and the patient was operated in an elective setting. There were no perforations at the site of the stent. The mean time between stenting and surgery was 27,1 days (range 1-75 days) In one patient a second stent was placed because of progression of the tumour while awaiting surgery.
Conclusion: preoperative stenting is a safe and effective procedure in patients presenting with malignant colonic obstruction.

Prevalence of adenomas in familial colorectal cancer

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Subjects with one or two first degree relatives (FDR) with colorectal cancer (CRC) have a moderate risk for developing CRC (relative risk 4-6). The Familial Colorectal Cancer Study (FACTS) was started in The Netherlands in 2002. It is a national randomized clinical trial to evaluate the optimal surveillance interval (3 versus 6 years) for subjects (age 45-65 years old) with one first degree relative with CRC diagnosed below the age of 50 years (Group A) or two first degree relatives with CRC diagnosed at any age (Group B). The study group is presented and the yield of first colonoscopy (t=0) is compared with the first life-time colonoscopy in a group of subjects (age > 40 years) comprising individuals from Lynch syndrome and FAP families who were found not to carry the mutation identified in the family[1]. A total of 551 subjects (242 male) met the selection criteria. Ninety-five subjects did have an earlier colonoscopy and were excluded from this study. Group A included 224 subjects and group B included 232 subjects. Sixty-nine percent of all CRCs diagnosed in the FDRs was confirmed by pathology reports. The control group included 142 subjects aged > 40 years. Adenomas were detected in 85 (18.6%) FACTS individuals and in 15 (10.6%) control subjects (P = 0.02). High risk adenomas occurred in 15 FACTS subjects (3.6%) and in 7 control individuals (4.9%)(NS). Two CRC were observed in the control group, and one CRC and one carcinoid in the FACTS group. Multiple adenomas were only seen in the FACTS individuals (30/456; 6.6%), P = 0.002. No difference in detection of adenomas was observed between FACTS group A and B (15.2% vs. 22.0%, P = 0.06). The prevalence of adenomas and of multiple adenomas in subjects with familial colorectal cancer (FCC) were significant higher compared to the general population. Individuals with and without FCC are at equal risk of high risk adenomas during first life time colonoscopy.
The FACTS will reveal the best surveillance interval for FCC. [1]de Jong AE et al. Am J Gastroenterol. 2005;100(1):139-43

Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial

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Infectious complications and associated mortality are a major concern in acute pancreatitis. Enteral administration of probiotics allegedly prevents infectious complications, but convincing evidence based on a randomised comparison is lacking.
We conducted a multicentre randomised, double-blind, placebo-controlled trial in 298 patients with predicted severe acute pancreatitis as defined by an Acute Physiology and Chronic Health Evaluation [APACHE II] score ≥8, or Imrie score ≥3, or C-reactive protein >150 mg/L. Within 72 hours after onset of symptoms a multispecies probiotic preparation or placebo was administered enterally twice daily for 28 days. The primary endpoint was the composite of infectious complications, *i.e.*, infected pancreatic necrosis, bacteraemia, pneumonia, urosepsis, or infected ascites, during admission and a 90-day follow-up. Secondary endpoints included mortality and adverse events. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN38327949.
Groups were comparable at baseline for patient characteristics and disease severity. Infectious complications occurred in 30.3 percent in the probiotics group (46 of 152 patients) and 28.5 percent in the placebo group (41 of 144 patients), resulting in a relative risk of 1.1 (95 percent confidence interval (CI) 0.8-1.5). Mortality was 15.8 percent in the probiotics group (24 of 152 patients) and 6.3 percent in the placebo group (9 of 144 patients), resulting in a relative risk of 2.5 (95 percent CI 1.2-5.3). In the probiotics group 9 patients developed bowel ischaemia (8 with fatal outcome), whereas none did in the placebo group (P = 0.004).
Conclusion: in patients with predicted severe acute pancreatitis, probiotic prophylaxis did not reduce the risk of infectious complications. Probiotic prophylaxis was moreover associated with an over two-fold increased mortality, and should therefore not be administered in this category of patients.

Can RNA interference (RNAi) combine with interferon-alpha in anti-HCV treatment?

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Background: Hepatitis C virus (HCV) infection is a major cause of chronic liver disease with nearly 200 million carriers worldwide. The current standard treatment Peg-interferon-alpha administered in combination with ribavirin is only effective in approximately half of the patients, prompting the need for alternative treatments. RNAi represents an attractive new approach to combat HCV, allowing direct knockdown of viral RNA or host factors involved in viral life cycle. However, one emerging concern is that RNAi monotherapies might ultimately fail to control viruses that can escape silencing by mutation or lack of an efficient siRNA delivery system. The aim of this study is to investigate the possibility of combining lentiviral mediated RNAi with interferon-alpha (IFN-α) for HCV treatment in vitro, using a HCV replication model.Methods: We constructed a lentiviral vector (LV-sh2) expressing two small hairpin RNAs which simultaneously target the HCV IRES sequence and the host entry receptor, CD81. Effects of treatment with LV-sh2, IFN-α, or a combination on HCV replication was tested in a human hepatoma replicon model, Huh7-ET, by monitored luciferase activity. Effects of IFN-α on lentiviral transduction were assessed using GFP (LV-GFP) vector. GFP positivity was determined by flow cytometry. Results: Pre- or simultaneously treatment of IFN-α did not significantly alter the transduction efficiency of LV-GFP in Huh7-ET or 293 epithelial cells. Quantitative real time RT-PCR showed that LV-sh2 treatment efficiently decreased CD81 mRNA by 90%, whereas exogenous IFN-α (100 UI/ml) had no effect. Most importantly, combination of IFN-α with LV-sh2 significantly enhanced antiviral activity in vitro (86.8% inhibition of HCV replication) as compared with IFN-α alone (72.5%; $p \leq 0.002$).Conclusion: Lentiviral vector containing two small hairpin RNAs can simultaneously target viral RNA and viral entry receptor, CD81. Exogenous IFN-α has no influence on lentiviral vector transduction. In contrast, lentiviral mediated RNAi and IFN-α act independently on HCV replication, without clear evidence of cross-interference. Combination of these two treatments significantly enhanced anti-viral effects. Therefore, this novel combination strategy may offer potential to eliminate HCV infection in chronically infected patients.

Perioperative enteral arginine supplementation in head and neck cancer patients improves long term survival

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Background: Arginine concentrations are decreased in patients with cancer, which indicates that arginine metabolism may be disturbed in presence of a malignancy. Arginine supplementation has been associated with positive effects on specific and non specific anti tumour mechanisms and has been shown to reduce tumour growth and prolong survival in some animal and human tumour models. Furthermore, patients with head and neck malignancies are often malnourished, because of insufficient swallowing and passage disturbance. Most studies report malnutrition in 35-50% of all head and neck cancer patients. This contributes to high morbidity and mortality in these patients. It is unknown whether perioperative enteral arginine supplementation has a positive effect on prognosis and survival.Objective: We studied the effect of perioperative enteral arginine supplementation in severely malnourished head and neck cancer patients undergoing surgery and evaluated long term (≥ 10 years) survival and appearance of local regional recurrence, distant metastases and second primary tumours.Design: Thirty-two patients were randomly assigned to receive 1) standard preoperative and postoperative enteral nutrition (n=15), or 2) arginine supplemented preoperative and postoperative enteral nutrition (n=17). All patients had histologically proven squamous cell carcinoma of the oral cavity, larynx, oropharynx, or hypopharynx.
Results: The groups did not differ in age, tumour stage, tumour localization, comorbidity, or weight loss. The ratio between combined mandibular resections and total laryngectomies and type of reconstructive surgery was not different between the two groups. There was a significant better overall survival (P=0,0292) and disease related survival (P=0,0349) in the group receiving arginine enriched nutrition. No difference was observed between the groups in local regional recurrence, occurence of distant metastases, or occurrence of a second primary tumour. There was a trend towards a longer local regional recurrence free period in the arginine group (P=0,0684).
Conclusion: Perioperative arginine enriched enteral feeding did significantly improve long term overall survival and long term disease related survival in head and neck cancer patients. Larger groups are needed to confirm these results. This study strongly suggest that arginine enriched nutrition given perioperatively may be a valuable tool to improve long term survival.

Stress induced visceral hypersensitivity after maternal separation in rats is transferred across generations in a behavioral and mast cell dependent fashion.

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Adverse parent-child interactions are associated with increased risk to develop IBS. This is mimicked in the maternal separation (MS) model in which changes in neonatal maternal care lead to stress-induced mast cell dependent hypersensitivity to colorectal distension (CRD) in adult rats. Earlier, we showed that the non handled (NH) offspring of MS, but not of NH female rats, develops stress-induced hypersensitivity to CRD. Here we investigated whether 1) this transfer across generations is due to behavior of the mother, and 2) the enhanced response to stress is mast cell dependent. Female MS or NH rats mated with a NH male and none of the subsequent offspring was subjected to the MS protocol. Male pups of NH and MS dams were cross fostered (2 animals/litter switched) within 12 hrs of birth. At the age of 3 months, all male offspring was equipped with EMG electrodes in the abdominal muscles to record the visceromotor response (VMR) to CRD. Visceral sensitivity was assessed by intermittent distention (1, 1.5, 2 ml) before and 24 hrs after water avoidance stress (WA). Individual cross fostered rats were considered hypersensitive when the post-WA 'volume-vs-response' area-under-the-curve (AUC) was >77 (cut off based on historical data). In a 2nd series of experiments, VMR was assessed before- and 24- and 48- hrs after WA. To evaluate the role of mast cells, animals were treated with mast cell stabilizer doxantrazole (10 mg/kg i.p.) or vehicle before the last distention protocol. AUC was used to compare responses between groups ($P<0.05$ is significant; Wilcoxon signed ranks). Results show that all 4 males delivered by MS dams, but nursed by NH dams, remained normo-sensitive to CRD after WA, whereas those delivered by NH dams and nursed by MS dams (n=4) became hypersensitive. In the 2nd series of experiments, adult male offspring (n=18) of 3 MS dams developed visceral hypersensitivity to CRD 24hrs after WA (AUC pre vs post: 70±2 vs 102±5, P=0.0002). Subsequent treatment of 9 rats with doxantrazole significantly reduced the VMR to CRD (48hrs after WA, 77±6, P=0.008), rats treated with vehicle remained hypersensitive (96±10, P=0.008, n=9). We conclude that stress-induced visceral hypersensitivity can be transferred across generations and that transfer is related to behavior of the (foster)-mother. Reversal of hypersensitivity by mast cell stabilization indicates that augmented responses in 1st and 2nd generation MS offspring are both mediated by mast cells.

The intestinal FXR-mediated Fgf-15 pathway contributes to the diurnal control of hepatic bile acid synthesis and bile formation in chow fed mice but its contribution is overruled during bile acid feeding and bile acid sequestration *

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The relative importance of the intestine-derived, FXR controlled fibroblast growth factor 15 (Fgf-15) in control of hepatic bile acid synthesis and bile formation has been assessed employing intestinal-selective FXR knockout (iFXR-KO) mice. Studies were performed under normal dietary conditions as well as during challenges with dietary taurocholic acid (0.5% wt/wt, 3 days) and a bile acid sequestrant (Cholesevalam HCl, 2% wt/wt, 7 days). The contribution of intestinal FXR to the control of hepatic Cyp7A1 expression turned out to be time-dependent. Increased Cyp7A1 was observed in iFXR-KO mice immediately after the active night period (0.27 ± 0.17 vs. 0.70 ± 0.44, ($P<0.05$) at 7 AM) but not at 7 PM when Cyp7A1 expression is on its maximum (1.47 ± 0.47 vs. 1.68 ± 0.58, iFXR-KO vs. wild-type respectively). Yet, biliary bile acid secretion as bile flow were higher in the iFXR-KO mice when compared to controls. By means of a microscale isotope dilution technique, it was found that absence of intestine FXR resulted in an increased cholate pool size. This was associated with an increase in the relative contribution of cholate to the bile acid pool. Total bile acid synthesis, as deduced from fecal bile acid loss, was significantly higher in the iFXR-KO mice (15.0 ± 1.0 vs. 23.6 ± 2.5 µmol/day/100g BW, + 57%). Biliary bile acid secretion was increased and decreased, respectively, in both groups upon feeding the moderate bile acid-enriched diet or Cholesevalam HCl. More importantly, most of the differences between the two groups observed upon chow feeding were lost upon feeding of these specific diets. Thus, intestinal FXR contributes to the control of hepatic bile acid synthesis and bile formation under normal dietary conditions, however, bile acid feeding or treatment with a bile acid sequestrant leads to a situation in which the contribution of intestinal FXR participates in control of the process is limited."This work is part of the project "Hepatic and adipose tissue and functions in the metabolic syndrome" (HEPADIP, see http://www.hepadip.org/), which is supported by the European Commission as an Integrated Project under the 6th Framework Programme (Contract LSHM-CT-2005-018734)."

Hepatic cytochrome p450 oxidoreductase knockout mice show altered bile salt, cholesterol and phospholipids excretion.

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Mouse models for severe inherited cholestatic liver disease like progressive familial intra-hepatic cholestasis type 1-3 display mild phenotypes when compared to corresponding human patients. These mouse models only develop cholestasis when challenged with hydrophobic bile salts. This discrepancy is possibly caused by the ability of mice to hydroxylate hydrophobic salts efficiently into hydrophilic bile salts. This hydroxylation is mediated by cytochrome P450 enzymes.The aim of the present study is to analyze bile salt metabolism in mice with impaired P450 activity. For this purpose we used mice with a hepatic disruption of the cytochrome P450 reductase activity, so called Hrn mice. Bile formation was studied in wild type (wt) and Hrn mice after infusion of taurodeoxycholic acid (TDC) or tauroursodeoxycholic acid (TUDC). Biliary concentrations of bile salt (BS), phospholipids (PL) and cholesterol (CH) as well as biliary bile salt composition was measured. Endogenous bile salt output in Hrn mice was 3-fold reduced compared to wt mice, most likely due to reduced P450-dependent bile salt synthesis. In wild type mice about 90% of the identified BS were trihydroxy BS, with 10% dihydroxy BS. In contrast in Hrn mice only 50% were trihydroxy BS with 45% dihydroxy BS and 5% monohydroxy BS. Concomitant with this shift in BS composition, the biliary excretion of PL and CH were increased in Hrn mice. Infusion of TUDC gave rise to equal biliary output rates of BS, PL and CH in wt and Hrn mice. However, infusion of TDC resulted in significantly reduced bile flow and biliary BS output (78.6±37.9 nmol/min*100g vs 206.1±116.9 nmol/min*100g) in HRN compared to wt mice, suggesting the onset of cholestasis. Conversion of TDC to TC during this infusion was strongly reduced in Hrn mice.
Conclusion: Hrn mice have a strongly reduced capacity to (re)hydroxylate bile salts and are therefore more susceptible for cholestasis induced by hydrophobic bile salts. Crossing Hrn mice with PFIC mouse models will be an attractive approach to develop more humanised models for these diseases. We expect that feeding such double mutant mice with human hydrophobic BS will result in phenotypes that resemble the human disease better.

Calcium signalling of neuronal cell line SH-SY5Y triggered by sera of cholestatic patients suffering from pruritus

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Pruritus is a common symptom of various, mainly cholestatic hepatobiliary diseases. However, the pathogenesis of pruritus in cholestasis is still poorly understood. Bile salts do not seem to be the main cause of this phenotype as there is no relationship between plasma bile salt levels and the extent of pruritus. Endogenous opioids have been postulated to play a role but the extent to which they contribute has not been unravelled. It is our working hypothesis that pruritogens, which are normally secreted into bile, accumulate in the circulation and either directly or indirectly activate neurons. Along these lines we aimed to identify such pruritogens in an in vitro assay. As a model of in vitro neuronal signalling, intracellular calcium concentrations were measured in the human neuroblastoma cell line SH-SY5Y by ratiometric fluorimetry with Indo-1. Calcium transients were measured in cell suspensions upon addition of diluted serum samples of patients with different forms of cholestatic pruritus. We used sera of women with pruritus due to intrahepatic cholestasis of pregnancy (ICP, n=30), and patients with pruritus due to primary biliary cirrhosis (PBC) undergoing nasobiliary drainage (n=3) or plasma separation (n=3) and compared those with sera of women with normal pregnancies (n=20) and healthy volunteers (n=14). All serum samples induced calcium transients to some extent. However, sera of PBC patients induced significantly higher intracellular calcium transients than healthy controls ($p<0.01$). Furthermore, sera of women with ICP showed the strongest calcium transients and these were significantly higher than those from PBC patients ($p<0.01$), normal pregnancies ($p<0.01$) and healthy controls ($p<0.001$). Activation was at least in part mediated by a protein, as shown by diminished signal after proteinase K treatment of the sera. In addition, partial activity was recovered by reverse phase chromatography of sera, indicating amphipatic small molecular substances as putative mediators. Thus, calcium transients in neural cells are triggered in vitro by yet unidentified compounds in sera of patients with cholestatic liver disease suffering from pruritus. The exact nature of these compounds will be further elucidated as they may play a role in inducing pruritus in cholestasis.

Differential gene expression in Caco-2 ATP8B1 knock down cells unrelated to FXR activation *

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A spectrum of cholestasis syndromes, PFIC1 and BRIC1, is caused by mutations in the *ATP8B1* gene, which encodes a putative aminophospholipid translocase. It was suggested that PFIC1 patients exhibit reduced Farnesoid X Receptor (FXR) target gene expression in liver and intestine, which could contribute to the disease phenotype. FXR is a bile salt-dependent nuclear receptor and plays a pivotal role in bile salt homeostasis in hepatocytes and enterocytes by regulating the transcription of key genes involved in synthesis and transport of bile salts.
To investigate if *ATP8B1* deficiency results in aberrant gene expression, we used quantitative RT-PCR (Q-PCR) and microarray technology to analyze 3 independent clones of the human intestinal cell line Caco-2, in which the expression of *ATP8B1* was targeted by RNA interference (RNAi). Immunofluorescence staining of ATP8B1 in differentiated control Caco-2 cells revealed apical localization, while this staining was undetectable in the knock down clones. The stably integrated RNAi constructs resulted in a 50-80% reduced ATP8B1 protein expression as assessed by immunoblot analysis.
Q-PCR analyses in differentiated Caco-2 *ATP8B1* knock down clones revealed no correlation between the amount of residual ATP8B1 protein and the expression of *FXR* and FXR target genes such as *OST*α , *IBABP* and *ASBT*. This result was confirmed by luciferase activity assays with *BSEP* and *IBABP* promoter constructs in *ATP8B1* Caco-2 knock down cells.
Of the 20,590 genes present on the microarray, 250 genes were significantly differentially expressed in all 3 differentiated Caco-2 *ATP8B1* knock down clones. This list did not include FXR target genes, thus confirming that FXR does not play a key role in the affected gene expression profiles of Caco-2 *ATP8B1* knock down cells. Gene Ontology analysis revealed that the list of 250 differentially expressed genes was significantly enriched in genes affecting lipid metabolism. Furthermore, this analysis revealed a marked and significant enrichment of plasma membrane associated proteins. Our data indicate that *ATP8B1* deficiency in Caco-2 cells has profound effects on the gene expression profiles, but that this does not involve FXR. We hypothesize that altered aminophospholipid translocase activity caused by *ATP8B1* deficiency might lead to aberrations of plasma membrane components, as observed at transcriptional level, contributing to the pathophysiology of PFIC1 and BRIC1.

Differential effects of PFIC1 and BRIC1 mutations on protein stability and canalicular trafficking of ATP8B1

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Mutations in ATP8B1 cause progressive familial intrahepatic cholestasis type 1 (PFIC1), benign recurrent intrahepatic cholestasis type 1 (BRIC1), and are associated with intrahepatic cholestasis of pregnancy. PFIC1 is a severe disease that, without treatment, leads to liver failure in the second decade of life. Patients with BRIC1, the milder variant of PFIC1, suffer from episodic attacks of cholestasis that resolve spontaneously. We have previously shown that ATP8B1 mediates inward translocation of phosphatidylserine from the exoplasmic to the cytoplasmic leaflet of the canalicular membrane. In PFIC1 nonsense mutations and deletions are frequently observed while BRIC1 is more often associated with missense mutations. However, it is not clear how these genotypic variations relate to the phenotypic differences between PFIC1 and BRIC1. The aim of the present study is to examine the effect of different PFIC1 and BRIC1 mutations on ATP8B1 expression and trafficking. We introduced three PFIC1 mutations (G308V, D554N, and G1040R) and the most common BRIC1 mutation (I661T) by site-directed mutagenesis. ATP8B1 mutants were expressed in Chinese hamster ovary (CHO) cells and in the hepatocyte model cell line WIF-B9. mRNA and protein levels were analyzed using real-time PCR and Western blotting. Furthermore, the localization of ATP8B1 mutants was studied by confocal laser scanning microscopy and quantified by cell surface biotinylation. Protein levels of the G308V, D554N, G1040R, and I661T mutants were reduced to 11, 23, 64 and 33% of wild-type ATP8B1, respectively, while mRNA levels were not affected. Incubation with the proteasome inhibitor MG-132 restored all mutant protein concentrations to wild-type levels. Cell surface expression of all mutants in CHO cells was dramatically reduced. Confocal microscopy of WIF-B9 cells revealed that all PFIC1 mutants were retained in the endoplasmic reticulum (ER). Interestingly, the BRIC1 I661T mutant was partially present in the canalicular membrane. When WIF-B9 cells cells were grown at lower temperature, only the PFIC1 G308V mutant was released from the ER and localized to the canalicular membrane.In conclusion, all PFIC1 mutations resulted in decreased protein stability and increased proteosomal degradation of the protein. All PFIC1 mutants except the G308V displayed impaired canalicular membrane trafficking. Although the BRIC1 I661T mutant protein was less stable, residual protein reached the canalicular membrane.

Fic1 deficiency results in hearing loss and degeneration of the cochlear hair cells *

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FIC1 deficiency is caused by autosomal recessive mutations in *ATP8B1*, which encodes the FIC1 protein, a putative aminophospholipid translocase. It is primarily characterized by cholestasis, either progressive (progressive familial intrahepatic cholestasis type 1, PFIC1) or intermittent (benign recurrent intrahepatic cholestasis type 1, BRIC1). In addition patients can have extrahepatic symptoms such as pancreatitis and chronic diarrhoea. As patients may also complain about a reduced hearing capability we set out to investigate the role of FIC1 in auditory function.
In both BRIC1 patients (n=10; mean age 37 years) and Atp8b1$^{G308V/G308V}$ mutant mice (n=5-12; age 1,3 and 6 months) we tested auditory function, using standard pure tone audiometry and auditory brainstem responses, respectively. As controls, 10 cholestatic patients including 3 BRIC2 patients with BSEP deficiency (mean age 36 years) and 7 PSC patients (mean age 47 years), as well as 5-7 age-matched wild type mice were tested. Immunohistochemistry was performed on cochlear sections and whole mount cochleas of wild type mice to determine the localisation of Fic1 in the inner ear. Light microscopy on cochlear sections of Atp8b1$^{G308V/G308V}$ mutant mice was used to investigate the effect of Fic1 deficiency on cochlear structure.
BRIC1 patients showed a significant hearing loss of more than 30 dB compared to the control patients, who showed less or no hearing loss. The Atp8b1$^{G308V/G308V}$ mutant mice in all age groups showed a severe and significant hearing loss exceeding 50 dB at 8 and 16 kHz and a combination of different frequencies ($p < 0.01$). At 32 kHz the difference was less marked at 3 and 6 months ($p < 0.05$ and NS, respectively). In the cochleas of wild type mice, Fic1 was specifically located in the stereocilia of the mechanosensory hair cells. In addition in Atp8b1$^{G308V/G308V}$ mutant mice Fic1 deficiency resulted in marked degeneration of these hair cells.
In conclusion we showed that FIC1 deficiency causes hearing loss which may be secondary to degeneration of the hair cells, consistent with specific localisation of Fic1 in the stereocilia of these cells. These data open the interesting possibility that the bile salt excretory function of hepatocytes and the mechanosensory function of the hair cells share some common molecular mechanisms and are both critically dependent on the aminophospholipid translocase activity of FIC1.

Cigarette smoke extract protects intestinal- and T-cells against death-receptor- and oxidative stress induced apoptosis: an explanation for dichotomal effects of smoking on ulcerative colitis and Crohn's disease?

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For long, smoking has been a known risk factor for inflammatory bowel disease, but with a remarkable opposite effect on Crohn's disease (CD) and ulcerative colitis (UC). Where smoking aggravates CD and makes it more resistant to therapy, it actually ameliorates UC and decreases the need for colectomy. A diminished barrier function of the colonic epithelial compartment and insufficient activation-induced apoptosis of the T-cell compartment is recognized in both diseases. We hypothesize that smoke further increases the resistance of T-cells to apoptosis in CD patients, whereas such components will provide cytoprotection to colonic epithelial cells in UC. Therefore, we studied the effect of cigarette smoke extract (CSE) on death-receptor- and oxidative stress-induced apoptosis in various intestinal- and T-cell lines.
Intestinal- (DLD-1, SW480, HCT116, Caco-2) and T-cells (Jurkat, MOLT-4) were exposed to different apoptotic stimuli in presence or absence of different percentages CSE (v/v). 25 ml culture medium was saturated with smoke from 2 standard 3R4F cigarettes (scientific reference) and defined as 100% CSE. Death-receptor-mediated apoptosis was induced by anti-FAS or cytokine mixture (CM; TNF-α + INF-γ + IL-1β). Oxidative stress-mediated apoptosis was induced by the superoxide anion donor menadione. Apoptosis was determined by measuring caspase-3 activity and cleaved PARP, and necrosis by Sytox Green staining.
Addition of 0-30% CSE to anti-FAS, CM or menadione treated cells resulted in a dose-dependent decrease of caspase-3 activity and PARP cleavage in all cell lines investigated. CSE alone did not induce apoptosis, but CSE concentrations above 50% induced necrosis. CSE inhibitory effects were most pronounced for menadione-induced apoptosis followed by CM and anti-FAS. A remarkable observation was that CSE abolished menadione-induced caspase-3 activity and induced a switch from apoptosis into necrosis for the highest concentrations of CSE used.
In conclusion CSE protects intestinal- and T-cells against death-receptor- and oxidative stress-induced apoptosis. Increased T-cell resistance against apoptosis is detrimental for CD, while increased colonic epithelial cell resistance against apoptosis, in particular resistancy to oxidative stress, is beneficial for UC.

Adaptation of carnivore-colonizing Helicobacter species to the diet of their host

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The acidic gastric environment of mammals can be chronically colonized by a diverse set of host-specific Helicobacter species. The major factor allowing colonization of the acidic gastric niche is the urease enzyme. Urease is a nickel-dependent enzyme, and thus these gastric Helicobacter species require nickel for acid resistance. However, the major sources of nickel in the stomach are thought to be restricted to vegetarian dietary components, and thus Helicobacter species colonizing strict carnivores may be subjected to long episodes of nickel-limitation. Recently, a putative second urease gene cluster (ureA2B2) was detected in three gastric Helicobacter species colonizing such carnivores, whereas it is absent in four other gastric Helicobacter species. The aim of this study was to characterize both urease systems using H. mustelae as model organism.H. mustelae strains were grown in medium with and without nickel and iron supplementation and urease expression levels were determined using immunoblotting and Northern hybridization. Urease activity was measured in nikR mutants lacking either UreAB or UreA2B2 expression, and acid-resistance was assessed by incubating H. mustelae at pH 1.5 in the presence and absence of urea for 30 min.Both urease homologs of H. mustelae were expressed in iron- and nickel-limited conditions. Interestingly the addition of nickel resulted in the induction of UreAB expression and in the complete repression UreA2B2 expression. The addition of iron resulted in the induction of UreA2B2 expression and did not affect UreAB expression. Insertional mutagenesis of the nikR gene (encoding a nickel-responsive regulator) resulted in constitutive expression of both urease homologs. In contrast to UreAB, the UreA2B2 did not require the urease accessory proteins for activation. Despite the difference in levels of urease activity, H. mustelae mutants expressing either UreAB or UreA2B2 were acid-resistant in the presence of urea.Three carnivore-colonizing Helicobacter species express a second urease system, this system is not detected in four other gastric Helicobacter species. Both ureases confer acid-resistance to H. mustelae, and their regulatory pattern ensures urease enzyme activity during periods of nickel-limitation and nickel-sufficiency. The expression of UreA2B2 may therefore represent an adaptation of carnivore-colonizing Helicobacter species to the nickel limited diet of their carnivorous host.

Macrophage mannose receptor deficient mice are more susceptible to *Helicobacter hepaticus* induced colitis.

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Background and Aim: the macrophage mannose receptor (MR) is a recycling receptor expressed by macrophages and selected dendritic cell populations. MR can recognise a large range of endogenous ligands such as lysosomal hydrolases and myeloperoxidase, mediating clearance of these molecules by macrophages; and limiting tissue damage. Moreover, the mannose receptor is a pattern recognition receptor shown to recognise a variety of microbes. We hypothesized that a lack of mannose receptor influences gut flora recognition thereby inducing susceptibility to inflammatory bowel disease. We assessed the role of MR in *H. hepaticus* induced colitis using MR deficient mice.
Methods: wildtype and MR deficient mice were fed with *H. hepaticus*, known to induce colitis in susceptible strains, on day 0, 2 and 4, and injected with anti-IL10 receptor each week for a period of 4 weeks. After four weeks mice were killed and inflammation was assessed in spleen and colon.
Results: histochemistry showed a more severe colitis in MR deficient mice compared to wildtype mice, with increase in inflammation, amount of lymphoid follicles, ulceration in the submucosa and spreading to the muscle layer. The colon inflammation score for MR deficient mice and control mice were 2.280 ± 0.6598; N=5 and 6.200 ± 1.463; N=5, respectively. Systemic disease was more severe in MR deficient mice as was shown by a 10% increase of granulocytes in the spleen compared to WT mice.
Conclusions: these data demonstrate that mannose receptor deficiency exacerbates *H. hepaticus* induced colitis, possibly due to lack of microbe recognition. This suggests that MR might play a role in inflammatory bowel diseases.

Tumor cell-fibroblast interaction generates myofibroblasts in colon cancer via Transforming Growth Factor-β activation

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We observed that in colonic tumors up to 90% of the fibroblasts are of the myofibroblast, Smooth Muscle Actin (SMA)-positive phenotype, compared to only 5% in normal tissue. Furthermore, cancer-associated myofibroblasts strongly expressed TGF-β signaling molecules. Therefore, we investigated the role of TGF-β in the trans-differentiation of colon cancer fibroblasts into myofibroblasts. SMA and TGF-β ELISAs on tissue homogenates revealed a strong increase of both parameters in colon cancer. Interestingly, both latent and active TGF-β levels were enhanced, but only active TGF-β1 levels showed stepwise increase with Dukes' stage. Since TGF-β is able to drive the trans-differentiation of fibroblasts into myofibroblasts in vitro, we determined the transcriptional activation using a TGF-β responsive construct (CAGA-luciferase). Colon cancer cell lines HCT116 and LS180 responded dose-dependently to TGF-β, whereas CaCo-2 and SW948 did not, presumably due to known mutations in the TGF-β signaling pathway. Smad4-deficient HT29 cells still responded to high TGF-β levels and showed TGF-β mediated invasion and metastasis. Expression of TGF-β target genes and tumor-associated proteinases were strongly increased in both HT29 and HCT116 cells upon TGF-β stimulation (2-7 fold, Real Time PCR). TGF-β stimulation of colon cancer-derived fibroblasts showed 2 to 9 fold up-regulation of MMP-2, -3 -9, TIMP-1, -2, -3, urokinase, PAI-1 and collagen I. TGF-β itself was 18-fold increased, indicating a strong autocrine regulatory TGF-β loop in tumor myofibroblasts. We next used the CAGA reporter-gene assay to study TGF-β activation in vitro. Fibroblasts were not able to activate exogenous small latent TGF-β (TGF-β/LAP). However, when combined with tumor cell medium, containing high levels large latent TGF-β (TGF-β/LAP/LTBP) and only minor amounts active TGF-β, signaling was strongly enhanced, and SMA expression was increased implying myofibroblast differentiation. Combining tumor cells with fibroblast-derived medium led to a comparable increase in signaling. This indicates that TGF-β is activated by interaction between fibroblasts and tumor cell-derived soluble factors.In summary, we show that interplay between tumor cells and fibroblasts in the colon cancer micro-environment enhances TGF-β activation and subsequent myofibroblast trans-differentiation. This leads to a cumulative production of latent TGF-β and its (proteolytic) activators, creating a cancer-promoting feedback loop.

The effect of Acute Tryptophan Depletion (ATD) on the activity and connectivity of an emotional arousal network during visceral pain.

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Acute tryptophan depletion (ATD) temporarily reduces serotonin (5-HT) synthesis in the brain and has been to shown to produce disinhibition of central arousal circuits, and alterations in visceral perception and emotional memory in IBS patients (Kilkens et al. 2004). We hypothesized that ATD-induced reduction in 5-HT synthesis would alter activity in an emotional arousal network previously shown to be involved in central pain amplification.

BOLD responses of 12 healthy women were assessed using fMRI (1.5 T) during 6 low and 6 high, individualized rectal balloon distensions (INF) and 12 non-INF or rest periods, following ATD by oral administration of a tryptophan-depleted drink, or placebo (PL). Multivariate spatiotemporal partial least squares (ST-PLS) was applied to test the interaction of treatment (ATD,PL) with a distributed pattern of brain activity discriminating the low and high INF conditions. Structural equation modeling (SEM) tested for group differences in the effective connectivity of the emotional arousal network.

ST-PLS revealed a network of brain responses that differentiated low and high INF and showed stronger engagement during ATD compared to PL. The network accounted for about 73% of the variance in the data analyzed, and permutation testing revealed significance at $p<.01$. This network included regions comprising the emotional arousal network (medial orbital frontal cortex (mOFC), rostral (rACC), and subgenual anterior cingulate cortices (sACC), and amygdala) as well as thalamus, insula, ventral tegmental area and periaqueductal grey. While most regions generally demonstrated sustained activity, amygdala and thalamic activity was only evident during the first 3 seconds (1st scan). Subjects receiving ATD showed the greatest engagement of the emotional arousal circuitry during high INF. Specifically, network analyses with SEM revealed significantly greater positive coupling between iACC →sACC and sACC → Amyg circuits (p values<.05) in ATD as compared to PL during the high INF.

Conclusions: together with our previous demonstration of ATD on visceral pain perception, these findings are consistent with the concept that acute lowering of 5-HT levels results in greater engagement of a central arousal network which is involved in central pain amplification

Famine in Early Life is Associated with an Increased Risk of Developing Irritable Bowel Syndrome, a Population Based Cohort Study.

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Introduction: Famine in early life is considered a risk factor in the development of several cardiovascular, endocrinological and metabolic diseases (Roseboom et al. Early Hum Dev. 2006). Especially as early life events have been suggested to play an important role in the development of irritable bowel syndrome (IBS), we evaluated whether famine in early life is also associated with an increased prevalence of IBS and whether this is associated with an altered response to stress.
Methods: The Dutch Famine Birth Cohort consists of 1423 eligible adults born as term singletons in the Netherlands, around the time of the 1944-1945 Dutch famine. An individual is considered exposed to famine in early life when the average ration for adults was less than 1000 calories a day. Therefore, persons born before May 5th 1945 were considered exposed and were compared to those born after May 5th 1945. The prevalence of IBS could be assessed in 850 subjects (59.7%) using the Rome II questionnaire. In addition, 709 subjects underwent a standardized stress protocol consisting of a Stroop test, a mirror-tracing test and a speech test during which salivary cortisol samples were collected.
Results: Of a total of 850 subjects, 9.5% (n=78, 52F) met the criteria for IBS. Intrauterine exposure to famine did not increase the risk of developing IBS (7.7% versus 8.7%, NS). However, after birth, age at exposure to famine significantly influenced the prevalence of IBS (odds ratio 2.36, 95% confidence interval 1.16-4.84, p=0.019, logistic regression, corrected for gender). Of all adults exposed to famine between 1 and 1.5 years of age 15.3% met the criteria for IBS compared to 8.4% of those not exposed to famine in early life (p=0.029). Baseline cortisol concentrations (exposed: 4.5 ± 0.2 nmol/l, not exposed: 4.5 ± 0.2 nmol/l, NS) and the peak cortisol response during the stress test (exposed: 3.0 ± 0.3 nmol/l, not exposed: 2.6 ± 0.2 nmol/l, NS), were comparable between the groups. Age at exposure to famine did not significantly influence the basal cortisol or the peak cortisol response levels.
Conclusions: Although famine in early life is not associated with an altered stress-response, this study shows that famine in early life is a risk factor to develop IBS in adulthood. To what extent this increased risk of developing IBS is attributable to famine alone or is (also) associated with the stressful environment of famine and war remains unclear.

Role of serine protease signaling in dyspeptic symptom generation; a pilot study

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Hypersensitivity to gastric distension has been demonstrated in a substantial portion of patients with functional dyspepsia (FD). Although mechanical hypersensitivity is considered to play a pivotal role in dyspeptic symptom generation, the molecular factors underlying this pathophysiological mechanism are unknown. Enhanced serine protease signaling via protease-activated receptor (PAR)-2 induces mechanical hypersensitivity directly by activating extrinsic primary afferents and indirectly by increasing paracellular permeability. Intestinal epithelial cells produce the serine protease trypsin IV (zymogen trypsinogen IV), which is capable of activating PAR-2. Trypsinogen mRNA expression is elevated in IBS colonic and duodenal mucosa. Moreover, IBS mucosal biopsy supernatant has been shown to induce hyperalgesia and allodynia in mice upon colorectal distension. The aim of this study was to gain insight into the possible role of altered serine protease signaling in FD symptom generation. Duodenal biopsies were investigated, since signaling at the level of the duodenum modulates gastric sensory function.Sixteen FD patients (11 female, mean age 44.8 years, range 18.9-66.5) fulfilling the Rome II criteria were included. Each patient completed a chronic dyspeptic symptom questionnaire. Ten age- and sex-matched healthy volunteers (HV), recruited through advertisement, were also studied. Any medication known to influence GI sensorimotor function was discontinued 1 week prior to upper GI endoscopy. Duodenal mucosal biopsies were taken. Trypsinogen IV transcript level was quantified by real-time RT-PCR. Gene expression was compared between patients and HV by independent student t-test.No abnormalities were seen during upper endoscopy in any of the subjects. The level of ACTB expression, the reference gene used for normalization, was comparable between patients and HV. No significant difference in trypsinogen IV mRNA expression was observed between patients and HV (HV, mean 9.25, SD 3.35, range 6-16; FD, mean 8.13, SD 3.68, range 3-17; $P>0.05$). However, FD patients displayed a larger variability in trypsinogen IV mRNA expression. Subdivisions based on symptom pattern did however not reveal grouping of patients with specific characteristics.
Conclusion: In contrast to IBS, trypsinogen IV mRNA expression is not increased in FD duodenal mucosa. This suggests that the serine protease trypsin IV does not contribute to dyspeptic symptom generation.

Effect of the $GABA_B$ receptor agonist AZD9343 on transient lower esophageal sphincter relaxations and acid reflux in healthy volunteers: a phase I trial

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Transient relaxations of the lower esophageal sphincter (TLESRs) are considered the main mechanism underlying gastroesophageal reflux both in healthy subjects and patients with reflux disease and therefore represent an interesting target for treatment. Baclofen, a $GABA_B$ receptor agonist, reduces the number of TLESRs and reflux episodes, but is not suitable for clinical application due to its central side effects. Therefore, new substances devoid of these side effects are required. In the present study, the effect of AZD9343, a new selective $GABA_B$ receptor agonist, was studied on meal-induced TLESRs and its safety profile was evaluated.

Twenty-seven healthy male subjects (19-47 yrs) were included in a placebo-controlled, randomized, two-centre phase I study. All subjects underwent esophageal manometry (10 channel water perfused sleeve assembly) and pH-metry during 3 hrs after ingestion of a solid meal. One and a half hour before meal ingestion, a single oral dose of placebo, 60 and 320 mg AZD9343 or 40 mg baclofen was given on 4 separate days at least 7 days apart. TLESRs and acid reflux episodes were identified according to previously published criteria (Holloway et al., 1995).

25 of the 27 studies were complete and suitable for analysis. Somnolence was most commonly reported as side effect after 320 mg AZD9343 and baclofen. Reversible short-lasting parasthesiae of mild intensity were reported after intake of 60 and 320 mg AZD9343. The highest dose of AZD9343 and baclofen significantly reduced the number of TLESRs in the postprandial period with an average of 32% (95% CI: 15-44%) and 40% (95% CI: 26-51%) respectively. Acid reflux episodes were also significantly reduced by both doses of AZD9343 and baclofen compared to placebo. Like baclofen, both doses of AZD9343 increased mean LES pressure before meal intake compared to placebo. Finally, 320 mg AZD9343 and baclofen reduced the number of swallows as compared to placebo (mean reduction of 22 % (95% CI: 6-35%) and 35% (95% CI: 18-49%) whereas no effect was seen after 60 mg AZD9343.

Conclusions: Like baclofen, the selective $GABA_B$ receptor agonist AZD9343 dose-dependently reduces the number of TLESRs and acid reflux episodes, increases basal LES pressure and reduces swallowing. These findings extend the concept that $GABA_B$ agonists are potent reflux inhibitors.

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Increased swallowing frequency in GERD is likely to be caused by perception of reflux episodes

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GERD patients swallow air more frequently and have more mixed liquid-gas and pure gas reflux episodes compared to healthy controls. One explanation may be that GERD patients primarily swallow more frequently and subsequently have more swallow- or TLESR-associated reflux episodes. Another explanation may be that GERD patients sense reflux episodes and swallow more often in response to these unpleasant sensations. To differentiate between these two mechanisms we investigated whether the number of swallows and reflux episodes is affected by PPI therapy. In 34 patients with typical reflux symptoms esophageal 24-h pH-impedance monitoring was performed both off and on PPI therapy. The number and type (liquid, mixed liquid-gas or gas reflux) of reflux episodes and number of swallows and air swallows was evaluated. The symptom association probability (SAP) was used to distinguish patients with a good relationship between symptoms and reflux episodes (SAP+) from those who do not sense the reflux episodes (SAP-). Off PPI therapy, the SAP+ patients (n=21) had significantly more gas reflux (p=0.01) and mixed reflux episodes (p=0.01) than the SAP- patients (n=13). Liquid and pure gas reflux episodes were not affected by PPI therapy, neither in the SAP+, nor in the SAP- patients (liquid reflux SAP+: 30.7 ± 6.0 off vs. 30.7 ± 5.2 on PPI, SAP-: 28.0 ± 5.2 off vs. 27.4 ± 7.0 on PPI; gas reflux SAP+: 35.3 ± 4.7 off vs. 36.1 ± 6.4 on PPI, SAP-: 18.8 ± 2.5 off vs. 21.9 ± 3.9 on PPI). The numbers of mixed reflux episodes were not influenced by PPI therapy in the SAP- patients, but were decreased in the SAP+ patients (SAP+: 48.7 ± 4.3 off vs. 39.6 ± 3.8 on PPI (p=0.02), SAP-: 30.5 ± 3.1 off vs. 34.5 ± 4.8 on PPI). In the SAP+ patients the number of swallows decreased on PPI (829.3 ± 84.7 off vs. 701.4 ± 79.4 on PPI, p=0.03), whereas the number of air swallows was not significantly affected (291.1 ± 35.8 off vs. 248.4 ± 35.3 on PPI, p=0.12). In the SAP- patients, the numbers of swallows (802.2 ± 92.6 off vs. 814.4 ± 68.9 on PPI, p=0.76) and air swallows (236.4 ± 44.6 off vs. 194.1 ± 34.3 on PPI, p=0.11) were not influenced by the PPI therapy. PPI therapy reduces the number of swallows and mixed liquid-gas reflux episodes in patients with a positive SAP, but not in those with a negative SAP. This finding supports the hypothesis that the increased incidence of swallows and mixed liquid-gas and pure gas reflux in GERD is brought about by responses to perceived reflux events.

Differences in acidity of the refluxate during TLESRs between healthy subjects and gastroesophageal reflux disease patients

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Standard pH metry to detect gastroesophageal reflux (GER) is performed 5cm above the lower esophageal sphincter (LES). However, esophageal damage and the risk to develop esophageal cancer may be determined by the degree of acid exposure immediately above or at the level of the squamocolumnar junction (SCJ). Knowledge on acid exposure at the level of the SCJ is limited. Therefore, we measured the occurrence of GER at the level of the SCJ using combined pH metry / impedance in healthy volunteers (HV) and GERD patients with and without hiatal hernia (HH). 10 HV (22-53, 7 M) without HH and 22 GERD patients (19-66, 12M, 12 patients with HH<3 (smallHH), 10 patients with a HH≥3cm (largeHH)) were studied in a 2hrs postprandial period. Manometry and impedance were performed using a water perfused sleeve catheter and 5 impedance sensors with the most distal sensor 3cm above the upper margin of the LES. In addition, pH metry was performed using a 2 channel pH catheter (sensors 4cm apart) with 1 sensor located 2cm above the upper border of the LES and 1 sensor in the LES. The number of TLESRs measured in the 2hrs period was comparable in HV and GERD patients (HV: 12.6±1.4; smallHH: 11.4±1.0; largeHH: 10.9±0.9, ns). The percentage of TLESRs associated with reflux (acid and non-acid) was comparable in HV and GERD patients (HV: 88±5%; smallHH: 90±3%; largeHH: 92±3%, ns). The occurrence of acid reflux however differed significantly between patients and HV. In HV, 60±7% of the TLESRs was accompanied by acid reflux detected at the level of the LES, compared to 73±5% (p=0.18) and 90±3% (p=0.02) in GERD patients with a small and large HH, respectively. At 2cm above the upper margin of the LES, acid reflux was only detected in 17±7% of the TLESRs in HV. In contrast, acid reflux was significantly more frequent during TLESRs in GERD patients (smallHH: 47±9%, p=0.008; largeHH: 58±9%, p=0.005).
Conclusion: the majority of TLESRs is accompanied by gastroesophageal reflux (acid + non-acid) in GERD patients and HV. At the level of the LES, the refluxate is mainly acidic in both groups, but becomes non-acidic 2cm above the LES in HV. In contrast, the refluxate in GERD patients remains acidic in the distal esophagus, suggesting differences in buffering capacity of the esophageal mucosa/saliva, the composition of the refluxate, or the dynamics of the acid pocket between patients and HV. Further studies are required to identify the underlying mechanisms of this interesting finding.

Scintigraphic imaging of the postprandial acid pocket in healthy subjects and gastroesophageal reflux disease patients

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Gastroesophageal (GER) reflux occurs twice as much during transient lower esophageal sphincter relaxations (TLESR) in GERD patients compared to healthy volunteers (HV). However, the mechanisms underlying this difference remain unclear. As the localisation of the postprandial acid pocket could be an important determinant for reflux to occur, we assessed this parameter in HV and GERD patients with and without hiatal hernia (HH), using a previously developed method allowing continuous visualisation of the acid pocket. 10 HV (22-53, 7M) without HH and 22 GERD patients (19-66, 12M, 12 patients with HH<3 (smallHH), 10 patients with a HH≥3cm (largeHH) were studied. During gastroscopy, the upper (ie. squamocolumnar junction, SCJ) and lower level of the HH were marked with radio-labelled clips. To visualize the acid pocket, 450 MBq 99mTc-pertechnetate was injected iv and images were acquired up to 2hrs postprandial. In addition, subjects underwent pHmetry using a 4 channel pH probe with the most proximal sensor 2cm above the LES. At 15, 30, 45, 60, 90 and 120 min after a meal, pull through was performed to double check the position of the acid pocket. In HV, the acid pocket was visualised from 15-120min after meal intake with a mean length of 2.7±0.1cm. In patients, the length of the acid pocket was significantly increased, especially in HH patients (smallHH: 3.5±0.2cm; largeHH: 5.8±0.3cm, p<0.001). Pull through measurements showed comparable findings (HV: 2.7±0.2cm; smallHH: 3.4±0.2cm: largeHH: 5.0±0.4cm, p<0.001). The distance between the upper border of the acid pocket and the SCJ did not differ between HV and smallHH and was located distal to the SCJ (HV: 1.8±0.2cm; smallHH: 1.2±0.2cm; p=0.28). However, in largeHH, the acid pocket extended 1.1±0.3cm above the SCJ during the entire postprandial period (p<0.001). In HV, 2.6±1.3 acid reflux episodes occurred 2cm above the LES. In patients, acid reflux rate was significantly increased (smallHH: 6.1±1.1, p=0.01; largeHH: 10.8±2.3, p=0.005). The postprandial acid pocket is significantly larger in GERD patients compared to HV. In patients with a large HH, the acid pocket is located within the hiatal sac and extends above the SCJ. In line with this, acid reflux occurs significantly more in GERD patients, especially in those with a large HH. These findings illustrate that the postprandial acid pocket differs in GERD patients compared to HV and may play an important role in the occurrence of gastroesophageal reflux.

Vagal nerve activity stimulates endo- and phagocytosis in intestinal and peritoneal macrophages via nicotinic acetylcholine receptor α4/β2 in mice.

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We previously showed that vagal nerve-derived acetylcholine blunts macrophage inflammatory cytokine production. As macrophage's primary function is phagocytosis, we hypothesized here that enhanced vagal nerve efferent activity may also affect macrophage capacity to take up antigens by endo- or phagocytosis.
nAChR expression was measured by RT-PCR in Mf4/4 spleen macrophages or primary peritoneal macrophages. NF-kB activity was measured in Zymosan (Sigma) stimulated cells (5particles/cell) after transfection of consensus kB luciferase constructs (Clontech). Phago- and endocytosis of labeled particles was assayed for 10 min and analyzed by FACS. Intracellular calcium signaling was assessed in FURA2 loaded macrophages. To assess vagal modulation of phagocytosis, mice were injected i.p. with 2*10exp7 heat-killed ecoli feacum bateria, after which the right cervical vagus nerve was electrically stimulated for 5min at 5Hz frequency. Uptake was assessed histologically 3 hrs thereafter.
nAChR beta2/alpha4 was expressed in Mf4/4 and primary peritoneal macrophages, while alpha7 transcripts were below detection level in these cells. In macrophages, nAChR activation by nicotine or acetylcholine reduces NF-kB transcriptional activity and pro-inflammatory cytokine production induced by Zymosan (down to 35% of control; $p<0.05$). On the other hand, nAChR activation by nicotine enhanced phagocytosis of opsonised or non-opsonised particles. Nicotine treatment (0-1000nM) enhances phagocytosis of Zymosan (2.0-fold;$p<0.05$), opsonised sheep red blood cells (1.8-fold;$p<0.05$), and endo-cytosis of acylated LDL (1.9-fold;$p<0.05$) in a dose-response fashion in Mf4/4 and peritoneal macrophages. Although the phagocytotic process requires Ca2+, the increase in phagocytosis by nicotine did not require Ca2+ influx nor did nicotine elicit intracellular Ca2+ release as measured by FURA2 probes. In conjunction with the enhanced uptake in vitro, electrical stimulation of the efferent vagal nerve led to increased uptake of i.p. injected heat-killed ecoli by phagocytes residing in the intestinal mucosa.
Conclusions: we conclude that vagal nerve-derived ACh stimulates phago-and endocytosis of intestinal and spleen macrophages while blunting their inflammatory response. The enhanced phagocytosis by nicotine involves a Ca2+ independent path-way. Our results imply that enhanced vagal nerve activity (i.e. following food intake) stimulates clearance of pathogens by mucosal phagocytes in the intestine.

The safety of pneumatic balloon dilatation in achalasia patients: results from a large cohort study

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Background and aim Pneumatic balloon dilatation (PD) of the lower esophageal sphincter (LES) is a regular treatment modality in achalasia patients. Esophageal perforation is the most serious adverse event among the complications related to PD. The incidence of PD complications in this population is insufficiently known, which may limit the use of PD. Aim of this study therefore was to evaluate the complications related to PD in a large cohort of patients with primary achalasia. Methods Between 1974 and 2006, 336 patients with primary achalasia (M/F 161/175, mean age 49.9±1.2 years) were treated with PD. Baseline PD was performed on 3 consecutive days with balloons of either the same or incremental diameter (30, 35 and 40 mm). Complications related to PD and clinical outcome were assessed.Results From a total of 985 PDs performed in 336 patients, 40 (4.1%) procedures with one or more complications related to PD were identified. The most common complications were pain (3.1%) and fever (1.6%). In 13 (1.3%) of the 985 PDs a esophageal perforation occurred. In 3 (23%) patients perforation occurred during the first dilatation, in 8 (62%) patients during the second, and in 2 (15%) patients during the third dilatation. Perforation occurred at balloon diameter of 30 mm in 1 patient (1% of dilatations at this diameter), 35 mm in 7 patients (6% of dilatations at this diameter) and 40 mm in 5 patients (0.7% of dilatations at this diameter). In 2 patients surgical treatment was required: 1 patient underwent primary repair of the esophagus and 1 patient esophageal resection. An esophageal stent was temporally placed in 1 patient. The other 10 patients underwent conservative treatment with antibiotics and no oral feeding. There was no mortality and all patients had a good clinical outcome and were discharged 17±7.9 days after the perforation. Perforations were associated with female sex and complete obliteration of the balloon's waist during PD ($p<0.001$). No differences between patients with and without perforation were found regarding age, LES pressure on manometry before PD and duration of achalasia symptoms prior to diagnosis.
Conclusion In patients with primary achalasia PD is a safe treatment modality with a low esophageal perforation risk. Perforations were more common in women and in patients showing complete obliteration of the balloon's waist during PD. Most perforations can be treated conservatively.

No effect of gut-directed hypnotherapy on rectal sensitivity in children with functional abdominal pain and irritable bowel syndrome

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Gut-directed hypnotherapy has recently been shown to be highly effective in treating children with functional abdominal pain (FAP) and irritable bowel syndrome (IBS). This study was conducted to determine to what extend this treatment success is due to improvement of rectal sensitivity.
46 patients (8-18 years) with FAP (n=28) and IBS (n=18), according to the ROME II criteria, were randomized to either 12 weeks of standard medical therapy (SMT) or gut-directed hypnotherapy (HT). To assess rectal sensitivity a pressure-controlled intermittent distension protocol (barostat) was performed before and after therapy. Rectal hypersensitivity (RHS) was defined as pain thresholds ≤ 9 mmHg above minimal distension pressure.
RHS was found in 6/23 (27%) patients in both treatment groups at baseline. No difference in rectal pain thresholds was identified between IBS and FAP patients (p=0.87). After treatment, clinical remission (> 80% improvement in abdominal pain scores) was seen in 13% SMT patients compared to 57% HT patients (p=0.005). Similar treatment outcomes were found in patients with and without RHS (p=0.35). Rectal pain thresholds had not changed significantly after treatment in both groups. In SMT patients pain thresholds changed from 16.6 (7.8) mmHg (mean (SD)) at baseline to 18.6 (8.5) mmHg at 12 weeks (p=0.10) and in HT patients from 20.7 (11.5) mmHg to 22.5 (10.1) mmHg (p=0.10). Subgroup analysis in patients with RHS showed a significant increase in pain thresholds from 7.0 (2.5) mmHg to 15.5 (9.9) mmHg in SMT patients (p=0.02) and from 7.5 (1.6) mmHg to 25.5 (12.8) mmHg in HT patients (p=0.03), but this increase in pain thresholds was not significant different between treatment groups (p=0.09) and not related to treatment success (p=0.60).
Conclusion: in this small patient sample, clinical success achieved with HT can not be explained by improvement of rectal sensitivity. In contrast to earlier findings hypersensitivity of the rectum was found in a minority of children with IBS. Further studies are needed to confirm our finding that no association exists between rectal barostat findings and clinical symptoms in children with pain related functional gastrointestinal disorders.

CT angiography and 24 hours tonometry: a novel and useful approach in the diagnosis of chronic gastrointestinal ischemia

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The combination of duplex ultrasound, followed by conventional digital subtraction angiography of the abdominal arteries and gastric exercise tonometry (GET) is the established approach for patients suspected of chronic gastrointestinal ischemia (CGI). GET is cumbersome and impossible to perform in a considerable proportion of patients. Recently, 24 hour gastric and jejunal tonometry (24hrTM) and computed tomography angiography (CTA) were introduced as possible alternative diagnostic methods. 24hrTM proved to be as accurate as GET for detection of CGI, while being less cumbersome and performable in every patient suspected of CGI. CTA seems a promising, minimally invasive technique to detect and define abdominal artery stenoses. We challenged the use of 24hrTM in combination with CTA as an alternative approach to evaluate patients suspected of CGI.
Patients referred for evaluation of possible CGI were prospectively evaluated using CTA and 24hrTM. All patients were discussed in a multidisciplinary team (consisting of a vascular surgeon, interventional radiologist and gastroenterologist) and a consensus diagnosis was made. Patients with abdominal arterial stenosis on CTA and abnormal 24hrTM (i.e. GI ischemia) were advised to undergo treatment. The definitive diagnosis CGI was made after persistent symptom relief on follow-up.
Forty patients were enrolled: M/F 9/31, mean age 59 (20-87) yrs: normal 24hrTM+CTA (13 patients), normal 24hrTM+abnormal CTA (3), abnormal 24hrTM+normal CTA (4) and 20 patients with abnormal 24hrTM+CTA (i.e. consensus diagnosis CGI). Of the 20 CGI patients 11 patients had 1-vessel, 8 patients 2-vessel and 1 patient had 3-vessel stenosis. In the CGI patients the presenting symptoms were weight loss (80%), postprandial pain (75%) and diarrhea (20%). Treatment was performed in 18 patients (90%): PTA and stent placement in 13 and 5 patients had surgical revascularization. After a mean follow-up of 9 months (range 1-24), 89% of patients were free of symptoms. Two patients were treated conservatively. The PPV of the consensus diagnosis is 89% with a NPV of 91%. Conclusions: The combination of 24hrTM and CTA provide a minimally invasive, reliable alternative diagnostic approach in patients suspected for CGI. This approach seems very useful in clinical practice and the main outcomes, in particular the association between the diagnostic test results and the outcome of treatment, are in line with earlier reports using the established approach.

Magnetic resonance imaging of the lumbosacral spine in children with chronic constipation and functional non-retentive fecal incontinence: a prospective study *

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Background: In a retrospective study magnetic resonance imaging (MRI) of the spine demonstrated an incidence of 9% of spinal abnormalities in children with intractable constipation. In asymptomatic adults, incidental spinal abnormalities such as lipomas are found in 1.5-5%. Aim: To prospectively determine the prevalence of lumbosacral spine abnormalities in children with constipation or functional non-retentive fecal incontinence (FNRFI). Methods: Pediatric patients aged 6-18 years referred for functional constipation or FNRFI (ROME III criteria) to our tertiary center were included. A pediatric neurologist performed complete neurological examination, with special attention for the lumbo-sacral spine region. MRI of the lumbo-sacral spine was performed. The neurologist was informed about the clinical status, but not about the MRI outcome. Results: Seventy four patients with constipation were included (46% male; age (±SD) 11.2 (±2.9) years). Mean symptom duration was 41.7 (±32.1) months. In none of patients abnormalities were found on neurological examination. One occult spina bifida and one terminal filum lipoma were seen on MRI. Both constipated patients had no urinary incontinence at intake. Defecation frequency normalized and fecal incontinence disappeared after medical and behavioral treatment in both children.Thirteen children with FNRFI were included (53.8% male; age 9.9 (±1.21) years) with mean symptom duration of 34.0 (±35.3) months. Again, no abnormalities were found on neurological examination. MRI showed a terminal filum lipoma in one child. This child had urinary incontinence at intake. Fecal and urinary incontinence disappeared after behavioral treatment. No neurosurgical treatment was performed in those children due to clinical improvement with conventional therapy. Conclusion: Spinal cord abnormalities were found in 2.7% of constipated children and 7.7% of FNRFI patients. Overall, terminal filum lipomas were found in 2.3%. It remains unclear whether the abnormalities found, play a role in the pathophysiology of constipation and/or FNRFI. More children are needed to reveal the true prevalence of spinal cord abnormalities in these children.

Human intestinal ischemia-reperfusion induced cell damage is rapidly reversed by shedding of injured enterocytes.

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Intestinal ischemia-reperfusion (IR) is an important factor contributing to the development of intestinal complications. Although intestinal IR is studied in animals, data on human intestinal IR are scarce. The aim of this study was to clarify sequelae of human intestinal IR, a phenomenon involved in eg necrotizing enterocolitis, small bowel transplantation and a disease entity itself with high mortality rates, using a newly developed human experimental model.In 24 patients undergoing pancreatico-duodenectomy we took advantage of the fact that in this procedure variable length of jejunum is removed. This enabled us to study IR induced cell damage in a harmless human jejunal IR model. Isolated jejunum (5 cm) was subjected to 30 minutes ischemia followed by reperfusion. Intestinal Fatty Acid Binding Protein (I-FABP) arteriovenous concentration differences were measured before and after ischemia to assess epithelial cell damage. I-FABP is a small cytosolic protein constitutively present in mature enterocytes and released upon cell injury. Tissue sections were collected after ischemia and at 25, 60 and 120 minutes reperfusion and stained with H&E, I-FABP and the apoptosis marker M30, detecting the Asp396 caspase cleavage site in cytokeratin 18. Bonferroni's test was used to compare I-FABP differences.Mean (SEM) arteriovenous concentration gradients of I-FABP across studied jejunum revealed rapid epithelial cell damage. I-FABP release significantly increased from 221 (44) pg/ml before ischemia towards 3505 (514) pg/ml immediately after ischemia ($p<0.001$) and declined gradually to 1226 (165) pg/ml after 2 hours reperfusion ($p<0.001$). Directly after ischemia the intestinal epithelial lining was microscopically normal, while subepithelial spaces appeared at the villus tip. However, after 25 minutes reperfusion M30 immunostaining was observed at the villus tip accompanied by shedding of mature epithelial cells into the lumen and I-FABP staining loss. Interestingly, within 60 minutes reperfusion the epithelial barrier resealed, while debris of apoptotic, shedded epithelial cells was observed in the lumen, M30 immunoreactivity was absent in intact epithelium.This is the first human study to clarify intestinal IR induced cell damage and its direct consequences, revealing a unique, endogenous clearing mechanism for injured enterocytes. Damaged enterocytes rapidly detach by apoptosis into the lumen, which is quickly followed by repair of the epithelial continuity.

Mannose-binding lectin null alleles are associated with preserved epithelial cell integrity following intestinal ischemia reperfusion in man.

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Mannose-binding lectin (MBL) is an initiating complement component of which both function and plasma levels are regulated by frequent polymorphisms in the mbl2 gene. Since MBL causes ischemia reperfusion injury in experimental models, we studied the influence of mbl2 genotypes on the development of cellular damage in a newly developed intestinal ischemia reperfusion model in man.In a Whipple's procedure (Pylorus Preserving Pancreatico-Duodenectomie, PPPD) a variable length of small bowel is resected, providing the opportunity to study ischemia reperfusion induced cell damage in a harmless human IR model of the jejunum. Intestinal Fatty Acid Binding Protein (I-FABP) arteriovenous concentration differences were measured in plasma before and after ischemia to assess epithelial cell damage induced by 30 minutes of ischemia followed by reperfusion. The MBL genotypes of 17 consecutively included individuals were assessed retrospectively using sequence-specific primers, enabling classification according to determinant polymorphisms in the mbl2 gene; A/A, A/O and O/O, where any of the known first exon variations is coded as O. Local ethical approval and informed consent were obtained. Data were analyzed by one-way analysis of variance (ANOVA) and unpaired two-tailed Students T-test.The amount of epithelial cell damage varied significantly between the carriers of different mbl2 genotypes (ANOVA, $p = 0.03$). Homozygous wildtype individuals (A/A, N=7; three women and four men) showed a mean (± SEM) I-FABP release of 4,300 (± 760 pg/ml) at reperfusion. Interestingly, heterozygous (A/O, N=8; four men and four women) and homozygous (O/O, N=2; two women) carriers of variant MBL alleles showed an I-FABP release of only 2,020 (± 670 pg/ml) ($p = 0.04$ compared to A/A) and 240 (± 60 pg/ml) ($p = 0.03$ compared to A/A), respectively. The data were corroborated by histological analysis of tissue samples collected at the end of reperfusion (mean reperfusion time 160 minutes). These pictures show the presence of a large amount of epithelial cellular debris in A/A individuals, whereas lesser debris is observed in A/O and O/O genotype carriers.If confirmed, our data may explain why mutations in the MBL coding sequence have survived selection pressure during human evolution.

Non-invasive evaluation of intestinal damage in celiac disease using I-FABP and L-FABP *

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In the clinical management of celiac disease, new non-invasive tools for evaluation of intestinal damage are needed for diagnosis and follow-up of diet effects. Fatty acid binding proteins (FABPs) are potentially useful for this purpose since these are small cytosolic proteins present in enterocytes and sensitive markers for intestinal mucosal damage. First, the distribution and microscopic localization of FABPs in the healthy human intestine was examined. Second, levels of circulating FABPs were measured in patients with celiac disease before and after introducing a gluten-free diet (GFD) and in healthy controls. The distribution and microscopic localization of FABPs in normal human intestinal tissue was assessed with surgical intestinal specimens of 39 patients. Circulating levels of Intestinal (I)-FABP and Liver (L)-FABP were determined using ELISA, in 26 healthy volunteers and 13 patients with biopsy proven celiac disease. Ten of these patients were re-evaluated within one year after starting GFD. Results were analyzed with the Mann Whitney U test and receiver operator characteristics (ROC). I- and L-FABP are predominantly present in the small intestine, mainly the jejunum. Moreover, FABPs are expressed in cells on the upper part of the villi, the initial site of destruction in celiac disease. Circulating levels of FABPs are significantly elevated in untreated patients with biopsy proven celiac disease compared to healthy controls (I-FABP: 784.7 pg/ml vs. 172.7 pg/ml, $p<0.001$; L-FABP: 48.4 ng/ml vs. 10.4 ng/ml, $p<0.001$). The area under the ROC curve of I-FABP and L-FABP is 0.91 and 0.87, respectively. The cut-off values, evaluated with ROC for I-FABP (405 pg/mL) and L-FABP (18 ng/mL), show both high sensitivity (96%, 97%) and specificity (86%, 79%), yielding high positive likelihood ratios (LRs) of 6.73 and 4.50 and low negative LRs of 0.04 and 0.04, respectively. In response to GFD the I- and L-FABP concentrations normalize. This study strongly suggests that FABPs can be used as a non-invasive method for assessment of intestinal damage in celiac disease. Besides a role in the diagnosis of celiac disease, FABPs potentially enable non-invasive monitoring of the GFD.

Intestinal permeability and inflammatory balance reflected by LPS binding protein and Angiopoietin 1 and 2, in brain dead and living donors.

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In this study we investigated the relation between the brain dead (BD) status of the donor and the effects on intestinal permeability and the pro- and anti-inflammatory balance. Previously, we found in our animal model that BD induces intestinal inflammation, as evidenced by accumulation of granulocytes and upregulation of adhesion molecules. Subsequently, we found an increased intestinal permeability after BD, as measured by elevated serum lipopolisacharide (LPS), LPS Binding Protein (LBP), an acute phase protein associated with gram–negative sepsis. We also found upregulation of intestinal gene expression of Angiopoietin 2 (ANG2), but not ANG1. The agonists ANG1 (anti-inflammatory) and ANG2 (pro-inflammatory) have a key regulatory role in regulating vascular integrity and quiescence.
To test the clinical relevance of our animal data, we measured LBP, ANG1 and ANG2 in serum from 20 human multi-organ donors and 20 living kidney donors. Serum samples were obtained during organ retrieval procedures from BD organ donors from 2004 to 2006. At two time points: immediately after the determination of BD (T0) and just before organ retrieval (T1). Serum from living kidney donors was used as a control. Serum LBP as well as ANG1 and 2 were measured by ELISA. In the serum of BD donors we found markedly higher LBP, ANG1 and ANG2 values at T0.

	Living donor		Brain dead donor		
	T0	T1	T0	T1	
LBP	11 ± 1	9 ± 1	32 ± 2[a]	26 ± 2[a]	µg/ml
ANG1	197 ± 32	156 ± 45	360 ± 57[a]	158 ± 18[b]	pg/ml
ANG2	295 ± 30	340±175	978 ± 159[a]	873 ± 177[a]	pg/ml

a significant different $p<0.05$ from living, b significant different $p<0.05$ from T0

Interestingly, the protective ANG1 response decreased significantly at the end of the BD period, suggesting a shift in of the inflammatory balance in the direction of activation.

In conclusion, in accordance with our animal data, we found an increase of intestinal permeability in the BD donors. Furthermore, we showed a shift of the inflammatory balance towards more inflammation. We therefore postulate that an increased intestinal permeability will provoke toxic compounds release from the intestine, which might enhance the inflammatory state. This may contribute to progressive organ dysfunction observed in BD donors.

Mast cell induced bacterial translocation in the pathogenesis of post-operative ileus studied in a mouse model

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Introduction: mast cell activation and inflammation of the bowel wall resulting from intestinal manipulation during surgery plays a crucial role in the pathogenesis of postoperative ileus (POI) in rodent models and human patients. Mast cell degranulation has been suggested to reduce intestinal barrier integrity, allowing luminal antigens to pass the epithelial barrier and activate mucosal immune cells. Given the importance of mast cells in the pathogenesis of POI, we investigated the role of mast cell induced intestinal barrier dysfunction in our mouse model of POI. In conjunction, we assessed whether IM induced muscular inflammation depends on bacterial recognition.
Methods: experiments were performed in WT, TLR4-/- and Myd88-/- mice (C57BL/6), and mast cell deficient Kit/Kitv mice. Mice underwent laparotomy (L) or L followed by a gentle manipulation of the bowel (IM) for 5 minutes. Twenty four hours after surgery, mice were killed and intestinal inflammation was expressed as the number of MPO-positive cells per mm^2 in the muscularis externa of the small intestine. Bacterial translocation following surgery was determined by plating homogenized mesenteric lymph nodes onto blood agar plates and counting of the colony forming units (CFU) forty eight hours after incubation at 37oC.
Results: IM induced a significant increase in the number of bacteria cultured from the mesenteric lymph node (L aerobic: 0.2±0.2; IM aerobic: 45.7±15.8; L anaerobic: 0.2±0.2; IM anaerobic: 51.6±19.9 CFU/mg). The number of bacteria translocated following IM did not differ in WT, TLR4-/- and MyD88-/- mice. The impaired barrier was dependent on mast cell activity, as bacterial translocation was significantly reduced in mast cell deficient mice (IM aerobic: 0.4±0.2; IM anaerobic: 0.3±0.2 CFU/mg). Neutrophil influx following IM (L: 20.8±10.1 vs. IM: 219.3±24.4 cells/mm^2) was significantly reduced in mice deficient in mast cells (IM Kit/Kitv: 112.7±59.3 cells/mm^2) and in mice deficient in Myd88 signalling (IM Myd88-/-:79.9 ± 17.5 cells/mm^2) but was not different in TLR4-/- mice (IM: 330.4±68.2 cells/mm^2).
Conclusions: IM during surgery induces bacterial translocation and inflammation of the manipulated bowel wall, which both depend on mast cell activation. However, as Myd88 but not TLR4 dependent signalling mediates the inflammatory response to IM, despite a similar bacterial load, bacterial recognition is unlikely to be a crucial factor in IM induced inflammation.

The composition of the dominant faecal microbiota in COPD patient receiving multispecies probiotics during and after antibiotic intake

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Healthy individuals have a unique intestinal microbiota (i.e. genetic fingerprint) that is relatively stable in time. Antibiotic intake is known to cause short-term disturbances in the composition of this microbiota and recently medium and long–term disturbances in specific bacterial populations have been described. Probiotics can affect the composition of the intestinal microbiota beneficially and may restore such a disturbance. However data in chronically ill patients with a possibly disturbed immune system and microbiota are very limited. The disturbance of the dominant faecal microbiota by antibiotics and the possible restoration by a multispecies probiotic was studied in patients with chronic obstructive pulmonary disease (COPD) treated with antibiotics for a respiratory tract infection. Five gram of a multispecies probiotic (5 lactobacilli, 3 bifidobacteria, 1 enterococcus) (10^9 cfu/gr) or placebo was given twice daily for two weeks starting simultaneously with antibiotic intake. From each patient fresh faecal samples were collected at day 0, 7, 14 and 63. Changes in the composition of the dominant faecal microbiota were determined by denaturating gradient gel electrophoresis (DGGE) of PCR-amplified V6-V8 regions of 16S rRNA genes and expressed as “similarity indices” (SI) between two samples and number of bands within each sample. Thirty patients completed the study (17 in the probiotic, mean age 60 yrs (13.3), and 13 in the placebo group, mean age 63 yrs (7.4)). Patients had a history of extensive antibiotic use (1-7 treatments in previous year). SIs were high and remained stable during and after antibiotic treatment, ranging from 84-94%. No effect of probiotic intake was observed. Mean band number was also stable over time, ranging from 14.4-15.4 bands. Conclusion: In this COPD population, no effect of antibiotics, and subsequently of probiotic intake, could be observed on the dominant faecal microbiota. Overall band number was lower and SIs were high and more stable compared to previous findings in healthy volunteers suggesting narrowing of the diversity of the dominant faecal microbiota due to extensive antibiotic use. This observation may have contributed to the lack of effect by probiotic and antibiotic intake in this COPD population.

Mastocytic enterocolitis: a new identity in patients with chronic diarrhoea?

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In gastrointestinal practice, we are often confronted with patients having chronic diarrhoea, defined as loose stools for more than 4 weeks and faecal weight ≥ 200 grams/24 hours. Sometimes the cause of the diarrhoea remains unknown. Jakate et al introduced a novel cause of chronic diarrhoea, termed mastocytic enterocolitis, a condition in which there is an increase of mucosal mast cells. This is defined as ≥ 20 mast cells per high power field(HPF), as demonstrated by immunohistochemistry staining for mast cell tryptase(MCT). The aim of this study is to assess if the amount of mucosal mast cells in duodenal and colon biopsies of patients with chronic diarrhoea is increased and if the presence of "mastocytic enterocolitis" could be correlated with chronic diarrhoea.
We included all normal duodenal and colon biopsies taken from January 2005 until November 2006 in our hospital in two groups: one group with chronic diarrhoea(group I, n=30) and a control group without diarrhoea in which biopsies were taken for iron deficiency anaemia, diverticulitis or amyloidosis(group II, n=60). All biopsies were randomly and blind assessed by the pathologist after staining with monoclonal mouse anti-human MCT for mucosal mast cells per high power field(HPF) and per mm2.
Overall, group I had a mean amount of 171 and group II 179 mucosal mast cells/mm2 (p=0.332). Looking at only duodenal biopsies group I(n=18) had 196 and group II(n=45) had 229 mast cells/mm2(p=0.179) and for colon biopsies group I(n=12) 133 and group II(n=15) 103 mast cells/mm2(p=0.129). We also compared the groups meeting the criteria as introduced by Jakate et al. Assessing colon biopsies, there were no patients with ≥ 20 mast cells per HPF. Looking only at duodenal biopsies, there were 3(16,7%) patients in group I and 4(8,9%) patients in group II meeting these criteria(p=0.397).
This study showed that there was no significant higher amount of mast cell count in patients with chronic diarrhoea. In addition we did not find significantly more individuals meeting the definition for mastocytic enterocolitis in the patient group than in the control group. Our study therefore does not support the concept that mastocytic enterocolitis is an important novel diagnosis and cause of chronic diarrhoea.

Pancreatic function after surgery for painful chronic pancreatitis

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Background: Surgery for chronic pancreatitis is indicated to treat intractable pain, but may also delay progression of disease. The aim of the present study was to evaluate long-term endo- and exocrine pancreatic function in patients who underwent various surgical procedures for painful chronic pancreatitis and to review current management of patients with pancreatic insufficiency. Methods: Between Jan 1992-Mar 2006 223 consecutive patients underwent surgery: 146 drainage (pancreaticojejunostomy), 40 drainage/resection (35 Frey/Beger; 5 pancreatoduodenectomy), 37 tail resection. Patient characteristics and operative morbidity/mortality were analyzed. Patients were identified by contacting general practitioners, pancreatic endo- and exocrine function was determined at propectively scheduled outpatient clinic visits.Results: Mean age was 48 years, male gender 61%, surgery-related morbidity 22%, perioperative mortality 1%. Median follow-up was 63 months, 44 patients had died (40% disease related), 137 of the remaining 179 patients (77%) were available for function evaluation. Preoperatively 45% of patients used pancreatic enzyme suppletion (NS between procedures). At follow-up exocrine insufficiency (fecal elastase <200 mg/g) was present in 77% (91/119) of patients with type of procedure as predisposing factor (drainage vs. tail OR 3.7; 95% c.i. 1.3-10.2; drainage/resection vs. tail OR 7.3; 95% c.i. 1.3-39.9; drainage vs. drainage/resection NS). After surgery, body weight increased in 66% of patients, was stable in 6%, and decreased in 28%. Twenty-five patients (18%) were endocrine insufficient at the time of surgery and 53 of the remaining patients (39%) developed endocrine insufficiency afterwards. Thirty-seven per cent (34/91) of exocrine insufficient patients were thus far unrecognized and received no medication, as well as 10% (8/77) of endocrine insufficient patients. Only 18% of patients that received antidiabetic medication were adequately treated (HbA1c <7%).
Conclusion: After surgery for chronic pancreatitis, three-quarter of patients suffer from pancreatic exocrine insufficiency on the long term, for which the type of procedure is a significant prognostic factor. Overall, recognition and medical treatment for exo- and endocrine insufficiency after surgery appears to be inadequate and this observation should prompt for a closer and more attentive follow-up scheme in these patients.

Complications after Endoscopic Retrograde Cholangiopancreatography: risk factors for pancreatitis, cholangitis and hemorrhage

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Various studies have evaluated possible risk factors for complications after Endoscopic Retrograde Cholangiopancreatography (ERCP) but their relative importance is unknown. The objective of this study was to examine risk factors for post-ERCP complications in order to help clinicians identify patients eligible for outpatient ERCP. Potential risk factors were identified from literature. In a single-center retrospective analysis (2001-2006), risk factors were examined in a multivariable logistic regression analysis. All risk factors were externally validated in a single-center prospective database (2006-2007). From 13 reviewed studies, 9 risk factors for post-ERCP pancreatitis were identified: younger age (OR:2.2), difficult cannulation (OR:3.4), gender (OR:1.8), pancreatic sphincterotomy (OR:1.3), previous pancreatitis (OR:3.6), precut sphincterotomy (OR:2.4), sphincter of Oddi dysfunction (OR:3.6), multiple pancreatic contrast injections (OR:1.6) and small bile duct (OR:1.5). The retrospective database included 1372 ERCPs performed in 588 patients (58% male, mean age 56.5+ 17) and 159 (12%) complications occurred after ERCP. Pancreatitis was observed after 39 (3%) procedures, cholangitis after 34 (3%), perforation during 6 (0.4%) and hemorrhage after 38 (3%). Multivariable analysis revealed 4 significant risk factors for complications after ERCP: cholangitis at presentation (OR:0.5, p=0.03), sphincterotomy (OR:2.7, p<0.01), precut sphincterotomy (OR:2.6, p<0.01) and ampullary resection (OR:6.1, p<0.02). Significant risk factors for post-ERCP pancreatitis were primary sclerosing cholangitis (OR:2.9, p<0.01) and age<60 yrs (OR:3.6, p=0.04). Placement of a self expandable metal stent (OR:3.6, p=0.02) was a significant risk factor for post-ERCP cholangitis whereas precut sphincterotomy (OR:11.0, p<0.01), sphincterotomy (OR:9.1, p<0.01) and ampullary resection (OR:61.6, p<0.01) were significant risk factors for hemorrhage. The prospective database included 178 ERCPs performed in 140 patients (61% male, mean age 59+12). From these, 24 (13%) complications were recorded, with similar effects of risk factors for post-ERCP complications.Conclusion: Our results further contribute to the assessment of patient- and procedure-related factors that predict the development of complication after ERCP. Further research is however needed to identify patients with a pre-defined low risk for complications, who may therefore safely be eligible for outpatient ERCP.

Feasibility of transgastric and transcolonic NOTES peritoneoscopy combined with intraperitoneal endoscopic ultrasonography

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Preoperative detection of peritoneal and small metastases can be difficult. Laparoscopy and laparoscopic ultrasonography (LUS) are frequently required to exclude metastases prior to resection. LUS has additional value over laparoscopy alone in selected patient groups. NOTES peritoneoscopy may be a future alternative to laparoscopy. Until now there have been no reports of intraperitoneal endoscopic ultrasonography (iEUS) in NOTES. Primary aim was to assess feasibility of transluminal iEUS in a porcine model. We evaluated the transgastric (TG) as well as a transcolonic (TC) approach.We performed 12 acute experiments on six 35-40 kg pigs under general anesthesia. Randomisation was performed to determine order of approach (TG or TC). Previous to access, 2 T-tags were placed to facilitate closure. Gastric access was created by needle knife puncture followed by dilatation with 18 mm CRE balloon. Colonic access was done by a 3mm colotomy using a needle knife followed by manoeuvring the endoscope through the colonic wall. Systematic peritoneoscopy was performed according to a pre-assessed list of locations. Locations included: peritoneum, diaphragm, surface of liver, hepatoduodenal ligament, omentum, anterior stomach and pelvis. For each visualized location 1 point was scored and 1 point added if touched as well, leading to a maximum score of 24 points. Subsequently, the endoscope was exchanged for linear EUS-scope (GF-UCT140, Olympus Medical Systems). The estimated percentage of visualization of different parts of the liver was recorded (0: not visible; 1: 30%; 2: 60%; 3: 100%; maximum score: 12 points). After withdrawal the protocol was repeated using the second natural orifice. The gastrotomy and colotomy were closed using multiple T-tags. Access was achieved without difficulties at all 12 sites. Peritoneoscopy via the TG approach resulted in a median of 23 points (range 20-24), via the TC approach the maximum of 24 points was recorded in all pigs. Via the TG approach it was not possible to adequately visualise (the inferior) liver surface in 3 pigs. TG-iEUS resulted in a median of 11 points (range 6-12) and TC-iEUS in a median of 12 points (range 8-12). Closure was successfully achieved in all pigs. At necropsy 3/ 6 gastrotomies and 4/ 6 colotomies were airtight. Transluminal intraperitoneal EUS is feasible during NOTES peritoneoscopy and results in an adequate ultrasonographic imaging of the liver. The TC approach might be superior to the TG approach.

Endoscopic ultrasonography is a valuable tool with high yield in screening of patients at high-risk patients for pancreatic cancer

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Introduction: Approximately 10-15% of all pancreatic cancers (PC) are familial or hereditary in origin. Despite improvements in imaging technology and surgery, survival remains dismal in patients with PC. We investigated the use of endoscopic ultrasonography (EUS) in screening patients at high-risk of developing PC. Methods: Patients eligible for screening were 1st degree members of families with familial PC as well as mutation carriers of PC prone hereditary syndromes (CDKN2A, PRSS1, STK11, p16) or patients with Peutz-Jeghers syndrome, or mutation carriers of other PC prone hereditary syndromes and clustering (>2 case per family) of PC (BRCA1/2, APC, p53, mismatch repair genes). All patients were asymptomatic and had not undergone EUS before. EUS was performed in 2 academic medical centers.Results: 43 patients (M/F 18/25), age 32 – 75 years, median 51 years, underwent their first screening with EUS. No complications occurred. Genetic background was diverse: 13 patients (8 were known p16 mutation carriers) were from families with FAMMM (familial atypical multiple mole melanoma), 21 patients were from families with familial PC, 3 patients were diagnosed with hereditary pancreatitis (proven mutations in PRSS1 gene), 2 Peutz-Jeghers patients, 3 BRCA1 and 2 BRCA2 mutation carriers with familial clustering of PC and 1 patient with a p53 mutation. In three patients (2 proven FAMMM syndrome, 1 with a BRCA2 mutation) asymptomatic mass lesions (12, 27 and 50 mm) were found in the body and tail of the pancreas. The smallest lesion was not visualised on subsequent CT and MRI. All underwent surgery and were found to have moderately differentiated adenocarcinomas. All lesions were competely removed, however the patients with the larger lesions were found to have N1 disease (5/11 and 1/9 nodes positive). Sidebranch intraductal papillary mucinous neoplasias (IPMN) were found in 7 patients: 3 with FAMMM syndrome, 3 in patients with familial PC (1 multifocal) and 1 in a BCRA1 mutation carrier.
Conclusion: Screening patients at high-risk for PC with EUS is feasible and safe. The incidence of clinically relevant findings is high with 7% asymptomatic cancers and 16% premalignant lesions in this series. Whether screening improves survival remains to be investigated, as is the optimal interval for screening. Sidebranch IPMN is frequently encountered in these patients and may serve as a precancerous marker lesion for early intervention to improve survival.

The diagnostic value of Endoscopic Ultrasonography in patients with a clinical suspicion of malignant pancreatic disease and inconclusive or negative CT scan.

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The use of computer tomography (CT) is preferred as the initial imaging modality in the assessment of patients with clinical suspicion of malignant pancreatic disease. Nevertheless results are not always conclusive. Lesions of the pancreas, which are not detectable on CT images, can often be visualised with endoscopic ultrasound (EUS).The aim of this study is to determine whether EUS with or without fine needle aspiration (FNA) was conclusive in patients with a clinical suspicion of pancreatic malignancy, in whom CT scan was negative or inconclusive.From Feb 2006 till Dec 2007, 89 consecutive patients with a clinical suspicion of malignant pancreatic disease underwent an EUS. Clinical suspicion included abdominal pain and/or painless jaundice and/or weight loss and/or double-duct sign on ERCP or abdominal US. In all patients a multidetector CT scan was performed. CT findings were classified as completely normal (group I), pancreatic lesion but inconclusive for malignancy (group II) or suspicious for malignancy (group III).Out of 89 patients, 34 had a negative (n=11) or inconclusive (n = 23) CT scan. EUS/FNA diagnosed a malignancy in 19/34 patients (12 adenocarcinoma, 2 neuroendocrine tumor, 1 melanoma, 1 cholangiocarcinoma, 1 metastatic lung-carcinoma, 1 IPMN and 1 mucinous cystic tumor). EUS/FNA revealed non-malignant disease in 7/34 cases (5 chronic pancreatitis, 2 pseudocysts). In 3/34 patients no lesions were found. Follow-up of 118 days (range 70 – 154 days) revealed no pancreatic disease. In 1/34 patient EUS was suspect for malignancy, but FNA revealed an autoimmune pancreatitis. In 4/34 patients EUS/ FNA was not able to establish a certain diagnosis. Of these 4 patients 1 had a pancreatic adenocarcinoma at surgery.1 patient had a chronic pancreatitis confirmed by surgery and the 2 other patients did not develop malignant disease during follow-up (91-503 days). EUS/FNA established a correct diagnosis in 30/34 cases (88%). In 19 out of 34 patients with negative or inconclusive CT findings, this diagnosis was conclusive for a pancreatic malignancy.
In conclusion we show that in patients with a clinical suspicion of pancreatic malignancy with negative or inconclusive CT findings, EUS with or without FNA was able to establish a diagnosis in 88% of cases. Complementary to CT the use of EUS-FNA should therefore be considered as an accurate diagnostic modality in the work-up of this complex group of patients.

Endoscopic elastosonography is highly predictive of definite pathology

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Background: Elastosonography is a technique that allows for real-time assessment of elasticity or stiffness of tissue with the aid of conventional ultrasound instruments. In recent years this technique has been developed for endoscopic ultrasound (EUS). Preliminary data show that it might be a useful adjunct to standard morphological criteria to define a lesion without FNA sampling, or to select the optimal location for FNA to increase the yield of tissue sampling. To further elucidate this hypothesis we evaluated the performance of elastosonography in series of patients referred for EUS.Methods: patients were examined by an experienced endosonographer with a linear echo-endoscope (Pentax 3830-UT) combined with a Hitachi EUB-8500 system to allow for realtime processing of elastonography images. Based on these images lesions were classified as either benign, malignant or indeterminate based on previously published data. A definite diagnosis was made on results of either EUS-FNA, surgical pathology or clinical follow-up (at least six months). Results: 41 procedures were performed in the same number of patients (M/F 17/24, age range 26 to 74 yrs): 25 procedures were done for mediastinal pathology, 13 for pancreatic masses, 1 each for rectal, adrenal and submucosal lesions. Elastosonograpy images were interpreted as benign in 10 cases (24%), indeterminate in 7 cases (17%), and malignant in 24 cases (59%). All patients with a benign result on elastosonography had benign disease during follow-up and EUS-FNA. Of the patients with lesions that were judged to be indeterminate on elasto-sonography (n=7; 17%) 5 had benign disease based on clinical follow-up and EUS-FNA whereas 2 had malignant disease based on EUS-FNA. In the group with malignant elastosonography (n=24) one patient had benign disease. A comparison of the elastography classes benign plus indeterminate versus malignant yielded a sensitivity of elastonosonography of 92%, a specificity of 94%, and negative and positive predictive values of respectively 96% and 88%.
Conclusion: Elastosonography is highly sensitive and specific in determining the nature of both mediastinal and pancreatic lesions with excellent positive and negative predictive values and can therefore be helpful in guiding EUS-FNA and patient management.

Contamination of the working channel during endoscopic ultrasonography guided fine needle aspiration of lymph nodes in staging of esophageal cancer results in false positive cytology.

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Endoscopic ultrasonography guided fine needle aspiration (FNA) of celiac lymph nodes in the preoperative staging of esophageal cancer is only possible after passage of the endoscope through the esophageal tumor. The biopsy channel of the echo-endoscope is open and it is conceivable that it is contaminated with malignant cells during tumor passage. The subsequent passage of the cytology needle through the contaminated biopsy channel could therefore result in a false positive FNA. There are no data available concerning the risk of contaminating the cytology needle solely by advancing it through the biopsy channel after the endoscope has passed an esophageal tumor.
Methods: A linear array ultrasound video endoscope (Pentax, EG-3870UTK: biopsy channel diameter 3,8 mm) was used according to a standardized staging protocol for patients with esophageal cancer. Passage of the endoscope through the tumor was a prerequisite. After withdrawal of the endoscope, a complete ex vivo sham FNA procedure was performed. An unused cytology needle (Medi-Globe, 22 G) was advanced through the biopsy channel. Giemsa staining was used for the cytology smears. The cyto-morphological results were scored using a semi quantitative scoring system with 1+ to 3+ for the amount of tumor cells. The same scoring system was used for both squamous and columnar epithelial cells. Results: Ex-vivo sham FNA procedures were performed in 8 patients with esophageal cancer (7 adenocarcinoma ; 1 planocellular carcinoma). We found positive cytology results for malignancy in 6/8 patients (5 pts 2+; 1 pt 1+). In 2 patients we found 1+ and in 6 patients 2+ for squamous cells. In 1 patient 1+ and another patient with 2+ for columnar cells.
Conclusion: An ex-vivo sham FNA procedure resulted in positive cytology in 6 out of 8 patients due to contamination of the endoscope's working channel in the staging of esophageal cancer. Because of the important clinical consequences of false positive EUS-FNA of celiac lymph nodes, we strongly recommend that the Standard Operating Procedure (SOP) of the EUS-FNA of celiac lymph nodes in patients with esophageal cancer are revised.

A randomized prospective trial comparing the cap-technique and multi-band mucosectomy technique for piecemeal endoscopic resection in Barrett's esophagus

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Endoscopic resection (ER) is an important treatment modality for patients with Barrett's esophagus (BE) containing high-grade dysplasia (HGD) or intramucosal cancer (IMC). The most widely used ER technique, the cap-technique (Cap), requires submucosal lifting and prelooping of a snare in the cap, making it technically demanding and laborious when used for piecemeal resections. In addition, a new snare is needed for every resection. The newer multi-band mucosectomy (MBM) technique uses a modified variceal band ligator and requires no submucosal lifting or prelooping of a snare, and multiple resections can be performed with the same snare. Aim of this study was to prospectively compare Cap and MBM for piecemeal ER in BE. In an ongoing randomized trial, patients with BE-HGD/IMC scheduled for piecemeal ER were included. After delineation of the area to be resected, patients were randomized to Cap or MBM. Assessment criteria were: number of resections/procedure, procedure time, time/-resected specimen, complications, maximum diameter of specimens, and costs of disposables.45 pts (35M, median age 70 yrs, median Prague C3M5) were randomized; 22 to Cap, 23 to MBM. Procedure time (29 vs 50 min, p=0.04) and costs (€240 vs €322, p=0.01) were significantly less with MBM compared to Cap. MBM resulted in smaller resection specimens than Cap (18 vs. 21 mm, p<0.001). There were two severe complications: two Cap resections were complicated by a perforation that healed after endoscopic treatment with clips (n=1) or stenting (n=1).
Conclusion: Data of this ongoing randomized study show that piecemeal ER with MBM is faster and cheaper than with the Cap, and may be associated with fewer complications. MBM, however, results in significantly smaller sized and possibly less deep resections and may, therefore, be more suited for resection of flat lesions with a low risk of submucosal invasion, whereas the Cap technique may be preferred for ER of elevated and nodular lesions.

Regulation of the T cell response to the hepatitis C virus

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The importance of the immune response in hepatitis C virus (HCV) infection is underscored by the observation that HCV-specific immunity is weak or absent in chronically infected patients. The mechanisms responsible for this impairment are still largely unknown. Therefore, we aimed to assess the functionality of the HCV-specific T cell response in chronically infected patients, and the possible role of immunosuppressive cytokines and regulatory T cells in suppressing this response. A total of 48 chronic HCV patients visiting our outpatient clinic participated in this study. Peripheral blood was collected and stimulated with a cocktail of HCV proteins or peptides to specifically stimulate CD4+ or CD8+ T cell responses in the PBMC fraction. Proliferative responses and cytokine production were assessed, in the presence or absence of neutralizing antibodies to the IL-10 receptor or to TGF-beta. In addition, assays were performed to assess the effect of regulatory T cells (Treg) on the HCV-specific immune response. A weak HCV-specific CD4+ T cell proliferation was observed in only 5 of 48 patients. Also, cytokines (IFN-γ & IL-2) induced upon stimulation with HCV proteins were only detected in a minority of patients. To determine if the HCV-specific CD4+ T cell response was suppressed in these patients, Treg were depleted from PBMC in a subset of patients, resulting in enhanced HCV specific proliferation. Interestingly, even in patients where proliferation was not detected when total PBMC were stimulated with HCV-proteins, depletion of Treg resulted in a proliferative response. Further negative regulation of the T cell response in a number of chronic HCV patients was found to be mediated via IL-10 and TGF-beta on cytokine production and proliferation, respectively.

Conclusions: HCV-specific T cell responses are weak or absent in chronic HCV patients. The inability to mount a strong immune response against the virus is considered an important factor contributing to the development of persistent infection. In this study we demonstrate that multiple immunosuppressive mechanisms regulate the T cell response to HCV, which may be an important factor in the establishment of persistent HCV infection.

Human plasmacytoid dendritic cells induce profound hyporesponsiveness and suppressive capacity in allogeneic T-cells

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Background: A major barrier for induction of liver transplant tolerance in humans is their large repertoire of allo-reactive memory T-cells, which rapidly respond to allo-antigens, even when these are presented by non-professional antigen-presenting cells. We investigated whether human plasmacytoid dendritic cells (PDC) can induce hyporesponsiveness and suppressive capacity in allogeneic T-cells containing memory T-cells. Methods: Purified PDC from human blood, were stimulated with Toll-Like Receptor (TLR)-7 agonist loxoribine (LOX) or TLR-9 ligand CpG A. After 20 hours, allogeneic T-cells containing $CD45RA^+$ naïve and $CD45RO^+$ memory cells, were added. T-cell proliferation, cytokine production, CD25 and Foxp3-expression were determined after 7 days. Hyporesponsiveness was assessed in re-stimulations with LPS-matured monocyte-derived DC (MoDC), and suppressive capacity was determined by adding graded numbers of PDC-primed T-cells to responder T-cells stimulated by mature MoDC, either derived from the same donor as PDC, or from a third party.Results: Toll-like receptor (TLR)-stimulated PDC primed allogeneic T-cells to produce IL10 (CpG-PDC: 668±260 pg/ml; LOX-PDC: 715±369 pg/ml). After stimulation with CpG-PDC or LOX-PDC 13±2% and 14±2%, respectively, of allogeneic CD4+ T-cells acquired Foxp3 and CD25-expression. CFSE-dilution showed that TLR-stimulated PDC induced proliferation of $CD4^+Foxp3^{hi}$ T-cells. No $Foxp3^{hi}$ T-cells were generated when $CD25^+$ T-cells were depleted from allogeneic T-cells prior to their stimulation with PDC, showing that their enrichment was due to expansion from pre-existing Treg. T-cells primed by TLR-stimulated PDC were hyporesponsive upon restimulation with mature MoDC derived from the same donor (90% decrease in proliferation compared with fresh T-cells), and suppressed responder T cells stimulated by mature MoDC in a dose-dependent and donor-specific fashion (55% inhibition of proliferation at suppressor:responder ratio of 1:2). Suppression was partly abrogated by anti-IL10 receptor antibody.
Conclusion: TLR-stimulated human PDC induced profound hyporesponsiveness nand suppressive capacity in allogeneic T-cells, including memory T-cells. Cellular immuno-therapy with PDC from donor blood may be considered as a promising approach to silence the allo-reactive repertoire of liver transplant recipients.

Migration of donor myeloid dendritic cells after human liver- but not after kidney transplantation: implications for liver graft acceptance?

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The classical paradigm states that allogeneic T-cell activation after organ transplantation results from transfer of donor-derived myeloid dendritic cells (MDC) from the graft into the recipient. Conversely, it has been postulated that the liver contains tolerogenic MDC, which may account for the tolerogenic properties of liver grafts. However, no formal proof that donor MDC migrate from human organ grafts into recipients has been provided. Here, we show that after human liver transplantation (LTx), but not after renal transplantation (RTx), donor-derived MDC circulate in the recipient. One day after LTx 4.2% (range: 0.0-18.1%) of MDC were or donor origin, and 4 days later still 0.6% (range 0.0-1.3%; n=11). MDC that detached from human liver grafts during vascular perfusion before transplantation were LFA-1^{high} and about 25% expressed CCR-7. Upon activation, about 35% acquired L-selectin, resulting in expression of all receptors required for homing into recipient secondary lymphoid tissues. To study the functional properties of MDC detaching from liver grafts, MDC were purified from leukocytes collected during routine vascular perfusions of the graft before transplantation. Purified liver perfusate MDC stimulated with a physiological concentration of LPS were, in comparison with blood MDC, poor inducers of IFN-γ production in allogeneic T-cells, although they were able to stimulate T-cell proliferation and IL-2 production. This was not due to LPS-resistance, since liver graft MDC produced higher amounts of cytokines after stimulation with LPS, and showed a higher expression of TLR-4 in comparison to blood MDC. However, although liver perfusate MDC produced equal amounts of the IFN-γ inducing cytokine IL-12 compared to blood MDC, they produced 15 times more IL-10, which inhibits IFN-γ production in T-cells.
In conclusion, human LTX, but not RTx, results in early transfer of donor-derived MDC into recipients. These hepatic MDC stimulate allogeneic T cell expansion but not T-helper 1 cytokine production, probably due to their prominent production of IL-10. It is hypothesized that migration of donor-derived hepatic MDC after human LTx may contribute to LTx-tolerance by early priming of proliferation followed by hypo-responsiveness of donor-reactive T-cells.

The hydrophobic iminosugar AMP-DNM increases biliary lipid secretion in mice via FGF mediated regulation of CYP7A1

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Treatment of ob/ob mice with the hydrophobic iminosugar AMP-DNM (N- (5'-adamantane-1'-yl-methoxy)-pentyl-1-deoxynojirimycin) ameliorates many symptoms of the Metabolic Syndrome including plasma glucose levels and hepatic steatosis. AMP-DNM has no effect on liver cholesterol but plasma cholesterol increases by about 20% and cholesterol synthesis (fecal neutral sterol) is also strongly increased indicating enhanced reverse cholesterol transport. The aim of this study was to investigate the effect of iminosugar treatment on biliary lipid secretion and regulation of the enzyme 7-alpha-hydroxylase (CYP7A1). Results. C57Bl6 mice were fed lab chow with or without 25mg/kg/day AMP-DNM. After four weeks the bile duct of these mice was cannulated and bile was collected for 15 minutes. AMP-DNM increased biliary bile salt secretion by 200% and had similar effects on cholesterol and phospholipid secretion. The ratio of BS/Chol or BS/PL did not change significantly indicating that the primary effect was on bile salt synthesis. The expression of CYP7A1 mRNA was upregulated about threefold. To investigate the underlying mechanism and relevance for the human situation the effect of AMP-DNM on expression of CYP7A1 in HepG2 cells was studied. In vivo, fibroblast growth factor 19 (FGF19) plays a primary role in regulation of hepatic CYP7A1 expression. Treatment with 10uM AMP-DNM for 2 hours prevented the downregulation of CYP7A1 with FGF19. Interestingly, the compound had no effect on FXR mediated downregulation of CYP7A1 by bile-salt (CDCA).
Conclusion: Four weeks treatment with the iminosugar AMP-DNM strongly increases biliary bile salt secretion in C57Bl6 mice. In vitro experiments with (human) HepG2 cells indicate that the effect is due to impairment of FGF19 induced downregulation of CYP7A1.

Reactive oxygen species are not involved in bile acid induced apoptosis of hepatocytes

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Background: exposure of hepatocytes to hydrophobic bile acids induces apoptotic cell death, characterized by caspase activation and nuclear condensation. It has been hypothesized that bile acids generate reactive oxygen species (ROS) via activation of membrane-bound NADPH-oxidase and that these ROS activate the Src-family member Yes which in turn is responsible for bile acid induced cell death. This hypothesis suggests that anti-oxidant therapy might be useful in cholestatic disorders. Aim: to investigate the role of ROS in bile acid induced death of hepatocytes. Methods: Primary cultures of rat hepatocytes were exposed to the hydrophobic bile acid glycochenodeoxycholic acd (GCDCA: 50 uM) for 4 hours with or without the addition of anti-oxidants: pegylated catalase (PEG-CAT), pegylated superoxide dismutase (PEG-SOD), N-acetylcysteine (NAC) and the cell permeable glutathione-derivative GSH-monoethylester (GSH-MEE). Membrane-associated NADPH-oxidase was inhibited using diphenylene iodonium (DPI) and the Src-kinase family member Yes was inhibited using SU6656. Apoptosis was determined via caspase-3 activity assay and nuclear condensation and necrosis via Sytox green staining. The oxidative stress responsive gene heme-oxygenase-1 (HO-1) was used as a parameter of oxidative stress. Results: none of the anti-oxidants tested abolished GCDCA-induced apoptosis, although PEG-SOD completely abolished superoxide anion (menadione) induced apoptosis and PEG-CAT completely abolished hydrogen peroxide induced necrosis. GCDCA did not induce HO-1 mRNA level, whereas menadione strongly induced HO-1 expression. The Yes inhibitor SU6656 inhibited GCDCA-induced apoptosis (-67%). Although the NADPH-oxidase inhibitor DPI reduced GCDCA-induced apoptosis (-75%), it strongly induced necrotic cell death (83% of cells).
Conclusion: our results do not indicate any oxidative stress induced by bile acids. Furthermore, anti-oxidants do not reduce GCDCA-induced apoptosis. The proposed role of NADPH-oxidase in GCDCA-induced cell death is questioned, since inhibition of NADPH-oxidase does not protect against cell death, but rather shifts cell death from apoptosis to necrosis. Finally, a role of the Src-family member Yes in GCDCA-induced apoptosis is confirmed. Our findings suggest that bile acid induced cell death is not mediated via reactive oxygen species and that anti-oxidant therapy in cholestatic liver diseases is likely to be ineffective.

Pharmacological inhibition of ACC activity by Soraphen reverses high fat-induced obesity and insulin resistance in mice *

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Acetyl-CoA carboxylase (ACC) enzyme activity is very important in both lipid and glucose metabolism. The ACC enzyme system consist of two isoforms, ACC1 and ACC2 and catalyses the conversion of acetyl-CoA into malonyl-CoA. Malonyl-CoA generated by ER-associated ACC1 is used in the lipogenic pathway as a precursor for fatty acid synthesis. In addition, malonyl-CoA also acts as the natural inhibitor of carnitine palmitoyltransferase (CPT) at the level of β-oxidation when generated by mitochondrial ACC2. Pharmacological inhibitors of the ACC system may be of potential benefit for the treatment of components of the metabolic syndrome. To test whether Soraphen, a general ACC inhibitor, is able to ameliorate development of obesity and insulin resistance in mice fed a high fat diet.Male C57Bl6/J mice were either fed a normal lab chow (control) diet, a high fat diet (beef lard, 36 energy% fat) or a high fat diet supplemented with Soraphen at doses of 50 mg/kg/d or 100 mg/kg/d for six weeks. Mice were then subjected to in vivo measurements of glucose metabolism under basal conditions and during a hyperinsulinemic euglycemic clamp after an overnight fast.Soraphen-treated mice gained less weight during the 6 weeks feeding period than the high fat fed mice (-4% and -9% for low and high dose resp.). Mice treated with both doses of Soraphen showed a significant, dose-dependent improvement in insulin sensitivity as compared to mice fed the high-fat diet. Rates of glucose infusion (GIR), glucose disposal (Rd) and metabolic clearance (MCR) in the Soraphen-treated mice were all similar to values observed in chow-fed mice (GIR 85% and 99%, Rd 83% and 108%, MCR 87% and 120% for low and high dose resp.). Values for high-fat fed mice were all significantly decreased compared to chow animals (GIR 67%, Rd 64% and MCR 64%).Several basal plasma and liver parameters in mice treated with Soraphen including triglyceride concentrations did not differ from the high fat fed mice, however, values for these three groups were elevated compared to the animals fed the chow diet. Inflammation markers were not altered in the mice treated with Soraphen. Hepatic expression of general genes involved in glucose and lipid metabolism were not altered by Soraphen.
Our results show that pharmacological inhibition of the ACC system may provide means for prevention or treatment of obesity and insulin resistance, although the exact mechanism of action is still unknown.

Noninvasive quantitative assessment of hepatic steatosis in the rat liver using 3.0 Tesla ^{1}H-Magnetic Resonance Spectroscopy

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The amount of hepatic steatosis is an important diagnostic parameter in therapeutic surveillance of NASH patients and in the pre-operative workup of patients for liver resection or living donor liver transplantation. The gold standard for quantitative steatosis determination is histopathological assessment of needle biopsies, which is invasive and subject to underscoring. ^{1}H-Magnetic Resonance Spectroscopy (^{1}H-MRS) using a conventional MRI scanner allows non-invasive quantification of steatosis by measuring resonance signals of proton containing fatty acid chains in liver tissue. The aim of this study was to validate 3.0 Tesla ^{1}H-MRS measurements in a rat steatosis model and to investigate the discriminative power of the ^{1}H-MRS.Steatosis was induced by feeding rats a methionine choline deficient (MCD) diet for 0, 1, 2, 3 or 5 weeks (n = 5 per group). 3.0 Tesla ^{1}H-MRS measurements of rat livers were performed and multiple samples were taken for hepatic fat analysis. Correlations (Spearman) were studied between ^{1}H-MRS, histopathology and total fatty acid concentration (gas chromatography). ^{1}H-MRS measurements of rat livers with macrovesicular steatosis (MAS) grades ranging from 0-25%, 25-50%, 50-75% and 75-100% were studied for determination of the discriminative power (Mann-Whitney U analysis). Histopathology revealed no macrovesicular steatosis (MAS) in control rats, whereas one week of MCD diet induced mild MAS (mean, range) of 6% (0-23%). After two weeks MCD diet, a significantly increased MAS was seen of 40% (31-70%) which after three and five weeks, was 60% (30-73%) and 84% (70-93%), respectively. A significant correlation was observed between ^{1}H-MRS measurements and histopathological MAS ($r = 0.93$, $p < 0.0001$). Also, ^{1}H-MRS correlated significantly with total fatty acids ($r = 0.94$, $p < 0.0001$). ^{1}H-MRS measurements of rat livers with increasing steatosis grades were significantly different: 0-25% versus 25-50% MAS ($p = 0.001$), 25-50% versus 50-75% MAS ($p = 0.017$), and 50-75% versus 75%-100% MAS ($p = 0.01$).
Conclusion: 3.0 Tesla ^{1}H-MRS measurements in a rat steatosis model correlate strongly with morphological and biochemical assessments of parenchymal fat. ^{1}H-MRS was also able to accurately discriminate between varying degrees of steatosis. These results encourage application of ^{1}H-MRS for non-invasive quantitative assessment of steatosis in a clinical trial.

Functional cellular copper uptake requires oligomerization of the high affinity copper transporter 1 (hCTR1)

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The transition metal copper is an essential trace element for all organisms that utilize oxygen. However, copper is potentially toxic, and an imbalance in copper homeostasis results in severe disorders. For instance, copper deficiency leads to severe developmental retardation. In contrast, patients with Wilson disease present with severe liver cirrhosis secondary to hepatic copper overload. Dietary copper uptake in the intestine is critically dependent on the high-affinity human copper transporter 1 (hCTR1). The aim of this study is to characterize cellular copper uptake using immunofluorescence localization, protein-protein interaction studies and functional copper uptake experiments. hCTR1 is a 35-kDa protein containing three transmembrane domains, which appeared localized both at the plasma membrane and in intracellular vesicles in different cell types. A novel transcription-based copper sensor, containing four metal responsive elements (MRE) of the mouse metallothionein 1A promoter upstream of the Firefly Luciferase open reading frame, was developed and used to monitor bio-available cytosolic copper as a measure of copper uptake activity. Expression of wild-type hCTR1 in HEK 293T cells resulted in strong reporter activation, with maximal induction at 1 ìM $CuCl^2$, consistent with the K^m of hCTR1. Conversion of two highly conserved methionines into isoleucines in the second transmembrane region of hCTR1 completely abolished hCTR1-dependent copper uptake. Interestingly, hCTR1-dependent copper uptake was inhibited in a dominant-negative manner when hCTR1 wild-type and this mutant were co-expressed, suggesting a direct functional interaction between the wild-type protein and the mutant. In concordance with this observation, co-immunoprecipitation of wild-type hCTR1 with different epitope tags confirmed oligomerization of hCTR1. Furthermore, the mutant hCTR1 was able to interact with itself and with the wild-type hCTR1 protein. Taken together, these data provide strong biochemical and functional evidence that hCTR1 requires oligomerization for functional high-affinity copper transport activity, thus permitting the formation of a permeable channel necessary for dietary copper uptake.

Confirmation of several genetic associations from the WTCCC study and identification of novel susceptibility loci in a large Dutch-Belgian Crohn's disease cohort.

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Inflammatory bowel diseases (IBD) are common chronic gastrointestinal inflammatory disorders with a complex genetic background that comprises two major forms – Crohn's disease (CD) and ulcerative colitis (UC). In the last year several genome wide association scans (GWAS) have been performed for CD. The largest one was the Wellcome Trust Case Control Consortium (WTCCC) study which identified several novel susceptibility loci.
We performed a replication study in 2505 Dutch and Belgian IBD patients (1592 CD and 913 UC). 39 markers that showed moderate or strong association in the WTCCC study were tested. In addition, we included the markers in *IL23R* and *ATG16L1* that were identified by previous GWAS.
First we confirmed the genetic associations with *IL23R* (rs11209026, p_{corr}=1.05E-10) and *ATG16L1* (rs2241880, p_{corr}=1.88E-05) which were also significant in Transmission Distortion Testing (p = 1.90E-05 for *IL23R* and p = 5.00E-04 for *ATG16L1*) Also the association of *IRGM* (rs13361189, p_{corr}=1.31E-04 and rs4958847, p_{corr}=8.81E-04), *NKX2-3* (rs10883365, p_{corr}=2.30E-04), a gene desert on 1q24 (rs12035082 p_{corr}=5.89E-04) and a gene desert on 5p13 (rs17234657, p_{corr}=1.02E-03) were confirmed. Secondly, we identified three novel genetic associations. The first is SNP rs916977 in the Hect Domain and RCC1-like Domain 2 (*HERC2)* with p_{corr} = 4.37E-03 and an OR of 1.39 (CI 1.16-1.68). The second is SNP rs3936503 in Cyclin Y (*CCNY*) with p_{corr} = 8.15E-03 and an OR of 1.31 (CI 1.11-1.54). The third is rs10761659 in a gene desert on chromosome 10q21 with p_{corr} = 3.49E-03 and an OR of 0.75 (CI 0.63-0.88). The latter association was also found by TDT (p = 1.60E-03). We subsequently pooled the data for *HERC2, CCNY* and 10q21 with the original WTCCC data hence yielding a total sample size of 3340 CD cases and 3983 healthy controls. Combined analysis resulted in lower p-values then in the original WTCCC report for all three SNPs, supporting a true genetic association. Several SNPs were found to be moderately associated with UC. However, none of these associations withstood correction for multiple testing.
In conclusion, in this large study, we not only replicated genetic associations with *IL23R, ATG16L1, IRGM, NKX2-3*, 1q24 and 5p13, but also report evidence for novel associations with *HERC2, CCNY* and the region on 10q21. Pooling our data with the results of the WTCCC even strengthens the results, suggesting genuine genetic associations.

Wnt-pathway activation in early IBD-associated colorectal carcinogenesis: a biomarker for colonic surveillance

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The molecular background of colitis-associated carcinogenesis differs from the sporadic pathway. It has been suggested that the Wnt-pathway dominates early sporadic carcinogenesis whereas the p53 pathway plays a pivotal role early in the colitis-associated counterpart. Activation of these pathways in non-dysplastic mucosa of inflammatory bowel disease (IBD) patients may function as an early biomarker of malignant transformation. The aims of this study were to determine expression of Wnt-signaling proteins and p53 during colitis-associated carcinogenesis and to assess their use as biomarkers of colonic field cancerization.A tissue micro-array was constructed with colonic samples from 5 groups of patients: healthy subjects (1), IBD without neoplasia (2), non-dysplastic IBD mucosa with neoplasia elsewhere in the colon (3), dysplastic lesions (4), and IBD-associated colorectal cancer (CRC) (5). Each group consisted of 10-12 patients, with a maximum of 9 tissue cores per patient. Immunohistochemistry was performed using monoclonal antibodies for β-catenin, cyclin D1 (products of an activated Wnt-pathway), and p53. The intensity of the staining was scored for p53 as - or + and for cyclin D1 as -, +, or ++. Nuclear and membranous β-catenin expression was assessed semi-quantitatively (0-10%, 10-50%, >50% positive cells).Mean age of patients was 45 years (SD 13) and 54% were male. Ulcerative colitis was present in 65% of cases in groups 2-5. Nuclear β-catenin expression was found in 0%, 0%, 50%, 66%, and 100% of the patients in groups 1, 2, 3, 4, and 5, respectively. Remarkably, non-dysplastic IBD mucosa with neoplasia elsewhere (group 3) showed an increased expression in 50% of the cases compared to 0% of IBD patients without neoplasia (p=0.02). As expected, membranous β-catenin staining declined when nuclear accumulation was observed. Cyclin D1 staining followed the same expression pattern as nuclear β-catenin. In groups 1, 2, 3, 4, and 5 positive staining was observed in, respectively, 22.2%, 33.3%, 50%, 70%, and 80% of the patients. Increased expression of p53 was only seen in group 4 (dysplasia: 66.7%) and 5 (CRC: 50%).
Conclusions: In contrast to previous findings, our results suggest a role for the Wnt-pathway in the early phase of colitis-associated carcinogenesis. Furthermore, Wnt-pathway activation may serve as a biomarker for colonic field cancerization, which may facilitate detection of neoplasia in colonic surveillance.

Genetic analysis of the innate immune system identifies CARD9 and the IL18 receptor locus as susceptibility genes for both Crohn's disease and ulcerative colitis

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The two main phenotypes of inflammatory bowel disease (IBD) – Crohn's disease (CD) and ulcerative colitis (UC) – are chronic intestinal inflammatory disorders with a complex genetic background. Many new loci involved in the genetic predisposition to CD have recently been described, but there is little insight into the genetic background of UC.We performed a large functional candidate gene analysis within the innate immune pathway in IBD using a three-stage design. In phase I, 354 SNPs from 85 carefully selected innate immunity genes located in 74 genomic regions were typed in a cohort of 520 Dutch IBD patients (284 CD, 236 UC) and 808 controls. In phase II, 9 SNPs showing association at p<0.006 in phase I were replicated in a second independent cohort of 545 Dutch IBD patients (326 CD, 219 UC). In phase III, 3 SNPs with p<0.01 in the combined phase I and phase II analysis were genotyped in an additional cohort of 786 Dutch IBD samples (452 CD, 334 UC). Joint analysis of 1,851 IBD patients (1062 CD, 789 UC) demonstrated strong association to the IL18R1-IL18RAP locus (rs917997) for both CD (p=3.05E-06, OR 1.44; CI 1.23-1.67) and UC (p=3.69E-05, OR 1.41; CI 1.20-1.66). A meta-analyis with the Crohn's disease dataset of the Wellcome Trust Case Control Consortium independently supported the association with CD (p=9.88E-09)In addition, an association of the CARD9 rs10870077 SNP with UC was observed (p=6.7E-04, OR 1.28; CI 1.11-1.47).
In conclusion we identified two new IBD susceptibility genes and our results further support the importance of the innate immune system in the predisposition to both CD and UC.

The glucocorticoid receptor gene polymorphism BclI which modulates glucocorticoid sensitivity is associated with inflammatory bowel disease

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The glucocorticoid receptor (GR) plays an important regulatory role in the immune system and glucocorticoids (GC) are widely used in the treatment of chronic inflammatory diseases, such as inflammatory bowel disease (IBD). Four polymorphisms in the GR gene are associated with altered GC sensitivity: the N363S and BclI polymorphisms are associated with a relative hypersensitivity to GCs, while the ER22/23EK and 9β polymorphisms are associated with relative GC resistance. Because differences in GC sensitivity might influence immune effector functions, we examined whether the GR polymorphisms N363S, BclI ER22/23EK and 9β are associated with susceptibility to develop Crohn's Disease (CD) or Ulcerative Colitis (UC).The presence of GR polymorphisms was assessed in 514 IBD patients, of which 304 CD and 210 UC patients, and compared to 532 healthy controls. All patients were classified according to the Montreal classification. Subsequently, the relationship between GR polymorphisms and disease phenotype was examined.Prevalence of GR polymorphisms was analysed in the total group of IBD patients and in the CD and CU groups separately. BclI carriers showed a significant lower prevalence in the IBD group compared to controls: OR=0.75 (95%CI 0.58–0.97, p=0.029). The association observed in the subgroup of CD patients was comparable: OR=0.69 (95%CI 0.51–0.92, p=0.013). A similar effect was seen in UC however this was not significant. No significant associations between the other three polymorphisms and CD or UC were found. For BclI we also found a decreased incidence of CD localization in the colon and the combination of both ileum and colon: OR=0.57 (95%CI 0.33–0.99, p=0.049) and OR=0.59 (95%CI 0.36–0.97, p=0.037) respectively compared to noncarriers.
Conclusions: The results suggest that the BclI polymorphism is associated with a decreased susceptibility to develop IBD, particularly in CD patients. Furthermore, this polymorphism might be involved in disease localization of CD. No evidence was found for associations between IBD, CD or UC and the polymorphisms N363S, ER22/23EK and 9β.The association between BclI and IBD suggests that a constitutionally determined (relative) GC hypersensitivity might have a protective effect in the development of auto-immunity, like IBD. In addition, these data indicate that altered GC sensitivity is associated with disease phenotype.

Crohn's associated genes ATG16L1 and IRGM are not associated with granuloma formation.

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Genome wide association studies have provided nine strong associations between single nucleotide polymorphisms (SNP) and Crohn's Disease (CD). Two of these SNP's are located on the Autophagy-related 16-like 1 gene (ATG16L1) and immunity-related guanosine triphosphatase gene (IRGM), which are both involved in autophagy. This suggests a role for autophagy in the pathogenesis of CD. Autophagy has a role in the elimination of invading pathogens by the formation of autophagosomes. It has been shown that the formation of granulomas can be attributed to impaired recognition of bacterial components by the innate immune system. Therefore, we hypothesised that genetic variations in autophagy related genes ATG16L1 and IRGM are of direct influence in autophagy pathways. Subsequent impaired pathogen clearance in the cell would therefore lead to an increased prevalence of granulomas in Crohn's patients. Genotyping of the SNP's in ATG16L1 (rs 2244180) and IRGM (rs 4958847) was performed in two academic hospitals. The results were transferred into our database, which comprises all information available on our CD patient cohort. Baseline criteria for inclusion in this study were as follows: genotyped CD patients with a PA report on intestinal biopsies in which granulomas were present or absent in the period between 1985 and 2007. In 46% of the 179 CD patients genotyped for ATG16L1 granulomas were found. In the homozygous mutant group (HH) 56% scored positive for granulomas against 49% and 37% for the heterozygous (HZ) and wild types (WT) respectively ($p<0.16$). Although a lower frequency of the ATG16L1 mutant allele was found in patients with granulomas, this was not statistically significant. In 42% of the 213 CD patients genotyped for IRGM granulomas were found. The mutant allele was not associated with granuloma occurrence. In the HH group 56% had granulomas versus 40% in HZ and 42% in WT ($p<0.67$). A total of 169 CD patients were genotyped for both genes, but we did not find evidence for association between mutant allele carriage and prevalence of granulomas.In our Dutch CD patient cohort we found no association between ATG16L1 or IRGM variants and the presence of granulomas. Furthermore, we found that there is no evidence for gene-gene interaction between ATG16L1 and IRGM and granuloma formation.This project is subsidised by the MLDS

Sex-related Inheritance and Transmission Pattern in Inflammatory Bowel Disease

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Background: Extensive epidemiological data indicate female predominance in inflammatory bowel disease (IBD). However, the exact character of sex-related inheritance in IBD is unknown. Aim: To characterize the sex-related inheritance and transmission pattern in inflammatory bowel disease.Methods: IBD patients with family history of IBD were identified in the IBD outpatient clinic database in two academic medical centers. Family relationship, sex and the type of the disease (Crohn`s disease – CD, ulcerative colitis – UC, unclassified - U) were retrieved from database and the patterns of sex and disease type distribution were compared to the baseline IBD population. The binomial distribution test was used to analyze the imprinting pattern in the families in which both, a parent and a child had IBD.Results: In total, 608 IBD (CD/UC/U; 363/233/12) patients from 289 families were included. The baseline IBD patients' database comprised 2700 patients (CD/UC/U; 1609/1009/82). In the familial IBD patients' population, a higher female predominance (F/M 369/239; ratio 1.5) was observed compared with baseline population (F/M - 1444/1174; ratio 1.2). This familial female predominance applied for both CD (F/M - 232/131; ratio 1.8) and UC (F/M - 128/105; ratio 1.2). Subsequently, the imprinting pattern was analyzed. In total, 87 families in which both, a parent and a child were affected were identified. A significantly higher number of mother to child transmissions (55 vs. 32 of father to child transmissions) was observed (p=0.004). The female imprinting was specifically related to CD (mother/father to child transmissions; 31/14; p=0.001), in UC no significant differences between mother and father to child transmission numbers were observed. The analysis of offspring sex distribution pattern revealed significantly higher female to female transmission compared with female to male transmission rate (36 vs. 18; p=0.005). No specific offspring sex-related transmission pattern was observed in the paternal transmission families.
Conclusion: In inflammatory bowel disease, the female predominance is associated rather with familial than sporadic occurrence of the disease. In Crohn`s disease, this female predominance may be related to the imprinting of the disease predisposition with a specific female to female transmission pattern.

Colonoscopic Surveillance in Inflammatory Bowel Disease Improves Survival after Colorectal Cancer Diagnosis

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Aim: Colonoscopic surveillance provides the best practical means for preventing colorectal cancer (CRC) in inflammatory bowel disease (IBD) patients. Strong evidence for improved survival from surveillance programs is sparse. The aim of this study was to compare tumor stage and survival of IBD patients with CRC between those who were part of a surveillance program and those who were not.
Methods: A nationwide pathology database was used to identify all IBD patients with CRC in all 8 university hospitals in The Netherlands over a period of 15 years. Patients were assigned to the surveillance group when they had undergone one or more surveillance colonoscopies prior to diagnosis of CRC. Patients who had not undergone surveillance served as controls. Tumor stage and survival were compared between the two groups. The chi-square, Fisher's exact and student's t tests were used where appropriate to compare patient characteristics. Kaplan-Meier and Cox-regression analyses were employed for survival calculations.
Results: 149 IBD-associated CRCs were found. Twenty-three had undergone colonoscopic surveillance before CRC was discovered and 126 had not. Patient characteristics showed no significant differences between the groups. Surveillance started after a median of 14.5 [range: 0-33] years after histological diagnosis of IBD. CRC developed after a median of 6.4 years [1-21] after initiation of surveillance. Median age at time of CRC diagnosis was 48 [38-71] and 49 [21-85] years in the surveillance and non-surveillance groups respectively. Mean follow-up time after CRC diagnosis was 57 months [0-188] in the surveillance group and 51 months [0-235] in the non-surveillance group. The 5-year survival rate of the surveillance group was 100% versus 74% in the control group (p=0.041). This association was also visible after a Cox-regression analysis with co-morbidity, primary sclerosing cholangitis and age at CRC diagnosis as co-variables (p=0.08). In the surveillance group, only 1 patient died as a consequence of CRC compared to 29 patients in the control group (p=0.047). More early stage tumors (AJCC stage 0 and 1) were found in the surveillance group (p=0.004). Likewise, in the surveillance group significantly fewer patients had Stages 3B-C and 4 tumors (p=0.049).
Conclusions: These results provide evidence for improved survival from colonoscopic surveillance in IBD patients as a result of detecting CRC at a more favorable tumor stage.

More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis

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Patients with inflammatory bowel disease (IBD) and concurrent primary sclerosing cholangitis (PSC) have been shown to have a higher risk of developing colorectal cancer (CRC) than IBD patients without PSC. Altered bile salt composition, differences in genetic background, and long-term subclinical activity of colitis have been suggested to explain this increased risk. The aim of this study was to investigate whether clinical differences were present between patients with CRC in PSC-IBD and those with CRC in IBD alone, as this may improve the knowledge on possible underlying pathophysiological mechanisms. Clinical data from patients with IBD-associated CRC with or without concurrent PSC diagnosed between 1980-2006 were retrieved from 8 Dutch university medical centers. The t-test and chi-square test, as appropriate, were used to determine significant clinical differences. Survival was calculated by the Kaplan-Meier method. Twenty-seven IBD-CRC patients with PSC (70% male) and 127 IBD-CRC patients without PSC (59% male) were included. Median follow-up time after diagnosing CRC was 2.4 (0-17) and 2.8 (0-20) years in patients with and without PSC, respectively (p=0.06). Mean age at diagnosis of CRC tended to be lower in the PSC group: 45 (SD 9.7) versus 50 years (SD 12.9) (p=0.07). No significant difference in age at diagnosis of IBD was found between both groups. The mean IBD-CRC interval was 15 (SD 9) years in the PSC group versus 18 (SD 10.7) years in the non- PSC group (p= 0.13). Sixteen (59%) PSC patients died versus 32 (25%) without PSC (p=0.001). However, CRC-related mortality was not significantly different between both groups (30% versus 18%, p= 0.28). Patients with PSC had a shorter survival after diagnosing CRC, with a 5-year survival of 42% versus 75% in the non-PSC group (log rank, p= 0.0009). Right-sided tumors were more frequently found in the PSC group (66.7%) compared to the non-PSC group (35.4%, p=0.005); adjusted for age and sex, this was still statistically significant (Odds Ratio= 4 (95% CI 1.9-9.9).
Conclusions: Patients with IBD and concurrent PSC have a shorter survival after diagnosing CRC compared to patients with IBD alone. However, no significant difference in CRC-related mortality was found. Furthermore, a higher frequency of right-sided tumors was found in patients with PSC, suggesting a different pathogenesis, such as a more toxic bile salt composition in PSC.

The risk of colorectal carcinoma in IBD patients is limited in non-tertiary cohorts: results of a nation wide long-term survey

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Surveillance guidelines in patients (pts) with inflammatory bowel disease (IBD) recommend initiating surveillance for IBD after 8-10 yrs of extensive disease and after 15-20 yrs for left-sided colitis, based on earlier reports demonstrating increased risk of colorectal carcinoma (CRC) in IBD pts. Most of these reports were based on selected tertiary care pts with chronic severe disease, and conflict with more recent data. Recently was demonstrated that in academical centers in The Netherlands, patients were diagnosed with IBD-related CRC even before the recommended start of surveillance. Whether this also reflects high-risk tertiary referrals is unknown. The overall epidemiology of CRC in IBD pts is relevant for monitoring and adaptation of clinical guidelines. We assessed the risk of IBD associated CRC in non-tertiary centers in The Netherlands.IBD related CRC pts in all non-tertiary centers in The Netherlands were identified using the nationwide network and registry of histo- and cytopathology (PALGA). Pts with IBD and CRC diagnosed synchronously or metachronously in a pathology report from 1990-2005 were included. In a 2nd search we included pts < 65 yrs old to minimize interference with sporadic CRC. Further clinical data were obtained to assess the IBD population and verify diagnosis of IBD associated CRC. Of selected pts clinical data including age, gender, type of IBD, extend of disease, date of diagnoses and follow-up of IBD and CRC were collected from patient charts.The initial PALGA search identified 2734 pts suggestive for an IBD associated CRC. Of these pts 1237 were < 65 yrs old. Further analysis of the pathology excerpts within the PALGA search showed 468 pts with possible IBD associated CRC. By December 1, 2007 we have collected data from 30 randomly selected hospitals in The Netherlands. In these hospitals 171 patient charts and pathology reports were assessed to confirm diagnosis and collect clinical data. Overall, in 94 pts the diagnosis of IBD related CRC could be confirmed (56 UC (59.6%), 38 CD (41.3%)). The average IBD population per hospital was 600 pts. On average 3 pts per hospital developed CRC in a time period of 15 yrs, consistent with a 0.5% CRC risk within 15 yrs follow-up per IBD patient and 0.03% per year per IBD patient, independent of other variables.
Conclusion: the risk for IBD-associated CRC is limited in a regular, secondary IBD population. Therefore current surveillance strategies in IBD pts need to be adjusted.

Magnetic Resonance Imaging for suspected IBD in a pediatric population *

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Inflammatory bowel disease (IBD) is diagnosed frequently in children, accounting for 25% of all cases of IBD. Diagnostic tests that are currently used for evaluation of suspected IBD are esophagogastroduodenoscopy (EGD), ileocolonoscopy (CS) and barium enteroclysis (BE). As Magnetic Resonance enterography (MRE) is non-invasive and does not use ionizing radiation, the diagnostic potential of this technique has been investigated in many studies in adult, but hardly in pediatric IBD patients. The accuracy and reproducibility of MRE in diagnosis and differentiation of IBD in pediatric patients was determined. Besides, the accuracy of MRE in the determination of disease activity was evaluated. Patients aged 8-18 years scheduled to undergo EGD, CS and BE to confirm or exclude IBD in 2 tertiary care hospitals were included and also underwent MRE. MR images were evaluated by 3 observers who were blinded to clinical and endoscopic findings as well as to findings at BE. The accuracy of MRE in the diagnosis of IBD and in differentiating between CD and UC was calculated, using the clinical diagnosis based on endoscopic, histopathological and BE examinations as reference standard. 33 patients were available for analysis (45% male, mean age 13.5±2.4 years). Observers had a sensitivity of respectively 61%, 61% and 91% and a specificity of 80%, 90% and 60% for establishing the correct final diagnosis. Differentiation between CD and UC based on MRE was accurately done by the observers in respectively 67%, 53% and 80% of CD patients and 0%, 14% and 43% of UC patients. Disease activity was understaged on MRE in respectively 65%, 80% and 45% of CD patients. A significant correlation was seen between bowel wall thickness measurements ($r=0.430$, $p<0.001$) between observer 1 and 2. Agreement on bowel wall enhancement and stenosis was moderate (kappa 0.59; 0.56 and 0.56 and kappa 0.62, 0.32, 0.30 respectively). The sensitivity of BE for the detection of inflammation of the terminal ileum was 50%, the specificity was 53%. MRE was more accurate in diagnosing terminal ileitis than BE; sensitivity values were respectively 60%, 50% and 80%. Specificity values were respectively 94%, 94% and 63%. The accuracy of MRE for diagnosis of IBD was moderate to good, with moderate to good specificity and interobserver agreement. CD, but not UC, was accurately diagnosed by MRE in a large proportion of pediatric patients. For assessment of the small bowel, MRE is more accurate than BE.

Scintigraphic identification of pancolitis and distal ileitis using ^{99m}Tc-labeled interleukin-8 in inflammatory bowel disease

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In patients with IBD, a non-invasive diagnostic test to assess disease activity is warranted. Data derived from rabbits with experimental colitis suggest that there is a role of using ^{99m}Tc -labeled interleukin-8 in the assessment of colitis by specifically visualizing infiltrating granulocytes. Furthermore, preparation of 99m Tc Il-8 is far less laborious compared to previously used radio pharmaceuticals such as radiolabelled leukocytes. We therefore evaluated the utility of ^{99m}Tc-labeled interleukin-8 scintigraphy for the assessment of IBD disease activity in patients as compared to colonoscopy.
Patients suffering from Crohn's disease (CD) or ulcerative colitis (UC) who were scheduled for a colonoscopy to assess disease activity were eligible for the study. ^{99m}Tc labeled interleukin-8 scintigraphy was performed and the intra-abdominal accumulation of ^{99m}Tc-labeled IL-8 was assessed qualitatively and semiquantitatively. The reference methods consisted of colonoscopy and histology.
A total of 31 patients (17 CD, 14 UC) participated. For CD, 56 colon and ileal segments were studied. There was complete concordance in 34 segments. For 22 segments, the reference method and ^{99m}Tc IL-8 scintigraphy disagreed. The sensitivity for the detection of ileal inflammation with ^{99m}Tc IL-8 scintigraphy was 85.7% with a specificity of 100% using colonoscopy and histology as gold standard. In UC we evaluated 40 colonic segments. There was complete concordance for 28 segments. Considering each colonic segment separately, sensitivity of ^{99m}Tc IL-8 scintigraphy was 81.3% with a specificity of 62.5%.
Conclusion: ^{99m}Tc IL-8 scintigraphy appears to be useful in IBD patients to evaluate disease activity and it deserves further exploration in patients with distal ileal CD and UC associated pancolitis.

Maintenance therapy with once-daily 2 g mesalazine (Pentasa) treatment improves remission rates in subjects with ulcerative colitis compared to twice daily 1 g mesalazine: Data from a randomised controlled trial

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Introduction and Aims: Ulcerative colitis (UC) is a debilitating disease.Non-compliance with treatment results in a failure to achieve optimally effective clinical outcome with therapies such as mesalazine. The purpose of this study was to determine if good clinical outcome with mesalazine therapy can be further improved using a once daily (od) versus a twice daily (bd) treatment regimen in subjects with quiescent disease. Methods: This was a multi-centre, single-blinded, randomised controlled trial. Subjects were recruited with mild to moderate UC who had experienced at least one clinical relapse within the previous year. They were randomised to once daily treatment with a single sachet of 2g mesalazine granules, or twice-daily treatment with 2 x 1g sachets. Disease activity was assessed using the UCDAI score. The study was designed to demonstrate clinical non-inferiority, defined as a difference in remission rates of not more than 10% using the UCDAI score following 12 months of treatment in both ITT and PP analysis. Results:362 patients were randomised (54.3% male; mean age 48.7 years). At 12 months the percentage of subjects in remission was 73.8% for the once daily and 63.6% for the twice daily regimen, respectively. Kaplan Meier analysis demonstrated an 11.9% higher probability to remain in remission during 12 months after randomisation for patients randomized to the od group (P=0.024). There were 72.3% and 62.5% of subjects, respectively, with no evidence of physician assessed active disease at end of study. Subjects undergoing once daily treatment had a reduced likelihood of rectal bleeding (20.4% vs. 29.3%), and also had increased rates of normal stool frequency (81.5% vs. 61.7%). No differences in the frequency of side effects were observed between both groups

Conclusion: Both alternative mesalazine regimens were effective in preventing remission in subjects with mild to moderate ulcerative colitis; however, once daily therapy with 2g mesalazine was superior to twice daily therapy with 1g mesalazine. Furthermore, once daily therapy improved a range of other important clinical parameters.

Treatment regimens of azathioprine or 6-mercaptopurine in inflammatory bowel disease in clinical practice

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Azathioprine (AZA) or 6-mercaptopurine (6MP) are useful agents in the treatment of inflammatory bowel disease (IBD). However, their use is limited by side effects, in particular leukopenia. TPMT screening (genotype (GT) or enzyme activity testing (EA)) and metabolite monitoring (MM) are shown to be useful to identify individuals at risk for side effects and to optimize therapy. Nonetheless, in clinical practice these techniques are used on a limited scale. Aim of the present study is to make an inventory of currently used thiopurine treatment regimens, including monitoring, by gastroenterologists in the Netherlands for treatment of IBD.A survey was mailed to one of the gastroenterologists at 90 Dutch hospitals. The survey comprised mainly closed questions exploring: dosing regimens, monitoring (investigations and frequency), and knowledge, use and expectations of TPMT screening and metabolite monitoring.The response rate was 60% (n=54). Respondents reported prescribing primarily AZA (70%), either AZA or 6MP (22%), or primarily 6MP (7%). Treatment is started according to the current advise with a full dose of 2-2.5 mg/kg AZA or 1-1.5 mg/kg 6MP by resp. 52% or 57% of respondents prescribing the drugs, while 35% reportedly use an increasing dosing regimen. Investigations most frequently performed prior to treatment include: full blood count (100%), liver function (96%), creatinin (87%), C-reactive protein (81%) and endoscopy (70%). While full blood count (100%), liver function (96%), and C-reactive protein (74%) are most often used to monitor treatment. The majority reports to monitor 2 (20%), 3 (33%), or 4 (37%) times during the first 8 weeks, and 3 monthly (78%) thereafter. Knowledge of GT, EA, and MM was reported by 80%, 83%, and 70% of the respondents. Expectations of added value of these tests were moderate or high in resp. GT: 31% and 36%, EA: 40% and 33%, and MM:33% and 38% of the respondents. Nonetheless, only 31% (n=17) reported to use one or more of these techniques sometimes (GT/EA/MM: n=6/7/8), mostly (n=2/0/2), or always (n=1/1/1).In conclusion, at present, a large variety of prescribing and monitoring regimens for thiopurine treatment in IBD patients are used in clinical practice. The majority of gastroenterologists reported knowledge of TPMT and metabolite monitoring techniques to optimize thiopurine treatment with reasonable expectations of additional value of these tests. However, uptake of these methods in clinical practice is limited.

Predictors for failing thiopurine therapy in IBD patients; treated at an academic or general district hospital

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Part of the IBD patients using the immune modulating drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) fail to benefit from thiopurines. Two cohorts of IBD patients with previous or present use of thiopurines from an academic and general district hospital were assessed to determine possible predictors for failure of thiopurine therapy. Methods:The data in this retrospective study are based on two 8-years hospital-based interception cohorts of previous or present thiopurine using IBD patients, treated at an academic and general district hospital. Thiopurines were prescribed according to the step-up approach as recommended in current IBD guidelines (ECCO) and were supervised by one gastroenterologist per hospital. Patients were defined as failures in case of discontinuation of thiopurines due to adverse events, refractoriness, both or non-compliance. Patients who continued thiopurines due to remission of IBD were defined as non-failures. Results:At the academic hospital 281/781 (36%) IBD patients were eligible for this study. Of these patients, 157 (56%) failed thiopurine therapy after a median duration of 6 months (range 0-174) due to adverse events (73%), refractoriness (25%) and non-compliance (2%). At the non-academic hospital, 72/416 (17%) IBD patients were included. Fifty percent failed therapy after a median duration of 1 month (range 0-64), due to adverse events (75%), refractoriness (22%) and non-compliance (3%). There was no significant difference in gender, age, IBD subtype, and localization between the failures and non-failures at both hospitals. Metabolite levels were only available in patients treated at the academic hospital. 6-MMP levels were 5190 pmol/10e8RBC and 1240 pmol/10e8RBC in the failures and non-failures, respectively (P= 0.000). Another associated factor for failing thiopurines in the described cohorts was the 6-MMPR:6-TGN ratio. The failures had a median ratio of 34.73 compared to 9.44 in the group that continued the use of thiopurines (P=0.000). There was no significant difference in 6-TGN levels between failures and non-failures (P= 0.210). Conclusion:Analysis of two large 8-year interception cohorts demonstrated that more than half of IBD patients discontinue thiopurine therapy, mostly due to the development of adverse events. The dropout rates were approximately the same for the academic and non-academic hospital. Positive predictors for failing thiopurine therapy were 6-MMP levels and the 6-MMPR:6-TGN ratio.

Thiopurine metabolite measurements during pregnancy in mother and child

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Background: Several studies demonstrated a good safety profile of thiopurine use in inflammatory bowel disease (IBD) patients during pregnancy. This profile is balanced against the potential risks of disease relapse for mother and foetus due to withdrawal of thiopurines. However, prospective data on pharmacokinetic effects of thiopurine use during pregnancy are lacking. Therefore, we performed a study in female IBD patients using thiopurines to determine the influence of pregnancy on thiopurine metabolite levels and the intrauterine exposure of infants to thiopurines. *Methods:* Female IBD patients using thiopurines for at least 8 weeks and planning to become pregnant were eligible for this prospective, multicenter study. Thiopurine metabolite levels (6thioguaninenucleotides (6TGN) and 6methylmercaptopurine (6MMP)) were determined according to the method of Dervieux before, during and after pregnancy. To determine intrauterine exposure, thiopurine metabolites were measured in blood drawn from the umbilical cord after delivery. *Results:* Ten patients (8 Crohn's disease, 2 ulcerative colitis) with a mean age of 32.8 years (±3.6) were included. All were on steady state azathioprine in a median dosage of 1.8 mg/kg (range 0.47-2.5). Metabolite levels varied highly during pregnancy, in 8/10 patients a decrease in 6TGN levels was observed, while in 3 of these patients 6MMP levels increased compared to baseline. In one patient, an increase of 6TGN level and leucopenia occurred, which normalized after delivery. Elevated liverenzymes were observed in another patient who developed elevated 6MMP concentrations during pregnancy, which normalized after delivery. Azathioprine dosage was not changed. Thiopurine metabolites were determined in eight infants. Median 6TGN concentrations, measured in eight infants, were significant lower compared to the mothers at time of delivery (133.5 versus 271.5 pmol/10e8RBC, P=0.042). No 6MMP could be detected in the infants. There were no preterm births or congenital malformations. All infants had a normal length, weight and Apgar scores ≥ 9 at 5 minutes. Full blood count and liverenzymes were determined in six infants and no abnormalities were found.
Conclusion: Thiopurine metabolite levels may vary highly during pregnancy in IBD patients. The placenta forms a (relative) barrier to azathioprine and its metabolites, as 6TGN seems to cross the placenta but 6MMP does not. Although the infants were exposed to 6TGN, none seemed to be affected.

Scheduled monitoring of vital signs during infusion with infliximab is not indicated

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Infliximab has been widely incorporated in the treatment for IBD. Most treatment algorithms involving infliximab state that during infusion vital signs (e.g. mean arterial pressure (MAP) and pulse) should be monitored in case acute infusion reactions (AIR) develop. However, AIR are relatively infrequent. The aim of our study was to assess the value of monitoring vital signs during the infusion with infliximab, both to measure and predict development of AIR.Consecutive patients (>18yrs) with a proven diagnosis of IBD who started treatment with infliximab in our referral center for IBD, from June 1999 to October 2007 were included in our study. No prophylaxis was given, unless AIR to infliximab developed during previous infusions. Blood pressure, and pulse were monitored at baseline before and during all infusions on a structured datasheet. These data were combined with clinical data on infusion reactions from medical files. Student t-tests were used to analyze differences in baseline vital signs between infusions with and without AIR. In patients experiencing AIR, baseline vital signs were compared with vital signs during AIR.A total number of 1941 infusions were given to 151 patients during the inclusion period (median number of infusions per patient: 10, range 1-70). A total of 17 AIR (0.82%) occurred in 13 patients (7.9%). Most documented symptoms during AIR were: dyspnea (41%), chest pain (41%) and dizziness (35%). Eight patients (62%) continued with i.v. corticosteroid and antihistamine prophylaxis, of these 3 patients (38%) experienced a new AIR. The majority (53%) of AIR occurred during the 5th and 6th infusion with infliximab. Baseline vital signs showed no difference in infusions with AIR (mean MAP=88, SD=14 and mean pulse=78, SD=9) compared to infusions without AIR (mean MAP=88, SD=13 and mean pulse=76, SD=13), p=ns. Subgroup analysis in 13 patients that experienced AIR resulted in the same non significant comparison: mean MAP=88, SD=14 and mean pulse=78, SD=9 in infusions with AIR, and mean MAP=83, SD=14 and mean pulse=74, SD=11 without AIR (p=0.2 and 0.3, resp.). During an AIR vital signs (mean MAP=90, SD=13 and mean pulse=77, SD=9) did not show a significant change compared to baseline (p=0.7 and 0.9, resp.).In conclusion, the incidence of acute infusion reactions on patient level is approximately 8%. Scheduled measuring of vital signs during infusion with infliximab, does neither indicate nor predict acute infusion reactions.

Serious events during nine years single centre experience with infliximab

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The TNF-α blocker infliximab is incorporated in the treatment guidelines for patients with IBD, based on positive results in randomized clinical trails. However, concerns about serious adverse events, such as death, malignancies and infections do exist. Here we evaluate the occurrence of serious events and safety of infliximab during nine years in a single center cohort of IBD patients.Consecutive patients (>18yrs) with a proven diagnosis of IBD who started treatment with infliximab in our referral centre for IBD, starting from June 1999 to October 2007, were included in our study. Infusion data were collected prospectively, medical records were reviewed retrospectively. All serious events were recorded and scored in the following categories: death, malignancies, and infections. Hospitalizations, length of stay and surgical procedures were assessed from the electronic patient records, and subdivided into gastrointestinal-related and other.A total number of 147 patients (32% male, mean age first infusion 37 year, SD=12) received a total number of 1937 infusions (median per patient=10, range 1-70). Nine patients (6%) developed malignancies during follow-up: 4 colorectal carcinomas, 1 carcinoid tumor with another primary signet-ring cell carcinoma of the small bowel, 1 breast cancer, 1 basal cell carcinoma, 1 squamous cell carcinoma and 1 superficial melanoma. During follow-up, 8 patients (5%) died: 6 as a result of malignancies (all patients with colorectal carcinoma, breast cancer and small bowel tumors), 1 patient died as a complication of short bowel syndrome and 1 patient by unknown reason. Ninety-five patients (65%) were hospitalized during follow up (median number of hospitalizations per patients was 2 (range 1-19)) with a median length of stay of 7 days (range 1-70). In 35 (37%) patients the occurrence of a serious infection was the main reason for hospitalization. Of all hospitalized patients, 72 patients (76%) underwent surgery, of which 48 (67%) were gastrointestinal related. In conclusion, in our nine years of single center experience we encountered an alarmingly number of malignancies which was often followed by death. Sixty-five percent of all patients were hospitalized after start of infliximab of which a considerate number underwent (gastrointestinal) surgery. Clinicians prescribing biological therapies should be aware of the development of serious events in their patients. Thorough monitoring of these patients is indicated.

Does immunogenicity play a role in adalimumab treatment for Crohn's disease?

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Infliximab, a chimeric monoclonal antibody to TNF, is an effective treatment for patients with Crohn's disease (CD). Chimeric antibodies like infliximab lead to antibody formation. Subsequently these antibodies to infliximab (ATIs) can lead to allergic reactions and to loss of efficacy. Adalimumab, a recombinant fully humanized monoclonal antibody has also found to be effective in CD. Little is known about the effect of ATIs and antibodies to adalimumab (ATAs) on adalimumab treatment outcome in CD patients previously treated with infliximab. The aim of this study was to assess whether ATAs or ATIs affect the efficacy of adalimumab therapy in CD patients.Patients with active luminal or fistulizing CD who failed to respond or were intolerant to infliximab were treated with adalimumab. The following subcutaneous regimen was used: 160 mg at week 0, 80 mg at week 2 and 40 mg every 2 weeks. Clinical response and side effects were assessed. The serum ATAs and ATIs levels were determined by a radioimmunoassay (cut-off values 12.4 AE/mL) during and prior to adalimumab treatment.In total 36 patients (M/F (9/27), median age 35 yrs, range 21-73) were included: 24 with luminal and 12 with fistulizing CD. Infliximab treatment was stopped due to a failed response (6/36), intolerance (25/36) and unknown reasons (5/36). Median adalimumab treatment duration was 313 days (range 71-632). Clinical response was 72% (responders (R): 26, non-responders (NR): 10) and side effects were observed in 42% (15/36) of patients. In 25 (19 R/6 NR) patients ATAs were assessed, of which 5 (20%) had positive ATAs. Of the 20 patients with negative ATAs; 18 (90%) were responders. The presence of ATAs was related to non-response to adalimumab (OR 12.7; CI: 1.7-92.6; p=0.05). ATIs were positive in 18 of 36 patients (50%), the mean ATIs level was 270.6±86.4 (SEM) AE/ml. ATIs levels were significantly increased in adalimumab non-responders (R vs.NR: 144.9±52.6 vs. 597.4±261.0 AE/mL, p<0.01). No relationship between the presence of ATIs and ATAs was observed.
Conclusions: Immunogenicity negatively influences response to adalimumab treatment due to the development of antibodies to adalimumab. In addition, high levels of antibodies to infliximab resulting from previous treatment may have an impact on therapeutic outcome of adalimumab.

Stepwise radical endoscopic resection for complete removal of Barrett's esophagus with early neoplasia: an international multicenter study.

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Endoscopic resection (ER) of high-grade dysplasia (HGD) or intramucosal cancer (IMC) in Barrett's esophagus (BE) is an effective and safe alternative to surgical treatment. After ER as monotherapy, recurrent lesions may develop elsewhere in the residual BE during follow-up (FU). Stepwise radical endoscopic resection (SRER) allows for removal of the whole BE by subsequent ER's, with histological correlation and has been shown to effectively eradicate early BE-neoplasia in single-center studies. The aim of this study was to evaluate the efficacy and safety of SRER for BE-HGD/IMC in 4 European tertiary referral centres that used a prospective SRER protocol in the past years.Patients with HGD or IMC in BE ≤ 5cm, without signs of submucosal infiltration or lymph node/distant metastases on endoscopy or endosonography, were included. Patients underwent ER sessions (cap, multiband mucosectomy or simple snare technique) with intervals of 4-8 weeks until complete eradication of BE. 151 BE patients with HGD or IMC, treated between Jan 2000 and Sept 2006 were included. Complete eradication of early neoplasia was achieved in 150 (99%) patients after a median number of two ER sessions (IQR 2-3). One patient with persisting IMC after 6 ER sessions was referred for esophagectomy. Complete removal of all intestinal metaplasia (IM) was achieved in 147 (97%) patients. Complications occurred in 1 % of ER procedures: 2 perforations treated conservatively and 2 delayed bleedings treated with endoscopic hemostatic techniques. 79 patients (52%) developed dysphagia that resolved with endoscopic dilatations in 77 patients. Two patients were perforated during endoscopic dilatation, one was treated conservatively and one patient underwent esophagectomy. During a median FU of 18 mo (IQR 7-31) 3 (2%) patients had recurrence of neoplasia, treated with repeat ER in 2 and curative surgery in one case. Seven patients (5%) had recurrence of visible BE mucosa (generally small islands) and 12 (8%) patients had IM detected distal to the neo-z-line. During FU, subsquamous IM was found in 9 patients (6%), all had undergone additional APC.
Conclusion: SRER for BE-HGD/IMC < 5 cm allows for removal of the whole BE with histological correlation and is associated with a low recurrence rate during FU since complete removal of BE is achieved in most patients. SRER is associated with esophageal stenosis especially in patients with a longer BE.

How adequate is endoscopic inspection of a Barrett's esophagus with early neoplasia by expert endoscopists? An international multi-center study with complete histological correlation of the whole Barrett's segment.

Endoscopic treatment of high-grade dysplasia (HGD) or intramucosal cancer (IMC) in Barrett's esophagus (BE) is a valid alternative to surgery. Submucosal cancer (SMC), however, has a high risk of lymphatic involvement and should be treated surgically. Many centers treat early BE neoplasia by endoscopic resection (ER) of the most involved area followed by ablation therapy (AT) of the remaining BE. Proper endoscopic work-up is of crucial importance here: SMCs that are not resected but ablated will be missed since AT lacks histological correlation. This may leave patients with a high risk of lymphatic involvement undiagnosed and undertreated. Aim of this study was to evaluate the rate of missed SMC in BE patients treated with stepwise radical endoscopic resection (SRER) after endoscopic work-up by expert endoscopists in 4 European tertiary referral centres. Patients with HGD/IMC in biopsies confirmed by an expert pathologist and BE <5cm were included. Work-up consisted of high quality endoscopy to inspect the BE completed with endosonography if desired. If there were no signs of deep submucosal invasion the endoscopically most involved area was resected followed by SRER. All ER specimens were retrieved, cut in 2-mm slices and reviewed by pathologists with extensive experience in this field, providing complete histological correlation of the whole BE.115 patients were included between Jan 2000 and Sept 2006. Two discontinued SRER due to unrelated morbidity. After a median of 2 ER sessions (IQR 2-3) complete eradication of dysplasia was achieved in 112 patients (99%). One patient with persisting IMC was referred for curative surgery. At the first ER only 5 patients (4%) were diagnosed with SMC, all superficial (T1sm1). No SMCs were diagnosed in any of the specimens of subsequent ER sessions to remove residual BE mucosa.Conclusion: Endoscopic work-up of BE patients with early neoplasia by experts in tertiary referral centres accurately identifies the most involved area of the BE. SMCs are effectively identified as an endoscopically visual lesion and diagnosed as SMC after ER. This suggests that after ER of the most involved area with histological correlation, the remaining BE can be safely treated with AT without a significant risk of undiagnosed and undertreated SMC.

Stepwise circumferential and focal radiofrequency ablation of Barrett's esophagus preserves esophageal diameter, compliance and motility

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Stepwise circumferential and focal radiofrequency ablation (RFA) using the HALO ablation system has been proven safe and effective for the eradication of Barrett's esophagus (BE) and appears not to be associated with esophageal scarring or stenosis. The aim of this study was to determine whether RFA for BE containing intramucosal cancer (IMC) or high-grade dysplasia (HGD) results in a change in esophageal diameter, compliance, or motility function. 12 patients (9M, median age 70yrs (52-76)) with IMC or BE-HGD (median BE length 7cm) treated with RFA were included. A balloon-based electrode was used for primary circumferential RFA and an endoscope-mounted electrode was used for secondary focal RFA. Measurement of the inner diameter was performed at 1cm intervals for the distal 10cm of esophagus using a non-compliant balloon and an automated pressure/volume system. Manometry was performed using a 10-channel water-perfused sleeve catheter. Compliance was evaluated using the functional luminal imaging probe (FLIP), measuring 8 cross sectional areas (CSA) at 4mm intervals from within a saline-filled bag with 2 pressure side holes; one proximal to and one inside the bag. Esophageal sizing, manometry and compliance (CSA/pressure) were recorded in patients at baseline and 2 months after the last RFA session. In addition, FLIP studies were performed in 10 healthy volunteers (HV) (7M, median age 22yrs (21-48)). All RFA patients had complete eradication of dysplasia and complete endoscopic and histological eradication of BE. After RFA, median esophageal diameter before and after treatment was 31.5 (25.3-33.0) mm and 31.3 (29.4-32.0) mm, respectively (n=10, p=0.41). LES resting pressure, LES length and esophageal contraction amplitude were not significantly different after RFA (n=7). Baseline compliance was different (p=0.05) between HV and BE patients. Compliance did not, however, change significantly in patients when comparing pre-RFA and post-RFA measurements (HV; 3.7±0.9 mm2/cmH2O; pre: 6.5±0.9 mm2/cmH2O; post: 7.3±1.3 mm2/cmH2O). Our study demonstrates that stepwise circumferential and focal RFA of BE results in neither impairment of esophageal motor function nor narrowing of the esophageal body inner diameter. In addition, esophageal compliance in BE patients is increased compared to HV, and more importantly, compliance is not changed by RFA. Based on these findings, we conclude that RFA is safe and preserves functional characteristics of the esophagus.

Endoscopic interobserver agreement for the Spigelman classification in patients with familial adenomatous polyposis (FAP)

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Background: The estimated lifetime risk of FAP patients to develop duodenal cancer is approximately 4 – 8%. For this reason, screening and surveillance of the upper gastro-intestinal tract is recommended for these patients. The main goal of such a surveillance-program is to identify the patients at highest risk for developing duodenal or periampullary cancer. For this purpose , the Spigelman classification was developed, enabling stratification of patients on both endoscopic and histological criteria. The endoscopic criteria are based on number and size of adenomas. It is estimated that patients in the highest stage (stage IV) have a 36% chance of developing duodenal cancer within 10 years and therefore surveillance should be intensified and surgical or endoscopic treatment considered. Thus, in the management of FAP patients the Spigelman stage plays a pivotal role.Aim: To assess the interobserver variation for the endoscopical Spigelman classification in FAP patients.Methods: Four experienced endoscopists from 3 academic centers with special interest in FAP patients reviewed high-quality videos of 16 gastroduodenoscopies in FAP patients using both end-viewing and side-viewing instruments in each patient. Patients were randomly selected from surveillance programs in the participating hospitals. The observers were blinded for each other's results. Items scored were number and size of polyps in the duodenal segments, antrum and aspect and size of the papilla. Results: Overall interobserver agreement between the endoscopists was moderate at best with a kappa value of 0.44. Kappa values of les than 0.40 are considered to be poor or fair whereas a kappa value of more than 0.80 is considered good. There was no significant difference in kappa values between early or advanced stage FAP patients. Individual kappa values ranged between 0.33 and 0.74. Remarkably, the highest kappa was reached between the two youngest endoscopists. Kappa did not improve between endoscopists from the same center.
Conclusions: although the management both with regards to surveillance interval and the timing of endoscopic and surgical intervention in FAP patients is guided by the Spigelman classification, this study clearly shows that interobserver agreement between endoscopists is moderate at best, even when done so by endoscopists with special interest and experience in FAP patients. This requests for caution when making important decisions based on the Spigelman classification.

Validation of interobserver agreement and accuracy of the combined use of autofluorescence imaging and narrow band imaging for differentiation of adenomatous and non-neoplastic colonic polyps in a non-expert setting

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Removal of colonic adenomas prevents the development of colorectal cancer, whereas resection of non-neoplastic lesions expands the endoscopic workload, increases pathology costs and has a risk of complications. Narrow band imaging (NBI) and autofluorescence imaging (AFI) are new imaging techniques enabling accurate differentiation of premalignant adenomas and innocent non-neoplastic polyps in expert hands. The combined use of both AFI+NBI has previously shown to increase the accuracy for differentiation. The aim of the present study was to assess the interobserver agreement and accuracy of NBI, AFI and combined AFI+NBI among non-expert endoscopists from non-university hospitals.Still images of 50 polyps (20 non-neoplastic; 22 adenomas; 8 serrated adenomas; median size 4mm) were randomly displayed to 7 non-expert endoscopists. After a short systematic training in pit pattern analysis, 50 NBI images were scored for Kudo pit pattern (I-V) and 50 corresponding AFI images were assessed for color (green, ambiguous, purple). Kudo type I-II and AFI-green color were considered non-neoplastic. Finally, 50 combined AFI+NBI images were scored: all AFI-green lesions as well as AFI-ambiguous lesions with Kudo type I-II on NBI were considered non-neoplastic. Images were additionally assessed as having high or low image quality.
The interobserver agreements for NBI-pit pattern, AFI-color and combined AFI+NBI were moderate among all assessors (kappa 0.50, 0.52 and 0.53 respectively). The interobserver agreement was significantly increased for images which were assessed as having high quality (overall kappa 0.70 versus 0.39). The accuracies of NBI, AFI and combined AFI+NBI were 70, 78 and 80% ($p<0.001$ for NBI *vs.* combined AFI+NBI); corresponding sensitivities were 79, 91 and 83% ($p=0.008$ for AFI) and corresponding specificities were 56, 58 and 75% ($p=0.001$ for combined AFI+NBI). The accuracies were significantly higher when image quality was high (73, 86 and 89%) and when serrated adenomas were excluded as adenomatous (74, 79 and 86%).
Conclusion: Among non-expert endoscopists, the interobserver agreements for NBI-pit pattern, AFI-color and combined AFI+NBI are equal. The results of this study confirm our previous finding that the combined use of AFI+NBI has the highest overall accuracy for polyp differentiation, although AFI has the highest sensitivity. Serrated adenomas have an unsuspicious endoscopic appearance, which negatively influences the accuracy for differentiation.

Diagnostic yield of colorectal neoplasia in daily clinical practice: consequences for future colorectal cancer screening?

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Introduction: In view of the relatively fixed, current endoscopic resources and the projected increased demand for endoscopic procedures related to a future CRC screening program, a clear insight in endoscopic utilization in daily clinical practice is mandatory. This insight might lead to changes in endoscopic utilization depending on initial clinical indication, thereby potentially alleviating (future) endoscopic workload. Objectives: 1). To assess the prevalence and location of advanced colorectal neoplasms in all patients clinically referred for lower G-I endoscopy. 2). To compare the yield of advanced neoplasms per indication in colonoscopies versus sigmoidoscopies. 3). To determine the predictive value of distal colonic findings with respect to advanced neoplasms in the proximal colon. Methods: A prospective multi-centre study (N=18) evaluating all colonoscopies and sigmoidoscopies performed in Northern Holland during a three months period in 2005. Results: In 8,637 patients, 5,652 colonoscopies and 3,444 sigmoidoscopies were performed. The prevalence of advanced neoplasms was 9,6% (N=828). In CRC patients (N=376), 74% and 26% had a distal and proximal tumour, respectively. Of all patients with right-sided advanced neoplasms (N=216), 50% had a normal distal colon, whereas 50% had a synchronous distal polyp. In all of the procedure indication clusters, the prevalence of right-sided advanced neoplasms ranged from 10-70%. Distally located hyperplastic polyps and/or small adenomas did not significantly increase the prevalence of advanced proximal neoplasia compared to no distal polyps, whereas distally located advanced neoplasms did (adjusted OR= 2.9; CI 2.0-4.2, $p<0.0001$).
Conclusion: Nearly 10% of all lower G-I endoscopies performed yielded an advanced neoplasia. Although our study included patients clinically referred for lower GI endoscopy, extrapolation of our data indicates that screening sigmoidoscopy might have missed 26% of advanced neoplasms. Based on clinical indication, no significant changes in endoscopic utilization can be realized to alleviate endoscopic workload since substantial numbers of right-sided advanced neoplasms are found in each indication cluster. In addition, there are no truly reliable distal markers to accurately decide on which patient should have a their entire colon visualized. As a result, our data suggest that colonoscopy should be the preferred endoscopic screening modality for a nation-wide CRC screening program.

Attendance to screening for colorectal cancer in the Netherlands; randomized controlled trial comparing two different forms of fecal occult blood tests and sigmoidoscopy

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Background & Aims: High attendance is a prerequisite for an effective colorectal cancer (CRC) screening program. We therefore conducted a randomized controlled trial to compare attendance to guaiac based fecal occult blood test (Haemoccult II; FOBT), immunochemical FOBT (OC-Hemodia Latex; FIT) and flexible sigmoidoscopy (FS) screening in an average risk screening naïve population.Methods: A representative sample of the Dutch population, consisting of 15,000 individuals, aged 50-74 years old were randomized prior to invitation to one of the three screening strategies (1:1:1) after stratifying for age, sex and social economic status (SES). At this moment the results of 12863 individuals are analyzable. Individuals with a history of CRC, inflammatory bowel disease or major health problems were excluded. Non-responders received a reminder. Repeated non-responders to FS screening were invited for FIT screening. Results: After excluding 569 (4%) subjects who met the exclusion criteria, died or moved away, the attendance rate was 49% (2019/4125; CI 50-53%) for FOBT, 58% (2405/4176; CI 56-59%) for FIT and 32% (1278/3993; CI 31-33%) for FS. Of the 2715 non-responders to FS screening 22% did perform a FIT, resulting in an overall attendance in the FS group of 47% (CI: 46-49%). Women demonstrated a higher participation rate to FOBT and FIT screening (FOBT 52%; FIT 61%; p<0.001) compared to men (FOBT 46%; FIT 55%; p<0.001) and lower response rate to FS screening (30%; men 34%; p<0.001). Subjects aged 50-54 were less likely to attend FIT or FOBT screening compared to older age groups (FOBT 43% vs 50%; p=0.002; FIT 53% vs 60%; p<0.001). No difference in attendance between age groups was found for FS screening. High SES resulted in a significant increased participation rate to FOBT and FIT screening compared to low SES (FOBT 54% vs 43%; FIT 65% vs 52%; p<0.001). Conclusions: This is the first randomized controlled population based trial showing differences in attendance between three screening strategies. The attendance was highest for FIT and lowest for FS screening. Age, sex and SES were independent predictors for attendance to CRC screening. This study, next to evidence from efficacy studies, gives necessary input for deciding on the preferred strategy for CRC screening.

Diagnostic yield of screening for colorectal cancer in the Netherlands; randomized controlled trial comparing two different forms of fecal occult blood testing and sigmoidoscopy.

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Comprehensive Cancer Center, Rotterdam[4].Background & Aims: Screening for colorectal cancer (CRC) is widely accepted, but there is lack of consensus about the preferred strategy for CRC screening. We conducted a randomized controlled trial to determine diagnostic yield of guaiac based fecal occult blood test (Haemoccult II; gFOBT), immunochemical FOBT (OC-Hemodia Latex; FIT), and sigmoidoscopy (FS) for CRC screening.Methods: A representative sample of the Dutch population, aged 50-74 years, was randomized prior to invitation to one of the three screening strategies (1:1:1). Individuals with a history of CRC, inflammatory bowel disease or major health problems were excluded. Colonoscopy was indicated for screenees with a positive gFOBT, FIT (cutoff 50ng/ml) or a high-risk FS, defined as (tubulo)villous histology, high-grade dysplasia, CRC, polyp size ≥10 mm, ≥3 adenomas or ≥20 hyperplastic polyps. At this moment the results of 6200 participants are analyzable.Results: gFOBT was performed by 2138 participants (men: 46%; mean age 61±7) and a FIT by 2494 participants (men 48%; mean age 61±7). 1568 (men 52%; mean age 61±6) individuals attended FS screening. The positivity rate was 2.6% for the gFOBT and 5.0% (cutoff 100ng/ml) or 7.3% (cutoff 50ng/ml) for the FIT. 158 (10%) of the FS screenees were classified as high-risk and referred for colonoscopy. 1358 screenees without polyps (n=921; 59%) or with non-advanced polyps (437; 28%) were discharged. The advanced neoplasia detection rate was 1.0% (CRC: 0.3%) for gFOBT, 2.2% (CRC 0.4%) for FIT (cutoff 100ng/ml) and 3.0% (CRC 0.5%) (cutoff 50ng/ml) and 7.6% (CRC 1.0%) for FS. Conclusions: This is the first randomized controlled population based trial showing differences in diagnostic yield between three screening strategies. The detection rate for advanced neoplasia was eight times higher for FS screening compared to gFOBT. A lower cutoff (50ng/ml) for a positive FIT resulted in a higher detection rate for advanced neoplasia, but also in more false-positives.

High prevalence of small adenomas in a colorectal cancer screening population using primary colonoscopy.

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Colorectal cancer (CRC) screening using colonoscopy offers the opportunity for early detection of CRC as well as prevention through removal of adenomas. The clinical significance of small adenomas has been addressed in several patient populations, but rarely in connection with CRC screening. Our aim was, to study prospectively the endoscopic and histological features of adenomas in relation to size and location, detected in a workplace-based population undergoing screening by primary colonoscopy. Demographic, endoscopic and histological data were collected in employees aged 50-65 yrs, invited for CRC screening by colonoscopy. Subjects with severe co-morbidity, prior colonoscopy ≤5 yrs and recent GI symptoms were excluded. Polyp size was measured using an open biopsy forceps. Advanced adenomas were defined as: ≥ 10 mm and/or villous component and/or high grade dysplasia according to guidelines (Gastroenterology 2006). Adenoma size was categorised as: < 6 (diminutive), 6-9 (small) and ≥10 mm (large). 385 employees (39.2% male) underwent a colonoscopy. Adenomas were found in 25.5% of participants (n=98), being significantly more frequent in males than females (31.8% vs. 21.7%, $p<0.05$). 39.8 % of subjects with adenomas (39 out of 98) had advanced adenoma(s). In the 98 subjects with adenomas, a total of 183 adenomas were detected (1.9 per subject). The numbers of adenomas being diminutive, small or large were 120 (65.5%), 25 (13.7%) and 38 (20.7%), respectively. Large adenomas were more frequently located in the distal colon (71.1%, $p<0.01$). Small and diminutive adenomas were as often located in the proximal as in the distal colon (50.8% and 56.0%)
Of the diminutive and small adenomas, 11.7% and 36.0%, respectively, were advanced lesions. Regarding all advanced adenomas (n=61), 22.9% was diminutive and 14.8% was small. Comparing different subgroups reported, no further difference with regard to age and gender were observed. Conclusions: In this workplace-based screening population, a high frequency of diminutive and small adenomas was found, a considerable proportion of them being advanced. Small adenomas were found as frequent in the proximal colon as in the distal colon. These findings stress the importance of accurate screening and subsequent removal of these lesions.

Nurse endoscopy for colorectal screening? A survey of expectations, opinions and future perspectives.

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Background: Colorectal cancer screening and surveillance is still not feasible in the majority of Europe. Nurse endoscopists (NE) may provide a solution for the high endoscopic demand and shortage of endoscopists. The aim of the present study was to determine expectations, opinions and future perspectives of nurse endoscopy in a Western European community. Methods: A postal questionnaire was send to all registered gastroenterologists (GE) (n=301) and gastroenterology residents (n=79) in the Netherlands in 2007. Topics that were evaluated included: presumed endoscopic quality, patient experiences and costs. In addition the attitude towards and potential endoscopic procedures to be performed by NE were evaluated. Results: 185 of 380 (49%) GE and residents completed the questionnaire. The distribution of academic versus general hospital employees was 31 vs 69% with a 79 to 21% M/F distribution. Overall, 51% had a positive attitude towards introduction of NE, whereas 17% were neutral and 32% negative. No difference in endoscopic quality (adenoma detection, complications and cecal intubation rates) between physician and NE was expected by 43% of respondents, 36% expected physicians to perform better and 21% expected nurses to perform better. With regard to patient experiences: 68% of respondents expected physicians to perform better than NE, 18% expected no difference and 14% expected NE to perform better. Screening sigmoidoscopy and colonoscopy were considered appropriate procedures to be performed by nurses according to respectively 89% and 70% of respondents. In contrast, only half of the respondents judged that diagnostic endoscopies would be appropriate for NE. Only 43% judged polypectomies of polyps smaller than 10mm appropriate for NE. GE and residents who expected better or comparable endoscopic quality of NE in comparison with physicians, were significantly more positive towards the introduction of NE (69 and 55% vs 35%; p=0.001). Multivariate analysis showed that the expected quality was an independent predictor for a positive attitude towards the introduction of NE (p=0.001). Respondents age, gender or type of hospital was not related with the attitude towards NE.
Conclusion: The majority of GE is positive towards the introduction of NE especially for screening sigmoidoscopy and colonoscopy. To determine the exact place of nurse endoscopy, precise assessment of endoscopic quality and patient experiences of well trained NE is highly needed.

Adjusting cut-off values of immunological FOBT allows tuning of CRC screening programs to colonoscopy capacity.

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Introduction: immunological faecal occult blood tests (i-FOBT's) have been proposed for population based colorectal cancer screening. i-FOBT has advantages over guaiac-based FOBT's: only one faecal sample is needed and no dietary restrictions exist because of specificity for haemoglobin of human origin. i-FOBT gives a quantative result which enables adjusting the threshold for calling a test positive and referring a screenee for colonoscopy. This can be relevant in a phase of gradually implementing a CRC screening program because of limited colonoscopy capacity. Different cut-off values may also influence cost-effectiveness. The optimal cut-off value of i-FOBT has not been clarified yet, but cut-off values of 50-100 ng/ml are currently used.
Aim: to assess to what extent test characteristics of i-FOBT (OC sensor®, Eiken chemical Co, Japan) are influenced by adjusting the cut-off value in terms of clinical yield of colorectal cancer and advanced adenomas.
Methods: all patients aged ≥18 years scheduled for colonoscopy in one of five participating hospitals, were asked to perform an i-FOBT the day prior to colonoscopy. I-FOBT was analyzed with the "OC-SENSOR μ" desktop analyser. Cut-off values of ≥50, ≥100, ≥150 and ≥200 ng haemoglobin per ml, respectively, were used and outcomes compared to colonoscopy. All cases of CRC and advanced adenomas (i.e. ≥1 cm in diameter and/or villous architecture and/or high-grade dysplasia) were scored. Patients with known IBD, patients in whom the caecum was not visualized and/or bowel cleansing was insufficient, were excluded.
Results: 1424 patients were eligible and included in this interim analysis. On colono-scopy, advanced neoplasia was found in 11.7% of the patients (CRC in 3.3% and advanced adenomas in 8.4%). The OC sensor® was positive in 8.8%, 9.9%, 11.7% and 13.6% at cut offs of 200, 150, 100, and 50 ng/ml, respectively (Table 1), resulting in 48,000 less colonoscopies between highest and lowest cut offs on a screening population of 1,000,000 while NPV for cancer remains largely stable.
Conclusions: a igher cut off for i-FOBT can reduce strain on colonoscopy capacity in the start up phase of CRC screening program, while NPV for cancer remains largely stable.

Disturbed Hepatic Carbohydrate Management During High Metabolic Demand in Medium-Chain Acyl-CoA Dehydrogenase (MCAD)-Deficient Mice *

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Medium chain Acyl-CoA dehydrogenase (MCAD) catalyses crucial steps in mitochondrial β-oxidation (mFAO), a process that is of key relevance for maintenance of energy homeostasis especially during high metabolic demand, e.g., fasting or infection. To gain insight into the metabolic consequences of MCAD-deficiency under these conditions, we compared hepatic carbohydrate metabolism in vivo in wild-type and MCAD-/- mice during fasting and during a lipopolysaccharide (LPS)-induced acute phase response (APR). Unexpectedly, MCAD-/- mice did not become more hypoglycemic upon fasting or during the APR than wild-type mice did. Microarray analyses revealed increased hepatic Pgc-1α and decreased Pparα and Pdk4 expression levels in MCAD-/- mice in both conditions, indicative for altered control of hepatic metabolism. Quantitative flux measurements showed that the gluconeogenic flux (GNG) towards glucose-6-phosphate (G6P) was not affected upon fasting in MCAD-/- mice. During the APR, however, GNG was significantly decreased (-20%) in MCAD-/- mice compared to wild-type mice. Remarkably, newly formed G6P was preferentially directed towards glycogen in MCAD-/- mice in both conditions. Together with diminished GNG, this led to a decreased hepatic glucose output during the APR in MCAD-/- mice: GNG and hepatic glucose output were maintained in wild-type mice in both conditions. The APR-associated hypoglycemia in both groups was mainly due to enhanced peripheral glucose uptake. Our data demonstrate that MCAD-deficiency in mice leads to specific changes in hepatic carbohydrate management upon exposure to metabolic stress. The deficiency, however, does not lead to reduced GNG during fasting alone which may be due to the existence of compensatory mechanisms orlimited rate control of MCAD in murine mFAO: the dogma that complete mFAO is essential do drive GNG under fasting conditions requires re-evaluation.

The role of IGFBP5 in liver fibrosis

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Liver fibrosis is caused by chronic liver damage due to drug abuse or viral infections. Since no effective treatment is available, it progresses to cirrhosis leading to hepatocellular carcinoma and/or liver failure. Hepatic stellate cells (HSC), the source of the excessive fibrous matrix, play a central role in the pathophysiology of liver fibrosis. In normal liver, HSC reside in the space of Disse, as vitamin A storage site. Upon liver injury, they become activated and eventually transdifferentiate into myofibroblast-like cells, acquiring contractile, proinflammatory, and fibrogenic properties. Treatments that specifically target activated HSC or reverse their activation may prevent progression of liver fibrosis.

To identify these targets, we performed gene expression profiling of the transformation process. One of the factors strongly induced by HSC activation is insulin-like growth factor binding protein 5 (IGFBP5). IGFBP5 can inhibit IGF1, and hence severely obstruct the IGF axis, as seen in liver fibrosis patients. Present in excess it causes lung and skin fibrosis.

To investigate if IGFBP5 has a pro-fibrotic role in liver we studied its effect on the human LX2 cell line, a model for partially activated HSC. Addition of recombinant IGFBP5 increased the survival of LX2 cells, as shown by a WST assay. This increase was not due to enhanced proliferation, since no effect of IGFBP5 was seen on BrdU incorporation. Instead, we found that IGFBP5 lowers the level of apoptosis. Using a Caspase 3/7 assay we observed a decrease in apoptosis for more then 50%. Addition of IGFBP5 increased the expression of fibrotic marker collagen 1a1, and anti apoptotic marker bcl2.

LX2 cells synthesize IGFBP5, but only in a small amount compared to fully activated cells. To confirm the role of IGFBP5 on stellate cells survival we silenced the endogenous synthesis using siRNA. siRNA treatment reduced the level of the IGFBP5 mRNA by 80%, and resulted in undetectable levels of IGFBP5 protein in these cells. This decrease in IGFBP5 level impeded the viability of the cells, and increased apoptosis for more then 30%. Silencing of IGFBP5 reduced the expression levels of genes involved in the development of fibrosis, such as TIMP1 and MMP1, involved in maintenance of extracellular matrix.

Since our data indicate that IGFBP5 seems to improve the survival of (partially) activated HSC, lowering its expression may reduce their number in fibrotic liver and thus inhibit disease progression.

Conditional inactivation of glutamine synthetase in the liver

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Due to its relatively high affinity for ammonia, glutamine synthetase (GS) is considered a crucial component of the ammonia-detoxifying function of the liver. However, this concept is largely based on *ex-vivo* assays in perfused livers. To assess the function of GS in the liver *in vivo*, we deleted hepatic GS expression using the Cre-lox technique. In AlfpCre$^{tg/-}$/GS$^{fl/LacZ}$ (GS-KO/L) mice, GS expression in the liver was selectively and effectively eliminated, but the animal's health remained unaffected. We investigated glutamine and ammonia metabolism in the portal drained viscera and liver in the fed and post-absorptive conditions, and as it adapted to a 4-day challenge with 0.28M NH_4HCO_3 in the drinking water. Compared to control mice, the predominant change in fed GS-KO/L mice was a 35-40% decline in arterial, portal-, hepatic-venous and hepatic glutamine levels. However, circulating ammonia levels and the flux of glutamine or ammonia across the portal drained viscera and liver were similar in GS-KO/L and control mice. The ammonia challenge unmasked the absent capacity of GS-KO/L liver to produce glutamine and the limited capacity to detoxify ammonia. However, since arterial ammonia levels were 3-fold increased in both genotypes, we conclude that hepatic GS is dispensable for ammonia detoxification.
Since GS in striated muscle is considered to be the main endogenous source of de novo synthesis of glutamine, we investigated the muscle's potential to detoxify ammonia in mice with a complete loss of GS expression in muscle. As GS-KO/L mice, MCK-Cre$^{tg/-}$/GS$^{fl/LacZ}$ (GS-KO/M) mice were healthy without differences in the net production of glutamine, other amino acids, or ammonia across the hindquarter in the fed condition. Upon fasting, the production of glutamine and ammonia across the hindquarter increased in control, but not in GS-KO/M mice. Furthermore, the net production of glucose, alanine, and lactate did not change in fasted GS-KO/M mice, whereas their consumption (glucose) or production (lactate, alanine) tended to be higher in control mice. By comparing GS-KO/M and control mice, we further established that muscle can detoxify ~35 µmol ammonia/25g bw.h in a GS-dependent manner. This capacity suffices to detoxify all ammonia from protein turnover in the body. Our findings, therefore, reveal an important capacity of muscle to detoxify ammonia.

The Bone Morphogenetic Protein Pathway is inactivated in the majority of Sporadic Colorectal Cancers.

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Transforming Growth Factor β (TGFβ) plays an important role in colorectal cancer (CRC). The finding of Bone Morphogenetic Protein (BMP) Receptor 1a mutations in Juvenile Polyposis suggests that BMPs, a subgroup within the TGFβ superfamily, also play a role in CRC. We investigated the BMP pathway in sporadic CRC.
We investigated BMP receptor (BMPR) expression using immunoblotting and sequenced microsatellites of BMPR2 in CRC cell lines. We investigated the effect of reintroduction of wild-type BMPR2 on BMP pathway activation in cell lines and investigated the effect of the 3'-untranslated region (3'UTR) microsatellite mutations in BMPR2 on protein expression using a luciferase construct coupled to the wild type or mutant BMPR2 3'UTR. We assessed the expression of BMPRs, SMAD4 and pSMAD1,5,8 in 72 sporadic CRCs using a tissue microarray and immunohistochemistry. CRC specimens were analyzed for microsatellite mutations in BMPR2.
BMPR2 protein expression is abrogated in microsatellite unstable (MSI) cell lines while SMAD4 protein expression is abrogated in microsatellite stable (MSS) cell lines. BMPR2 is mutated in all MSI cell lines at a microsatellite region within the 3'UTR and in none of the MSS cell lines. Reintroduction of wild type BMPR2 into non-expressing cell lines leads to activation of the BMP pathway. The mutant 3'UTR leads to lower levels of protein expression. BMPR2 expression is impaired more frequently in MSI CRCs than MSS (85% vs 29%:$p<0.0001$) and shows a mutually exclusive pattern of impaired expression compared to SMAD4 as seen in cell lines. Nine of eleven MSI-cancers with impaired expression of BMPR2 have mutations at the same 3'UTR microsatellite. The BMP pathway is inactivated, as judged by nuclear pSMAD1,5,8 expression, in 70% of CRCs and this correlates with BMPR and SMAD4 loss.
Our data suggest that the BMP pathway is inactivated in the majority of sporadic CRCs. In MSI CRC this is associated predominantly with impaired BMPR2 expression due to microsatellite mutations within the 3'UTR and in MSS CRC with impaired SMAD4 expression.

Diminished epithelial protection during post-natal development and suckling-weaning transition in Mucin 2 deficient mice *

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The structural component of the colonic mucus layer is the mucin Muc2. In ulcerative colitis and necrotizing enterocolitis, diminished synthesis of Muc2 contributes to the impaired mucosal barrier function. We recently demonstrated that loss of Muc2 affects the protective capacities of the mucus layer, leading to colonic inflammation. At birth, the intestine is sterile and is subsequently rapidly colonized with commensal bacteria which interact with intestinal epithelial cells influencing mucosal homeostasis. We hypothesized that lack of Muc2 influences bacterial-epithelial interactions, leading to altered epithelial proliferation and induction of inflammation. Therefore, we studied the changes in colonic morphology both during early postnatal development and suckling-weaning transition in Muc2 knockout (Muc2-/-) and wild-type (WT) mice. Muc2-/-] and WT mice were sacrificed at embryonic (E)18.5, postnatal (P)1.5; 7.5; 14; 21; 28 days and adults. These mice were monitored for clinical symptoms (weight, bleeding, diarrhea), and colonic histological changes. Proliferation and inflammation was studied by immunohistochemistry. Following birth the mice received breast milk and weaning took place at day 21. Before birth (E18.5) there were neither weight differences nor distinct histological changes between the Muc2-/- and WT mice. First signs of inflammation in the distal colon, characterized by an increase of CD3+ cells, thickening of the mucosa, epithelial cell flattening and general destruction of architecture, were induced shortly after birth in Muc2-/- mice, and aggravated during postnatal development (onset of colitis at P1.5 vs full blown colitis in adults). Interestingly, significant weight differences, histological changes and increased proliferation were induced in Muc2-/- mice when the mice were transferred form breastfeeding to standard rodent pellets.
Conclusions: This study demonstrates that a diminished epithelial protection due to absence of Muc2, combined with colonization of the intestine after birth, plays a major role in the induction and perpetuation of inflammation in the intestine. The Muc2-/- mouse model provides a powerful tool to investigate the influence of intestinal microbiotic composition, epithelial-bacterial interactions and subsequent signaling pathways responsible for the altered epithelial homeostasis and inflammation during post-natal development and suckling-weaning transitions

Prospective multicenter study on the incidence of neoplastic progression in Barrett esophagus patients

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Barrett esophagus (BE) is a premalignant disorder, predisposing to esophageal adenocarcinoma (EAC). The latter is assumed to develop through the cascade of intestinal metaplasia (IM), low-grade dysplasia (LGD) and high-grade dysplasia (HGD). Regular endoscopic and histologic follow-up is recommended for the detection of progression in BE patients. It has been reported that the incidence of EAC and of BE is increasing over the last decades in Western countries, however these reported incidences show considerable variation. We evaluated the incidence of progression from no dysplasia (ND) towards LGD and from ND or LGD towards HGD and EAC in a Dutch BE cohort. In this prospective, multicenter study, 783 BE patients were included with ND (n=664) or LGD (n=119) at baseline and a BE segment (with a histologic diagnosis of IM) of 2 cm or more. Endoscopic and histologic surveillance was performed according to the ACG guidelines (2002). The annual risk of progression towards LGD, HGD and EAC was analyzed with incidence densities.Within the 2-year follow-up period, 80/783 (10%) patients were lost-to-follow-up. Of these, 15 patients had died from other causes than EAC and 65 patients refused further participation. Mean age (± SD) at baseline (n=703) was 60.3 ± 11.1 years (73% males). Fivehundred sixty-one (80%) patients were previously known with BE with a median follow-up of 4.0 years (interquartile range 2.0 to 8.0). Mean (± SD) follow-up time in this study was 2.0 ± 0.4 years with a total of 1192 patient-years of follow-up for patients with only baseline ND and a total of 1383 patient-years of follow-up for patients with ND and LGD. During 1192 patient-years of follow-up, 32/604 BE patients with baseline ND developed LGD, which equals one LGD case per 37 patient-years. HGD developed in 11/703 BE patients and EAC in 11/703 BE patients during 1383 patient-years of follow-up, which corresponds to one HGD case per 125 patient-years and one EAC case per 125 patient-years. This equals 22/703 BE patients with progression to HGD or EAC during follow-up, yielding an incidence of one case of HGD or EAC per 63 patient-years.

Conclusion: In BE patients with a columnar BE-segment of two cm or more and ND or LGD at baseline, the annual risk of progression towards HGD or EAC is 1.6%. BE patients with baseline ND had an annual risk of developing LGD of 2.7%. Longer follow-up is needed to accurately establish the natural history of BE in this cohort.

Flow CYtometry in BARrett Esophagus (CYBAR study): a prospective cohort study

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The incidence of esophageal adenocarcinoma (EAC) has increased rapidly over the last decades. Barrett esophagus (BE) predisposes to EAC, with an annual risk of developing EAC of approximately 0.5%. Surveillance aims to detect neoplastic lesions at an early and curable stage. Due to sampling error and interobserver variation, histological evaluation is presumably of limited value in differentiating the risk for neoplastic progression. It has been suggested that biomarkers may aid in identifying high risk patients. The aim of this study was to determine the value of flow cytometry (FC) for the risk of neoplastic progression in BE patients.In this multicenter, prospective cohort study we included 703 BE patients with a BE segment of 2 cm or more and either no dysplasia (ND; n=604) or low grade dysplasia (LGD; n=99) at baseline. FC analysis was performed on paraffin embedded biopsies. BE patients were stratified for different surveillance schemes based on FC result (normal =diploid DNA-content; abnormal=aneuploid DNA-content) and baseline histology, which was based on consensus of at least 2 pathologists. Progression towards HGD and EAC was analyzed with Kaplan-Meier curves and Cox regression to estimate hazard ratios (HR) with adjustment for potential confounding variables.Eleven patients showed progression to HGD and 11 to EAC, accounting for a 2-yr cumulative risk for neoplastic progression of 6.1% (95%CI: 2.3-9.9%). Patients with baseline ND and diploidy (n=479) had a risk for progression to HGD or EAC of 3.7% (95%CI: 1-6.4%) compared with a 0% risk for patients with aneuploidy (n=78; log rank test p=0.19). Patients with baseline LGD and diploidy (n=84) had a progression risk of 30% (95%CI:21.5-39%) compared with 20% (95%CI: 3-37%) for patients with aneuploidy (n=15;log rank test p=0.50). Multivariable analysis (adjusted for age, gender and presence of dysplasia) showed no association of aneuploidy with development to HGD or EAC (HR 0.9; 95%CI:0.3-3.1). The presence of LGD was associated with an increased risk of developing HGD or EAC (HR 7.1; 95%CI:2.9-18). Similar results were found in repeated analyses for development of HGD or EAC alone. Conclusion: Patients with LGD at baseline had a 7 times increased risk of developing progression towards HGD or EAC. Aneuploidy, determined in paraffin embedded biopsies, had no evident predictive value for neoplastic progression in BE patients after two years of follow-up, although longer follow-up is needed.

Low-grade intra-epithelial in Barrett's esophagus: over-diagnosed but under-estimated

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IntroductionLow grade intra-epithelial (LGIN) is a difficult diagnosis in Barrett's esophagus (BE) surveillance practise. According to some studies only a minority of cases progresses to high-grade intra-epithelial neoplasia (HGIN) or cancer whereas other small-sized studies have shown a high progression rate for LGIN cases with an expert consensus diagnosis. The aim of the present study was to review all cases of LGIN in a large (non-university) cohort of BE patients by two expert pathologists and to relate these findings outcome with endoscopic follow-up.MethodsWe indentified all patients diagnosed with LGIN between 2000 and 2006 in 6 non-university hospitals that participate in a partly retrospective and partly prospective BE registry in the Amsterdam area. Pathology specimens of these patients were retrieved and reviewed in consensus by two GI-pathologists with extensive experience in Barrett's neoplasia. From all patients follow-up endoscopies with corresponding pathology were then retrieved from our retrospective and prospective BE database. In case of a diagnosis of LGIN or HGIN during follow-up, these pathology specimens were reviewed by the study pathologists.ResultsIn total 1306 BE pts were identified in the 6 participating hospitals. 110 pts were diagnosed with LGIN and reviewed by the expert panel. The following consensus diagnoses were made: LGIN in 10 pts, indefinite for dysplasia in 13 pts, and non-dysplastic BE (NDBE) in 87 pts.During a median follow-up of 42 months (IQR 23-56) 5 pts were diagnosed with HGIN or cancer, all with a prior consensus diagnosis of LGIN. Two pts with a consensus diagnosis of indefinite for dysplasia progressed to LGIN. Of those patients down staged to NDBE none progressed to LGIN, HGIN or cancer. Pts with a consensus diagnosis of LGIN had a cumulative risk of developing HGIN or cancer of 81% in 5 years (see figure). This was significantly different from pts with a consensus diagnosis of indefinite for dysplasia or NDBE (log rank $p<0.0001$).
Conclusion: LGIN in Barrett's esophagus is over-diagnosed in general practise: 77% of LGIN diagnoses were down-staged to NDBE by our expert panel and these patients were found to have a negligible rate of progression during FU. Yet the relevance of a diagnosis of LGIN in BE was underestimated since patients in whom the diagnosis was confirmed by our expert panel were found to have a high risk for progressing to HGIN or cancer during follow-up.

Ursodeoxycholic acid treatment for unconjugated hyperbilirubinemia: promising results in Gunn rats *

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We aim to develop an oral treatment for unconjugated hyperbilirubinemia. Oral bile salt therapy is used extensively for cholestatic conditions with conjugated hyperbilirubinemia. It has remained unclear, however, whether bile salts could be applied as treatment for unconjugated hyperbilirubinemia. We determined the effects of dietary bile salt treatment with ursodeoxycholic acid (UDCA) or cholic acid (CA) on plasma unconjugated bilirubin (UCB) concentrations and kinetics in the Gunn rat model of unconjugated hyperbilirubinemia. Gunn rats were fed standard diet or the same diet supplemented with UDCA (0.5 wt%) or CA (0.5 wt%) for either 1 wk or 6 wks. After 6 wks, UCB kinetics were determined under steady state conditions, applying IV administration of ^{3}H-UCB (0.3Ci/100g BW). UCB and ^{3}H-UCB were measured in plasma, bile and in feces during the experiments and allowed determination of UCB pool size, fractional UCB turnover and total UCB turnover. Urobilinoids, intestinal breakdown products of UCB, were determined in the feces. UDCA or CA treatment for 1 wk profoundly decreased plasma UCB concentrations (-21% and -30%, resp) compared with controls ($p<0.01$) and was effective within 3 days. UDCA or CA treatment for 6 wks resulted in a stable decrease (~ -40%, both groups; $p<0.001$) in plasma UCB concentrations from wk 2 on. Both treatments increased combined fecal output of UCB and urobilinoids during the first four days of treatment (+52% and +32%, resp; $p<0.01$). Furthermore, both treatments decreased total UCB poolsize (-33% and -32%, resp; $p<0.05$), increased fractional UCB turnover (+33% and +25%, resp; $p<0.05$%) and had no effect on total UCB turnover.
In conclusion: dietary treatment with either UDCA or CA induces a sustained decrease in plasma UCB concentrations in Gunn rats. The mechanism involves both increased UCB turnover and fecal disposal. Present results support the feasibility of oral bile salt treatment of patients with unconjugated hyperbilirubinemia.

(Non)toxigenic Clostridium difficile colonization and the risk of atopic manifestations in infancy

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Several studies have reported an association between colonisation with Clostridium difficile and atopic diseases. An underlying mechanism could be through breaking oral tolerance, as this bacterium can cause intestinal inflammation, leading to increased permeability of the mucosal barrier and penetration of allergens. The enteropathogenicity of C. difficile is associated with the production of toxins A and B, which both disrupt epithelial cell tight junctions. According to the hypothesized mechanism, it is expected that especially infants colonized with toxin-producing strains are at increased risk of developing atopic diseases, especially food allergy.
The aim of our study was to investigate which factors influence (non)toxigenic C. difficile colonisation and examine the role of C. difficile toxigenicity on the development of atopic manifestations. Faecal samples of 957 one-month-old infants, participating in the KOALA study, were subjected to real-time PCRs for the detection of C. difficile and its toxins A and B. Information on potential determinants of (non)toxigenic C. difficile colonisation, atopic symptoms and potential confounders was available from repeated questionnaires. Specific IgE was measured in blood samples collected at the infant's age of 1 and 2 years. A clinical diagnosis of eczema was made at the age of 2 years (UK Working Party criteria). 200 infants were colonised with nontoxigenic and 40 with toxigenic C. difficile. Hospital delivery was associated with higher colonisation rates of both toxigenic and nontoxigenic C. difficile compared to home-born infants. Infants being exclusively breastfed were less often colonised with (non)toxigenic strains compared to infants receiving formula feeding. Infants colonised with nontoxigenic C. difficile were at increased risk of developing parentally reported eczema (adjusted odds ratio (ORadj) 1.45; 95% confidence interval 1.04-2.03), clinically diagnosed eczema (ORadj 1.83; 1.10-3.04) and sensitisation to food allergens (ORadj 1.85; 1.14-3.00) compared to uncolonised infants. Colonisation with toxigenic C. difficile was associated with an increased risk of recurrent wheeze (ORadj 3.92; 1.62-9.44).
Conclusions: Nontoxigenic and toxigenic C. difficile strains share the same environmental origin, but are differently associated with atopic manifestations.This demonstrates the importance of studying the effect of gut bacteria in health and disease beyond the genus and species level

Long-term follow-up and outcome of a cohort of pediatric patients with functional constipation - MLDS-project SWO 03-13

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Follow-up studies in children with functional constipation indicate that symptoms persist for many years in a substantial subgroup. Yet, scarce data exists about the outcome of childhood constipation at adult age. This study aimed to assess outcome of constipated children, referred to a tertiary outpatient clinic, up to 15 years after first presentation. From 1993 until 1999, constipated children older than 5 years at intake participated in several studies evaluating therapeutic modalities for functional constipation. After an initial 6-week intensive treatment protocol, all children were subsequently enrolled in this follow-up study, with prospective data collection at 6 and 12 months and annually thereafter, using a standardized questionnaire. Successful outcome was defined as ≥3 bowel movements/ week for a period of 4 weeks with <2 fecal incontinence episode/ month, irrespectively of laxative use. For each time point of follow-up successful outcome was computed. Correlation between clinical characteristics and successful outcome was analyzed using a logistic regression model.Four hundred-eighteen patients (266 male; median (25th-75th percentile) age 8.0 (6.4-9.9) years) were included. Median duration of follow-up was 10 (7-13) years. The cumulative percentage of children with success was 52%, 67% and 81% at 1, 5 and 10 years of follow-up respectively.
According to biological age, successful outcome was found in 60% of the children at 12 years of age with a steady increase to 81% at the age of 18 years. Thereafter this percentage remained stable in those who had reached adulthood. At last follow-up two hundred-eighteen children (135 male) reached the age of 18 years. This subgroup had a median age of 21.0 (19.5-22.6) years with median follow-up duration of 13 (11-13) years. Successful outcome at adult age was significantly associated with male gender (OR 2.27 [95%CI 1.12-4.60], p=0.02), a higher defecation frequency at intake (OR 1.19 [1.03-1.38], p=0.02) and negative family history for defecation disorders (OR 2.40 [1.06-5.44], p=0.04).
Conclusions: Childhood constipation persists beyond the age of 18 years in one out of five patients. Successful outcome in young adults is more likely in males and in those patients presenting with a higher defection frequency and/or without a family history for defecation disorders. A favorable outcome of childhood constipation can not generally be assumed and therefore intensive treatment and follow-up are essenti

Association of catechol-O-methyltransferase gene variants with chronic pancreatitis in 2 independent Dutch and Hungarian cohorts.

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Objective: pain is the major presenting symptom of chronic pancreatitis (CP). Catechol-O-methyltransferase (COMT) is one of the enzymes that regulation of the levels of catecholamines and enkephalins. Several single-nucleotide polymorphisms (SNPs) modulate the catecholamine-clearing abilities of the COMT enzyme and influence human pain perception. The aim of our study was to investigate COMT SNPs in 774 samples from a Dutch cohort and a second, replication Hungarian cohort.
Methods: we genotyped 4 COMT gene SNPs (rs6269, rs4633, rs4818, rs4680 (Val^{158}Met polymorphism) using real-time PCR in 2 independent cohorts (Dutch cohort 174 CP patients, 190 controls & Hungarian cohort 140 CP patients 220 controls). Data was analyzed using the Chi-square test and Haploview software.
Results: in the Dutch cohort, single marker analysis showed significant associations for 3 SNPs (rs6269: Chi Square statistic 24.7; rs4818: 25.5; rs4680: 6.1) with the presence of CP in comparison to healthy controls (P< 0,01). SNP rs4633 was not associated with CP (Chi square 1.72, p=0.19)
No difference in the COMT genotypic distribution was observed in the Hungarian replication cohort. (rs6269: Chi Square statistic 0.7; rs4818: 0; rs4680: 0.2, rs4633: 0)
Conclusions: these findings in the Dutch cohort support the hypothesis that pain in CP is influenced by genetic variation in the COMT gene. However, these findings could not be confirmed in replicative Hungary cohort. These results illustrate the importance of large case-control studies with independent cohorts in order to avoid spurious results.

Genome-wide association study in coeliac disease: identification of novel genetic risk loci

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Coeliac disease (CD) is a common inflammatory intestinal disease, caused by an immune response to wheat, rye and barley. The major genetic risk factor that is required for disease development is the DQ2 or DQ8 HLA haplotype; however HLA can explain only ~30% of disease heritability. To search for additional genetic factors predisposing to CD we have performed a genome-wide association (GWA) study in 778 CD cases and 1422 controls from the UK using the Illumina HumanHap300 BeadChip. As expected, strong and extended association in the HLA region was confirmed. In addition a locus on 4q27 containing IL2 and IL21, was associated at the genome-wide significance level (p=2.0x10-7). Association with the IL2-IL21 gene locus was confirmed in three independent CD populations of Dutch, Irish and UK origin. Moreover, we observed a similar association of the IL2-IL21 gene region in other autoimmune diseases (type 1 diabetes, rheumatoid arthritis), suggesting that this locus is a common autoimmune locus.

In addition to the IL2-IL21 locus, a greater number of significant single nucleotide polymorphisms (SNPs) were observed in the WGA, than expected by chance. We followed up the 1,020 top genome-wide associated SNPs in multiple independent cohorts from three populations (5,049 samples). Preliminary results of this follow-up study revealed seven new loci, six of which contain genes controlling the immune response.

In the GWA study and the follow up we have identified new biological mechanisms for CD. This study shows the power of GWA studies to uncover the genetics of complex traits.

Endoscopic treatment of duodenal polyposis in familial adenomatous polyposis (FAP)*

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Duodenal adenomas are common in patients with FAP and currently, duodenal carcinoma is one of the leading causes of death in these patients. Duodenal carcinoma risk is assessed according to the endoscopic and histological Spigelman classification system (stage I-IV) with stage IV patients being most at risk. In these patients, prophylactic duodenal surgery is associated with high morbidity and mortality rates. Endoscopic resection may be an alternative for the removal of duodenal adenomas. We designed a prospective treatment-schedule to assess the value of endoscopic treatment of duodenal adenomas in patients with FAP.Patients with a Spigelman classification III/IV and either an ampullary adenoma (high-grade dysplasia or increasing in size) or extra-ampullary adenomas with high-grade dysplasia (HGD) were included in this study. These patients underwent a therapeutic procedure under conscious sedation. Ampullary adenomas were resected using snare cauterization after which a temporary plastic stent was placed in the pancreatic duct. Extra-ampullary adenomas were resected by endoscopic mucosal resection followed by APC if necessary. After treatment, endoscopic surveillance was continued and further endoscopic treatment scheduled according to same criteria. Successful endoscopic treatment was defined as complete resection or down-staging of the lesions. In this ongoing study 10 patients were included in whom 24 lesions were resected: 5 ampullectomies and 19 mucosectomies. Median size was 15mm (interquartile range 10-24mm). Complete macroscopic resection was achieved in 5/5 (100%) ampullary adenomas and 17/19 (89%) extra-ampullary adenomas. Complications occurred in 2 patients: delayed bleeding (<48 hours) at the resection site in 2/24 (8%) lesions. One was successfully treated with Gold Probe and one was embolised and needed transfusion. At follow-up endoscopies, so far performed in 8/10 patients during a median period of 20 months, 3 patients needed a second procedure for HGD adenomas (6/24). No carcinomas were detected, all incompletely resected lesions showed down-staging of dysplasia and no surgery needed to be performed. This interim analysis shows that endoscopic resection of duodenal adenomas in patients with FAP is an effective and feasible treatment method, but complicated by delayed bleeding in 8% of lesions. Long term analysis in more patients is needed to further assess the value of endoscopic treatment of duodenal polyposis in FAP.

Sulindac potentiates rhTRAIL-induced apoptosis in colon adenoma cells

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TNF-Related Apoptosis Inducing Ligand (TRAIL)-receptor agonistic agents are promising novel anti-cancer drugs, which induce apoptosis in human colon adenoma and cancer cell lines and human ex-vivo adenomas. NSAIDs exhibit moderately chemopreventive action. Therefore combining the two, may lead to more effective chemoprevention. The aim of this study was to investigate whether NSAIDs and rhTRAIL potentiate each other in apoptosis induction of colon adenoma cells.
Two human colon adenoma cell lines (VACO 235 and VACO 330) were exposed to aspirin (0-10 mM) or sulindac (0-200 μM) alone or in combination with rhTRAIL (0-1.0 μg/ml) for 24 hours. Induction of apoptosis was determined by M30 immunoreactivity. Levels of caspase-8, cFLIP and caspase-3 were assessed using Western Blotting. Cell surface levels of the TRAIL death receptors DR4 and DR5 were measured before and after exposure to NSAIDs using flow cytometry. The Ls174T colon cancer cell line with doxycycline-inducible expression of dominant negative T-Cell Factor-4 (dnTCF-4) was used to investigate the role of TCF-4 and Wnt signaling in the sensitizing effect of sulindac on rhTRAIL-induced apoptosis.
Aspirin and sulindac induced apoptosis in a dose-dependent manner in the colon adenoma cell lines VACO 235 and VACO 330. Aspirin and especially sulindac enhanced apoptosis induction by rhTRAIL in the adenoma cell lines (2.2 and 1.9 fold increase in apoptosis by aspirin, 4.2 and 7.4 fold increase by sulindac). Increased apoptosis was reflected by increased caspase-3 activation. Sensitizing effects of NSAIDs on rhTRAIL-induced apoptosis could not be explained by changes in membrane expression of the TRAIL death receptors DR4 and DR5. cFLIP was not detectable in the adenoma cells. The ratio of pro-caspase-8 and cleaved caspase-8 decreased upon combination therapy with an NSAID and rhTRAIL, indicating increased activation of caspase-8.
Overexpression of dnTCF-4 completely blocked the sensitizing effect of sulindac on rhTRAIL-induced apoptosis indicating that the sensitizing effect of sulindac on rhTRAIL induced apoptosis is mediated through TCF-4.
Conclusion: We show for the first time that aspirin and especially sulindac sensitize colon adenoma cells to rhTRAIL-induced apoptosis. Together, these results support further exploration of NSAIDs in combination with rhTRAIL for chemoprevention.

Supported by grant 2005-3361 of the Dutch Cancer Society.

plattegrond

Alfabetische lijst van standhouders ***B = Beneluxhal K = Kempenhal Standnr.***

Abbott BV	B 14
ALTANA Pharma BV Asacol	K 5
Alvleesklliervereniging	B 23
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B.Braun medical BV	B 28
Boston Scientific Benelux. BV	K 7
Bristol-Myers Squibb	B 12
Campro Scientific	B 25
Cobra medical BV	K 3
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Danica Nederland BV	B 27
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Hitachi Medical Systems	B 6
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Medicor	B 3
Medtronic Trading NL	B 29
Minntech BV	K 2
MTW Endoscopie	B 2
Nationaal Hepatitis Centrum	B 20
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Olympus Nederland BV	K 10b
Olympus Nederland BV	K 10
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Naam : M / V*
Evt. meisjesachternaam :
Voorletters :
Geboortedatum :

Werkadres

Instituut :
Afdeling :
Straat :
Postcode en plaats :
Telefoon :
e-mail :

Huisadres

Straat :
Postcode en plaats :
Telefoon :

geeft zich hierbij op als lid van de Sectie Endoscopie Verpleegkundigen en Assistenten van de NVGE tot schriftelijke wederopzegging. *Let wel, het lidmaatschap is persoonsgebonden en niet overdraagbaar. Verenigingspost zal uitsluitend naar uw huisadres worden gestuurd.*

U bent verpleegkundige / doktersassistent(e) anders, nl. ……*

Datum:…… Handtekening:…….

** aangeven wat van toepassing*

☐ Hierbij machtig ik de penningmeester van de Sectie Endoscopie Verpleegkundigen en Assistenten om de verschuldigde contributie, ad. € 20,00 per jaar, tot wederopzegging automatisch van mijn bank-rekening af te laten schrijven. Betaling geschiedt pas nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen.

Bankrekeningnummer Handtekening

Indien u geen machtiging tot incasso geeft ontvangt u automatisch een acceptgiro.
N.B. Het lidmaatschap loopt per kalenderjaar, eventuele opzeggingen voor 1 januari (schriftelijk) .

Dit formulier sturen naar:
Centraal Secretariaat NVGE (ledenadministratie SEVA) Postbus 657 - 2003 RR Haarlem

AANMELDINGSFORMULIER
LIDMAATSCHAP NVGE/VMDLV

Naam : M / V*
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BIG registratienummer : _____ datum registratie:_____

geeft zich hierbij op als lid van de Vereniging Maag Darm Lever Verpleegkundigen van de Nederlandse Vereniging voor Gastroenterologie tot schriftelijke wederopzegging. *Let wel, het lidmaatschap is persoonsgebonden en niet overdraagbaar. Verenigingspost zal uitsluitend naar uw huisadres worden gestuurd.*

Datum:…… Handtekening:…….

** aangeven wat van toepassing is.*

☐ Hierbij machtig ik de penningmeester van de Vereniging Maag Darm Lever Verpleegkundigen om de verschuldigde contributie, ad. € 27,50 per jaar, tot wederopzegging automatisch van mijn bank-/girorekening af te laten schrijven. Betaling geschiedt pas nadat u door de eerstvolgende ledenvergadering als lid bent aangenomen.

Indien u geen machtiging tot incasso geeft ontvangt u automatisch een acceptgiro.

(Post)bankrekeningnummer Handtekening

……

N.B. Het lidmaatschap loopt per kalenderjaar. Opzeggen dient volgens de statuten vier weken voor het aflopen van het kalenderjaar **schriftelijk** te gebeuren.

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Centraal Secretariaat NVGE (ledenadministratie VMDLV)
Postbus 657 - 2003 RR Haarlem