Voorjaarsvergadering

NEDERLANDSE VERENIGING VOOR GASTRO-ENTEROLOGIE

voortzetting van de Vereniging van Nederlandse maag-darmartsen, opgericht 26 oktober 1913

22 en 23 maart 2012

CONGRESCENTRUM

NH KONINGSHOF

VELDHOVEN

NEDERLANDSE VERENIGING VOOR GASTRO-ENTEROLOGIE

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

NEDERLANDSE VERENIGING VOOR GASTRO-INTESTINALE CHIRURGIE

NEDERLANDSE VERENIGING VAN MAAG-DARM-LEVERARTSEN

Programma voorjaarsvergadering 22 en 23 maart 2012
NH Conference Centre Koningshof Veldhoven

NEDERLANDSE VERENIGING VOOR GASTROENTEROLOGIE

Sectie Gastrointestinale Endoscopie
Netherlands Society for Parenteral and Enteral Nutrition
Sectie Neurogastroenterologie en Motiliteit
Sectie Experimentele Gastroenterologie
Sectie Gastrointestinale Oncologie
Sectie Inflammatoire Darmziekten IBD
DEGH-Meeting
Sectie Kinder-MDL
V&VN MDL

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

NEDERLANDSE VERENIGING VOOR GASTROINTESTINALE CHIRURGIE

NVGIC Nederlandse Vereniging voor GastroIntestinale Chirurgie

NEDERLANDSE VERENIGING VAN MAAG-DARM-LEVERARTSEN

MDL

INHOUDSOPGAVE **pag**

Tijdstippen diverse ledenvergaderingen donderdag:

Nederlandse Vereniging voor Gastroenterologie	22 maart, 11.30 uur – Brabantzaal
Nederlandse Vereniging voor Hepatologie	22 maart, 15.00 uur – Baroniezaal

INHOUDSOPGAVE **pag**

Vrijdag 23 maart 2012

Tijdstippen diverse ledenvergaderingen vrijdag:

V & VN MDL	23 maart, 11.50 uur – Diezezaal
Oprichtingsvergadering Sectie IBD	23 maart, 14.50 uur – Brabantzaal
Ledenvergadering Sectie Exp. Gastroenterologie	23 maart, 15.15 uur – Baroniezaal

VOORWOORD

Hierbij treft u het volledige programma aan van de voorjaarsvergadering die gehouden wordt op 22 en 23 maart a.s. in NH Conference Center Koningshof te Veldhoven. Zoals gebruikelijk wordt ons congres vooraf gegaan door het cursorisch onderwijs op 21 maart, waarvan u het programma aantreft op bladzijde 6 en 7.

Het programma zal donderdag 22 maart om 10.00 uur van start gaan met twee parallelle sessies van de NVGE in het Auditorium en de Parkzaal. In de Baroniezaal start de Dutch Experimental Gastroenterology and Hepatology Meeting, een gezamenlijk initiatief van de sectie experimentele gastroenterologie van de NVGE en de sectie basale hepatologie van de NVH, voor het vijfde achtereenvolgende jaar. De eerste sessie met vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie start om 10.30 uur in de Brabantzaal. Vanaf 12.00 organiseert de DEGH postersessies in de Meierij.
U vindt van deze posters een overzicht vanaf pagina 51.
Na de lunchpauze kunt u vrije voordrachten van de Nederlandse Vereniging voor Gastrointestinale Chirurgie en de Nederlandse Vereniging voor Gastroenterologie bijwonen in respectievelijk de Brabantzaal en de Parkzaal. De Werkgroep Coloproctologie van de NVGIC organiseert in aansluiting aan de abstractsessie een minisymposium getiteld: 'De behandeling van hemorroïden anno 2012'**.** De DEGH vervolgt na de postersessie vanaf 13.30 het programma in de Baroniezaal. In het Auditorium zijn vrije voordrachten te volgen van de Sectie Neurogastroenterologie en Motiliteit. Om 17.00 uur vindt in de Brabantzaal de Frieda den Hartog Jager lecture plaats, verzorgd door Dr. F.M. Nagengast. De lezing is getiteld: **'**30 jaar (erfelijk) darmkanker onderzoek'. Aansluitend volgt om 17.30 uur de President Select, zoals gebruikelijk ook plenair. Deze sessie duurt tot 18.30 uur en sluit daarmee het programma van de donderdag af. In de avond zijn er geen verdere lezingen meer ingepland, zodat er gelegenheid is voor diner en ontspanning.
Op vrijdagochtend zijn er vanaf 08.30 uur vrije voordrachten van de Sectie Gastrointestinale Endoscopie en parallel daaraan vrije voordrachten van de Nederlandse Vereniging voor Gastro-enterologie in het Auditorium. In Zaal 80 start vanaf 09.30 uur de abstract meeting van NESPEN. Na de koffiepauze abstracts van de Sectie Gastrointestinale Endoscopie en de Sectie Kinder MDL respectievelijk in de Brabantzaal en het Auditorium. Gedurende de gehele vrijdag zijn er behalve deze sessie met genodigde sprekers en vrije voordrachten van de DEGH, ook het NESPEN symposium en het Symposium en de oprichtingsvergadering sectie inflammatoire darmziekten (IBD). In de Diezezaal worden door de Vereniging Verpleegkundigen en Verzorgenden Nederland MDL (V&VN MDL) eigen programma's met lezingen verzorgd.

Graag tot ziens in Veldhoven!

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

Belangrijke mededeling
over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de voorjaarsvergadering

De Nederlandse Vereniging voor Gastroenterologie kent een jarenlange samenwerking met de farmaceutische industrie. De vereniging stelt de farmaceutische industrie in de gelegenheid aanwezig te zijn bij de wetenschappelijke vergaderingen met een stand. Mede hierdoor kan de vereniging haar wetenschappelijke bijeenkomsten organiseren.
In de Geneesmiddelenwet die per 1 juli 2007 in werking is getreden is een hoofdstuk Geneesmiddelenreclame (hoofdstuk 9) opgenomen waarin de regels hieromtrent zijn vastgelegd. Daarnaast gelden per 1 juli 2007 de 'Beleidsregels nadere invulling begrip gunstbetoon'. De wet zegt dat - onder strikte voorwaarden - de farmaceutische industrie alleen reclame mag maken voor receptgeneesmiddelen voor personen die bevoegd zijn om dergelijke geneesmiddelen voor te schrijven. Alle andere personen (inclusief bijvoorbeeld verpleegkundigen, endoscopie-assistenten en biochemici) worden beschouwd als "publiek". De farmaceutische industrie mag geen reclame maken voor receptgeneesmiddelen voor publiek.
De Nederlandse Vereniging voor Gastroenterologie is een wetenschappelijke vereniging voor personen die beroepsmatig betrokken zijn bij zorg, onderwijs en onderzoek ten behoeve van patiënten met maag-, darm- en leveraandoeningen. Dat betekent dat ook personen die geen arts zijn, lid van de NVGE kunnen zijn.
De aanwezigheid van artsen, niet-artsen en farmaceutische industrieën tijdens de voorjaarsvergadering kan de NVGE ongewild in aanraking brengen met de inspectie voor de gezondheidszorg, sectie reclametoezicht, en daarmee in diskrediet worden gebracht.
Dat willen wij te allen tijde voorkomen.

Wij delen u dan ook het volgende mede:
Reclame-uitingen en merkproductinformatie van farmaceutische industrieën in het voorliggende programmaboekje zijn alleen gericht op personen die bevoegd zijn om de betreffende geneesmiddelen voor te schrijven.
Al het aanwezige reclamemateriaal, reclame-uitingen en merkproductinformatie van farmaceutische industrieën die aanwezig zijn op het voorjaarscongres, zijn alleen bedoeld en alleen gericht op personen die bevoegd zijn om de betreffende geneesmiddelen voor te schrijven. Wij maken u erop attent dat het voor niet-artsen dan ook niet is toegestaan de stands van de aanwezige farmaceutische industrieën te bezoeken.
De NVGE en farmaceutische industrie (sponsoren) meent u allen, en met name de niet BIG geregistreerde personen, voldoende te hebben ingelicht en kunnen niet verantwoordelijk worden gehouden indien u geen acht slaat op deze mededeling.

Het bestuur van de NVGE

Cursorisch onderwijs in maag-darm-leverziekten, 21 maart 2012 Auditorium

Cursuscommissie: Prof. dr. P.D. Siersema (voorzitter) (MDL-arts, UMCU)
Dr. E. van der Harst (chirurg, Maasstad Ziekenhuis)
Dr. D.J. de Jong (MDL-arts, UMCN)
Prof. dr. J.H. Kleibeuker (MDL-arts, UMCG)
Dr. R. Timmer (MDL-arts, Antonius Nieuwegein)
M. Bargeman (aios MDL, UMCG) en J. Bosman (aios MDL, UMCU)

Onderwerp: **Spoedeisende zorg**

Voorzitter: R. Timmer

15.00 – 15.15	Opening met toets
15.15 – 15.35	Acute bolusobstructie *Dr. M.A.C. Meijssen, MDL-arts,* *Isala Klinieken, Zwolle*
15.35 – 15.55	Caustisch letsel *Dr. F.T.M. Peters, MDL-arts,* *Universitair Medisch Centrum Groningen*
15.55 – 16.15	Corpora aliena *Prof. J.F.W.M. Bartelsman – Amsterdam*
16.15 – 16.35	Slokdarmperforatie iatrogeen/spontaan/traumatisch *Prof. dr. P.D. Siersema, MDL-arts,* *Universitair Medisch Centrum Utrecht*
16.35 – 16.55	Casus Acute Dysfagie *Leids Universitair Medisch Centrum*
16.55 – 17.25	Pauze

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

Voorzitter: P.D. Siersema

17.25 – 17.55 Preventie/behandeling complicaties ERCP
Dr. E.A.J. Rauws, MDL-arts,
Academisch Medisch Centrum, Amsterdam

17.55 – 18.25 Leverziekten tijdens de zwangerschap
Dr. C.J.M. van Nieuwkerk, MDL-arts,
VU medisch centrum, Amsterdam

18.25 – 18.55 Buikpijn bij metabole syndromen
Prof. dr. J.P.H. Drenth, MDL-arts,
Universitair Medisch Centrum St. Radboud, Nijmegen

18.55 – 19.15 Casus metabole ziekte
Albert Schweitzer Ziekenhuis, Dordrecht

19.15 Diner

Voorzitter: D.J. de Jong

20.30 – 21.00 (Lijn) sepsis
M. van der Kolk, chirurg-intensivist,
Universitair Medisch Centrum St. Radboud, Nijmegen

21.00 – 21.20 Preventie/behandeling complicaties poliepectomie colon
Prof. dr. P. Fockens, MDL-arts,
Academisch Medisch Centrum Amsterdam

21.20 – 21.50 Acute buik
Dr. L.P.L Stassen, chirurg,
Maastricht Universitair Medisch Centrum

21.50 – 22.05 Kennistoets tweede keer

22.05 Einde programma

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 22 maart 2012

Donderdag	Brabantzaal	Baroniezaal	Auditorium	Parkzaal
10.00			Vrije voordrachten Ned. Vereniging voor Gastroenterologie pagina 11-12	Vrije voordrachten Ned. Vereniging voor Gastroenterologie pagina 14-16
10.00 - 11.30	Vrije voordrachten Ned. Vereniging voor Gastro-intestinale Chirurgie pagina 10	DEGH-meeting Gastspreker: Prof. F. Lemaigre pagina 13		
11.30 - 12.00	Ledenvergadering NVGE	Geen programma i.v.m. Ledenvergadering NVGE	Geen programma i.v.m. Ledenvergadering NVGE	Geen programma i.v.m. Ledenvergadering NVGE
12.00 - 13.00	Lunch in expositiehal	Lunchbuffet-postersessie	Lunch in expositiehal	
13.00 - 13.30	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie pagina 17-18		Symposium MDL-oncologie: 'Activiteiten van de MDL-arts binnen de MDL-oncologie' pagina 24	Vrije voordrachten Ned. Vereniging voor Gastroenterologie pagina 27-29
13.30 – 14.00		DEGH-meeting Gastspreker: Prof. G.R. van den Brink pagina 19-21		
14.00 – 14.30	Minisymposium NVGIC:			
14.30 – 15.00	Hemorroïden anno 2012			
15.00 - 15.30	Theepauze	Theepauze + ALV NVH	Theepauze	Theepauze
15.30 - 17.00	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie pagina 21-22	DEGH-meeting pagina 20-21	Vrije voordrachten Neurogastroenterologie en Motiliteit pagina 25-26	Vrije voordrachten Ned. Vereniging voor Gastroenterologie pagina 29-30
17.00 - 17.30	Frieda den Hartog Jager Lecture pagina 23			
17.30 - 18.30	President Select pagina 23-24			
18.30 - 19.30	Borrel in expositiehal			
19.30 - 22.00	Diner Genderzaal			
22.00 - 01.00	Borrel / Muziek in foyer			

In het programma vindt u achter de titel het paginanummer van het betreffende abstract

Vrijdag 23 maart 2012

Vrijdag	Brabantzaal	Baroniezaal	Auditorium	Zaal 80
08.30	Vrije voordrachten sectie Gastrointestinale Endoscopie pagina 31-33		Vrije voordrachten Ned. Vereniging voor Gastroenterologie pagina 35-36	
09.00 – 09.30		DEGH-meeting Gastspreker: Prof. J.C. Fernández-Checa pagina 39-40		
09.30 – 10.00				Vrije voordrachten NESPEN pagina 44-45
10.00 – 10.30				
10.30 - 11.00	Koffiepauze	Koffiepauze	Koffiepauze	Koffiepauze
11.00 - 12.00	Vrije voordrachten sectie Gastrointestinale Endoscopie pagina 33-34	DEGH-meeting Gastspreker: Prof. J. Raes pagina 40-41	Symposium Kinder-MDL: Galgangatresie pagina 37	Symposium: Nutritional assessment, do's and don'ts in clinical nutrition pagina 45-46
12.00 - 12.30				
12.30 - 13.00	Ledenvergadering NVMDL			
13.00 – 14.00		Lunch in expositiehal	Lunch in expositiehal	
14.00 – 15.00	IBD symposium inclusief oprichtingsvergadering	DEGH-meeting pagina 43	Voordrachten Sectie Kinder-MDL	
15.00 – 16.00	pagina 41-42		pagina 37-39	

Vrijdag 23 maart 2012
programma V&VN MDL

Vrijdag	Diezezaal	Zaal 52	Zaal 55	Zaal 51
10.00 – 12.15	Plenair ochtendprogramma V&VN MDL pagina 47			
12.15	Lunchbuffet in Kempenhal			
13.50 – 15.30	Parallel Workshop: Endoscopie-verpleegkundigen pagina 48	Parallel Workshop: Leververpleegkundigen pagina 48-49	Parallel Workshop: IBD verpleegkundigen pagina 49	Parallel Workshop: Voedings-verpleegkundigen pagina 50
15.30	Einde Programma			

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

10.00 Inschrijving, koffie

Voorzitters: M.I. van Berge Henegouwen en J.P. Ruurda

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

10.30 Determination of the HER-2 status in esophageal adenocarcinoma. HER-2/neu is associated with survival (p. 54)
M.J.D. Prins[1], J.P. Ruurda[1], R. van Hillegersberg[1], F.J.W. Kate ten[2], [1]Dept. of Surgery, University Medical Center Utrecht, [2]Dept. of Pathology, University Medical Center Utrecht, The Netherlands

10.40 The influence of young age on outcome in oesophageal cancer (p. 55)
A.M.J. van Nistelrooij[1], J.J.B. van Lanschot[1], M.C.W. Spaander[2], H.W. Tilanus[1], B.P.L. Wijnhoven[1], Depts. of Surgery[1] and Gastroenterology[2], Erasmus MC, Rotterdam, The Netherlands

10.50 Surgical treatment of gastric GIST in the imatinib era (p. 56)
J. Stiekema[1], S. Kol[1], A. Cats[2], F. van Coevorden[1], J. van Sandick[1], [1]the Nederlands Cancer, Institute – Antoni van Leeuwenhoek hospital, Surgical Oncology, [2]the Nederlands Cancer, Institute – Antoni van Leeuwenhoek Hospital, Gastroenterology, Amsterdam, The Netherlands

11.00 Safety of epirubicin, cisplatin and capecitabin chemotherapy in patients with resectable oesophageal or gastro-oesophageal junction adenocarcinoma outside clinical trials (p. 57)
P.C. van der Sluis[1], I. Ubink[2], S. van der Horst[1], J. Boonstra[3], E.E. Voest[2], I.H.M. Borel-Rinkes[1], M.J. Wiezer[4], M.E.I. Schipper[5], P.D. Siersema[6], M. Los[3], R. van Hillegersberg[1], M.P. Lolkema[2], University Medical Center Utrecht, [1]Division of surgery, [2]Dept. of Medical Oncology, [5]Dept. of Pathology, [6]Dept. of Gastroenterology and Hepatology, St. Antonius Hospital Nieuwegein, [3]Dept. of Internal Medicine and Oncology, [4]Dept. of Surgery, The Netherlands

11.10 End-to-end cervical esophagogastric anastomoses require a higher number of endoscopic stricture dilations compared with end-to-side anastomoses after esophagectomy (p. 58)
L. Haverkamp, P.C. van der Sluis, R.J.J. Verhage, J.P. Ruurda, R. van Hillegersberg, UMC Utrecht, The Netherlands

11.20 Increase in brown adipose tissue activity in morbidly obese subjects after bariatric surgery (p. 59)
G.H.E.J. Vijgen[1,2], N.D. Bouvy[1], G.J.J. Teule[3], B. Brans[3], P. Schrauwen[2], W.D. van Marken Lichtenbelt[2], Maastricht University Medical Center, [1]Dept. of General Surgery, [2]Dept. of Human Biology, [3]Dept. of Nuclear Medicine, The Netherlands

11.30 Einde abstractsessie, aansluitend in deze zaal de ledenvergadering van de NVGE

09.30 Inschrijving, koffie

Voorzitters: J.J. Keller en H.F.A. Vasen

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

10.00 Failure to record a family history of familial cancer in patients' notes is associated with early stage colorectal cancer (p.60)

K. Kessels[1,2], N.L. de Groot[1], H.H. Fidder[1], R. Timmer[2], M.F.J. Stolk[2] , M.G.H. van Oijen[1], G.J. Offerhaus[3], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Dept. of Gastroenterology and Hepatology, Sint Antonius Hospital, Nieuwegein, [3]Dept. of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

10.10 Barriers to genetic testing for Lynch syndrome (p. 61)

C.H.M. Leenen[1], M. den Heijer[2], C. van der Meer[2], R. Timman[3], E.J. Kuipers[1,4], M.E. van Leerdam[1], A. Wagner[2], Dept. of Gastroenterology and Hepatology[1], Dept. of Clinical Genetics[2], Dept. of Medical Psychology and Psychotherapy[3], Dept. of Internal Medicine[4], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

10.20 Patients with Lynch-compatible colorectal cancer without identifiable germline mutation do not have a positive family history of Lynch syndrome (p. 62)

C.H.M. Leenen[1], M.E. van Leerdam[1], A. Wagner[2], W.N.M. Dinjens[3], H.J. Dubbink[3], E.J. Kuipers[1,4], E.W. Steyerberg[5], Dept. of Gastroenterology and Hepatology[1], Dept. of Clinical Genetics[2], Dept. of Pathology[3], Dept. of Internal Medicine[4], Dept. of Public Health[5], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

10.30 Aspirin use is associated with lower stage CRC at diagnosis compared to non users (p. 63)

K. Soufidi[1], M.G.H. van Oijen[1], H.M. Smeets[2,3], L.I.H. Overbeek[4], P.D. Siersema[1], R.J.F. Laheij[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Agis Health Insurance, Amersfoort, [3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, [4]PALGA, the nationwide network and registry of histo- and cytopathology, Utrecht, The Netherlands

10.40 Metachronous colorectal neoplasia after adenoma removal. A multivariate analysis of risk factors for non-advanced and advanced neoplasia (p. 64)

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

10.50 Gastrointestinal carcinomas of Peutz-Jeghers syndrome patients, a further look (p. 66)

S.E. Korsse[1], W. van Veelen[1], K. Biermann[2], M.G.F. van Lier[1], A. Wagner[3], E. Dekker[4], G.J.A. Offerhaus[5,6], E.M.H. Mathus-Vliegen[4], E.J. Kuipers[1,7], M.E. van Leerdam[1], [1]Dept. of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Rotterdam, [2]Dept. of Pathology, Erasmus MC University Medical Center, Rotterdam, [3]Dept. of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, [4]Dept. of Gastroenterology & Hepatology, Academic Medical Center, University of Amsterdam, [5]Dept. of Pathology, Academic Medical Center, University of Amsterdam, [6]Dept. of Pathology, University Medical Center, Utrecht, [7]Dept. of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

11.00 Pancreatic cancer risk in Peutz-Jeghers patients, results of a large Dutch cohort study and implications for surveillance (p. 67)

F. Harinck[1], S.E. Korsse[1], M.G.F. van Lier[1], K. Biermann[2], G.J.A. Offerhaus[3,4], N. Krak[9], C.W.N. Looman[5], W. van Veelen[1], E.J. Kuipers[1,6], A. Wagner[8], E. Dekker[7], E.M.H. Mathus-Vliegen[7], P. Fockens[7], M.E. van Leerdam[1], M.J. Bruno[1], [1]Dept. of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Rotterdam, [2]Dept. of Pathology, Erasmus MC University Medical Center, Rotterdam, [3]Dept. of Pathology, Academic Medical Center, University of Amsterdam, [4]Dept. of Pathology, University Medical Center Utrecht, Utrecht, [5]Dept. of Public Health, Erasmus MC University Medical Center, Rotterdam, [6]Dept. of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, [7]Dept. of Gastroenterology & Hepatology, Academic Medical Center, University of Amsterdam, [8]Dept. of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, [9]Dept. of Radiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

11.10 Prospective evaluation of psychological impact of pancreatic cancer surveillance in high-risk individuals (p. 69)

F. Harinck[1], T. Nagtegaal[2], I. Kluijt[3], C.M. Aalfs[4], E. Smets[5], J-W. Poley[1], A. Wagner[6], G. Sidharta[2], J.E. van Hooft[7], H. van Dullemen[8], R. Sijmons[9], P. Fockens[7], M.J. Bruno[1], E. Bleiker[2], [1]Dept. of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, [2]Dept. of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, [3]Familial Cancer Clinic, The Netherlands Cancer Institute Amsterdam, [4]Dept. of Clinical Genetics, Academic Medical Center Amsterdam, [5]Dept. of Medical Psycho-logy, Academic Medical Center University of Amsterdam, Amsterdam, [6]Dept. of Clinical Genetics, Erasmus Medical Center Rotter-dam, [7]Dept. of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, [8]Dept. of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, [9]Dept. of Genetics, University of Groningen, University Medical Center Groningen, The Netherlands

11.20 Chromosomal aberrations implicated in colorectal adenoma to carcinoma proression as markers of high risk colorectal adenomas (p. 69)

J.S. Terhaar sive Droste[1], A.S. Bolijn[2], M.K. van Burink[2], N.C.T. van Grieken[2], B. Carvalho[2], C.J. Mulder[1], G.A. Meijer[2], B. Diosdado[2], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Pathology, VU University Medical Center, Amsterdam, The Netherlands

11.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie in de Brabantzaal

DEGH-Meeting **Baroniezaal**

Voorzitters: J. Drenth en F. Lemaigre

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

Theme **G&H-Cancer**

10.30 Heterozygous knockout of ß-catenin in Apc1638N mice prevents gastro-intestinal tumor formation but predisposes for mammary lesions (p. 70)
E.R.M. Bakker[1], E. Hoekstra[1], P. Franken[2], W. Helvensteijn[1], W. van Veelen[1], E.J. Kuipers[1,3], R. Smits[1], Dept. of [1]Gastroenterology and Hepatology, [2]Experimental Pathology, [3]Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

10.42 Rock-inhibitors reduce the induction of Epithelial-to-Mesenchymal Transition, migration and invasionin SMAD4 deficient colorectal cancers caused by Bone Morphogentic Protein Signaling (p. 71)
P.W. Voorneveld[1], L.L. Kodach[1], R.J. Jacobs[1], D.W. Hommes[1], G.R. van den Brink[2], M.P. Peppelenbosch[3], J.C.H. Hardwick[1], [1]Dept. of Gastroenterology & Hepatology, Leiden University Medical Center, Leiden, [2]Tytgat Institute for Liver & Intestinal Research, Academic Medical Center, Amsterdam, [3]Dept. of Gastroenterology & Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

10.54 Bone Morphogentic Protein 4 signaling alters microRNA-145 expression in the esophagus (p. 72)
J.W.P.M. van Baal[1], M. Fassan[2], R.F. Souza[3], S.J. Spechler[3], M. Rugge[2], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands, [2]Dept. of Medical Diagnostic Sciences and Special Therapies, Surgical Pathology and Cytopathology Unit, University of Padova, Padova, Italy, [3]Dept. of Medicine, UT Southwestern Medical Center, Dallas, TX, USA

11.06 Enhanced tumor growth after portal vein embolization in a rabbit VX2 tumor model (p. 73)
L.T. Hoekstra[1], K.P. van Lienden[2], J. Verheij[3], M. Heger[1], T.M. van Gulik[1], [1]Dept. of Surgery, Academic Medical Center, Amsterdam, [2]Dept. of Radiology, Academic Medical Center, Amsterdam, [3]Dept. of Pathology, Academic Medical Center, Amsterdam, The Netherlands

11.18 **Invited Speaker**
Bile duct development in relation to cholangiopathies
Prof. F. Lemaigre, de Duve Institute, University Leuven, België

12.00 Lunch en postersessie

Postersessie DEGH **Meierij Foyer**

12.00 De postersessie van de DEGH vindt plaats tussen 12.00 en 13.30 uur met vanaf 12.45 de mogelijkheid om u aan te sluiten bij een begeleide sessie langs de posters. Vier tot vijf posters per categorie, 7 minuten per poster, zie pagina 51 e.v.
De posters moeten tot aan het eind van het programma op vrijdagmiddag blijven hangen. Over de posterprijzen wordt vrijdag tijdens de lunch beslist.

13.30 Vervolg DEGH-programma.

Nederlandse Vereniging voor Gastroenterologie **Parkzaal**

Voorzitters: A.A. van Bodegraven en P.C.F. Stokkers

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

10.00 Clarifying the role of the HLA in Ulcerative Colitis by extensive finemapping of a Dutch cohort (p. 74)
R.M. Nijmeijer[1,2], E.A.M. Festen[2,3*], D.J. de Jong[4,5], H.W. Verspaget[6], C.Y. Ponsioen[5], R.K. Weersma[3], [1]Dept. of Surgery, University Medical Center Utrecht, Utrecht, [2]Dept. of Genetics, University Medical Center Groningen and University of Groningen, Groningen, [3]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, [4]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, [5]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [6]Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands * Equal contribution*

10.10 Once-daily versus twice-daily mesalazine (Pentasa®) for active ulcerative colitis. Efficacy results from MOTUS, a multicentre, controlled, randomised, investigator-blinded study (p. 75)
J.Ph. Kuyvenhoven[1], B. Flourié[2], H. Hagège[3], G. Tucat[4], Masclee[5], M. Pierik[5], O. Dewit[6], P. Broberg[7], W.K.H. Man A Hing[8], [1]Kennemer Gasthuis, Haarlem, The Netherlands, [2]Lyon Sud Hospital, France, [3]ANGH (Association Nationale des Gastroentérologues des Hôpitaux), France, [4]CREGG (Club de Réflexion des Cabinets et Groupes d'Hépato-Gastroentérologie), France, [5]Maastricht University Medical Center, The Netherlands, [6]UCL Saint Luc, Brussels, Belgium, [7]Ferring Pharmaceuticals, Switzerland, [8]Ferring BV, The Netherlands

10.20 Is there a difference in quality of life or costs between ulcerative colitis patients with a pouch or an ileostomy? (p. 76)
M.E. van der Valk[1], M.J.J. Mangen[2], G. Dijkstra[3], A.A. van Bodegraven[4], H.H. Fidder[1], D.J. de Jong[5], M. Pierik[6], C.J. van der Woude[7], M.J.L. Romberg-Camps[8], C.H.M. Clemens[9], J.M. Jansen[10], P.C. van de Meeberg[11], N. Mahmmod[12], C.Y. Ponsioen[13], C. Rogge-Wolf[14], J. Reinoud Vermeijden[15], P.D. Siersema[1], M.G.H. van Oijen[1,2], B. Oldenburg[1] on behalf of the COIN study group and Dutch Initiative on Crohn and

Colitis, [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, [3]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, [4]Dept. of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [5]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, [6]Dept. of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [7]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [8]Dept. of Gastroenterology and Hepatology, Orbis Medical Center, Sittard, [9]Dept. of Gastroenterology and Hepatology, Diaconessenhuis, Leiden, [10]Dept. of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, [11]Dept. of Gastroenterology and Hepatology, Slingeland Hospital, Doetinchem, [12]Dept. of Gastroenterology and Hepatology, Antonius Hospital, Nieuwegein, [13]Dept. of Gastro-enterology and Hepatology, Academic Medical Center Amsterdam, [14]Dept. of Gastroenterology and Hepatology, Reinier de Graaf Groep, Delft, [15]Dept. of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, The Netherlands

10.30 Ulcerative colitis patients with an inflammatory response upon mesalazine cannot be desensitized. A single-blind randomized study (p. 77)

D.J. Buurman[1], J.G.R. De Monchy[2], R.C.A. Schellekens[3], L.A. van der Waaij[4], J.H. Kleibeuker[1], G. Dijkstra[1], [1]Universitair Medisch Centrum Groningen, afdeling Maag-darm-leverziekten, [2]Universitair Medisch Centrum Groningen, afdeling Immunologie en Allergologie, [3]Universitair Medisch Centrum Groningen, afdeling klinische pharmacologie, [4]Martiniziekenhuis Groningen, afdeling Maag-, darm-, leverziekten, The Netherlands

10.40 Fatigue in IBD patients is associated with differences in immune parameters (p. 78)

C. de Haar[1], L. Vogelaar[1], B.Aerts[1], M.P. Peppelenbosch[1], E.J. Kuipers[1], C. Janneke van der Woude[1], [1]Dept. of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, The Netherlands

10.50 Anti TNF-α therapy is a major cost driver in inflammatory bowel disease. Results from the COIN study (p. 79)

M. E. van der Valk[1], M.J.J. Mangen[2], G. Dijkstra[3], A.A. van Bodegraven[4], H.H. Fidder[1], D.J. de Jong[5], M. Pierik[6], C.J. van der Woude[7], M.J.L. Romberg-Camps[8], C.H.M. Clemens[9], J.M. Jansen[10], P.C. van de Meeberg[11], N. Mahmmod[12], C.Y. Ponsioen[13], C. Rogge-Wolf[14], J. Reinoud Vermeijden[15], P.D. Siersema[1], M.G.H. van Oijen[1,2], B. Oldenburg[1] on behalf of the COIN study group and Dutch Initiative on Crohn and Colitis, [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, [3]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, [4]Dept. of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [5]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Center, Nijmegen, [6]Dept. of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, The Netherlands, [7]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [8]Dept. of Gastroenterology and Hepatology, Orbis Medical Center, Sittard, [9]Dept. of Gastroenterology and Hepatology, Diaconessenhuis, Leiden, [10]Dept. of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, [11]Dept. of Gastroenterology and Hepatology, Slingeland Hospital, Doetinchem, [12]Dept. of Gastroenterology and Hepatology, Antonius Hospital, Nieuwegein, [13]Dept. of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, [14]Dept. of Gastroenterology and Hepatology, Reinier de Graaf Groep, Delft, [15]Dept. of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, The Netherlands

Donderdag 22 maart 2012

11.00 Parent of origin effects for IL12B and NOD2 in Inflammatory Bowel Disease (p.80)

K. Fransen[1,2], M. Mitrovic[1,3], C.C. van Diemen[1], B.K. Thelma[4], S. Senapati[4], U. Potocnik[3], H. W. Verspagert[5], C.IJ. Ponsioen[6], D. de Jong[7], I. Nolte[8], R. K. Weersma[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands, [2]Dept. of Genetics, University Medical Centre Groningen and University of Groningen, Groningen, The Netherlands, [3]Center for Human Molecular Genetics and Pharmacogenomics, Medical Faculty, University of Maribor, Maribor, Slovenia, [4]Dept. of Genetics, University of Delhi, South Campus, New Delhi, India, [5]Dept. of Gastroenterology and Hepatology, University Medical Centre Leiden, University of Leiden, Leiden, The Netherlands, [6]Dept. of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands, [7]Dept. of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [8]Dept. of epidemiology, University Medical Centre Groningen and University of Groningen, Groningen, The Netherlands

11.10 Screening for opportunistic infections prior to TNF-alpha inhibitor treatment in Crohn's disease and the risk of severe infections (p. 81)

T.D.G. Belderbos[1], M. van der Have[1], H.H. Fidder[1], M. Leenders[1], G. Dijkstra[2], C.P. Peters[3], E.J. Eshuis[3], C.Y. Ponsioen[3], P.D. Siersema[1], M.G.H. van Oijen[1], B. Oldenburg[1] on behalf of the Dutch Initiative on Crohn's and Colitis (ICC), [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, [3]Dept. of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

11.20 Extensive screening for opportunistic infections prior to biological therapy in patients with Crohn's disease is not cost-effective (p. 82)

M. van der Have, B. Oldenburg, H.H. Fidder, T. Belderbos, F. van der Scheer, P.D. Siersema, M.G. van Oijen, Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, The Netherlands

11.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie in de Brabantzaal

12.00 Lunchbuffet in de expositiehal

Nederlandse Vereniging voor Gastrointestinale Chirurgie **Brabantzaal**

Voorzitters: E.J.R. de Graaf en J. Heisterkamp

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

13.00 Impact of nasojejunal, jejunostomy and parenteral feeding after pancreatic-oduodenectomy (p. 83)
A. Gerritsen[1], M.G. Besselink[1], K.P. Cieslak[1], M.R. Vriens[1], E. Steenhagen[2], R. van Hillegersberg[1], I.H. Borel Rinkes[1], I.Q. Molenaar[1], [1]Dept. of Surgery, University Medical Center Utrecht, [2]Dept. of Dietetics, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

13.10 How to further lower the complication rate after laparoscopic chole-cystectomy (p. 84)
K. Kortram[1], S.C. Donkervoort[2], L. Dijksman[3] , B. van Ramshorst[1], D.J. Gouma[4] , D. Boerma[1], [1]St. Antonius Hospital Nieuwegein, Dept. of surgery, [2]Onze Lieve Vrouwe Gasthuis Amsterdam, Dept. of surgery, [3]Onze Lieve Vrouwe Gasthuis Amsterdam, Dept. of epidemiology, [4]Academic Medical Centre Amsterdam, Dept. of surgery, The Netherlands

13.20 Single port transanal surgery vs. transanal endoscopic microsurgery for rectal tumours: a case control study (p. 85)
R.M. Barendse[1], W.A. Bemelman[2], P. Doornebosch[3], P. Fockens[1], E. Dekker[1] and E.J.R. de Graaf[3], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept. of Surgery, Academic Medical Center, Amsterdam, [3]Dept. of Surgery, IJsselland Hospital, Capelle aan den IJssel, The Netherlands

13.30 Transanal Endoscopic Microsurgery: colorectal surgeons' learning curve (p. 86)
R.M. Barendse[1], M.G. Dijkgraaf[2], U.R. Rolf[1], A.B. Bijnen[3], E.C.J. Consten[4], C. Hoff[5], E. Dekker[1], P. Fockens[1], W.A. Bemelman[6] and E.J.R. de Graaf[7], [1]Dept. Of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Clinical Research Unit, Academic Medical Center, University of Amsterdam, Amsterdam, [3]Dept. of Surgery, Medical Center Alkmaar, Alkmaar, [4]Dept. of Surgery, Meander Medical Center, Amersfoort, [5]Dept. of Surgery, Medical Center Leeuwarden, Leeuwarden, [6]Dept. of Surgery, Academic Medical Center, Amsterdam, [7]Dept. of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands

13.40 Prevention of parastomal hernias and incisional hernias in old stoma wounds: a pilot study (p. 87)
K.W.Y. van Barneveld[1], M.H.F. Schreinemacher[1], W.A. Buurman[1], J.W.M. Greve[2], G.L. Beets[1], N.D. Bouvy[1], [1]Dept. of General Surgery, Maastricht UMC+, Maastricht, [2]Dept. of Surgery, Atrium MC Parkstad, Heerlen, The Netherlands

13.50 Treatment of chronic presacral sinus after low anterior resection with preoperative radiotherapy for rectal cancer (p. 88)
D.A.M, Sloothaak[1], C.J. Buskens[1], W.A. Bemelman[1], P.J. Tanis[1], [1]Dept. of Surgery, Academic Medical Centre Amsterdam, The Netherlands

14.00 Einde abstractsessie

Symposium Nederlandse Vereniging voor Gastrointestinale Chirurgie Brabantzaal

Voorzitters: E.J.R. de Graaf en J. Heisterkamp

De behandeling van hemorroïden anno 2012
georganiseerd door de Werkgroep Coloproctologie

14.00	Behandeling van hemorroïden, de huidige stand van zaken *Dr. J.W.A. Burger, chirurg Erasmus MC, Rotterdam*
14.15	Wanneer en wat voor endoscopie bij de patiënt met hemorroïden *C. Hoff, chirurg, Medisch Centrum Leeuwarden, Leeuwarden*
14.30	Hemorroïdopexie, met of zonder dopplergeleide ligatie *Dr. P. Go, chirurg, Antonius Ziekenhuis, Nieuwegein*
14.45	Ligatie hemorroïdopexie versus gestapelde hemorroïdopexie *Dr. S.O. Breukink, chirurg, Maastricht UMC*
15.00	Theepauze expositiehal

DEGH-Meeting **Baroniezaal**

Voorzitters: G.R. van den Brink en R.K. Weersma

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

Theme **Colitis**

13.30 Cholinergic anti-inflammatory pathway in DSS-induced colitis (p. 90)
C. Cailotto[1], B.J. Olivier[1], L. Costes[1], J. van der Vliet[1], W.J. de Jonge[1], G.E. Boeckxstaens[2], [1]Tytgat Institute for Liver and Intestinal Research, AMC, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, University Hospital Leuven, Belgium

13.42 Ischemia-induced mucus barrier loss and bacterial penetration are rapidly counteracted by increased goblet cell secretory activity in human and rat colon (p. 91)
J. Grootjans[1], I.H. Hundscheid[1], K. Lenaerts[1], B. Boonen[1], I.B. Renes[2], F.K. Verheyen[3], C.H. Dejong[1], M.F. von Meyenfeldt[1], G.L. Beets[1], W.A. Buurman[1], [1]Dept. of Surgery, NUTRIM School for Nutrition, Toxicology & Metabolism, Maastricht University Medical Center, Maastricht, [2]Laboratory of Pediatrics, Division of Neonatology, Erasmus MC-Sophia, Rotterdam, [3]Dept. of Molecular Cell Biology, Electron Microscopy Unit, Maastricht University Medical Center, Maastricht, The Netherlands

13.54 The human colon is more resistant to ischemia-reperfusion induced tissue damage and early inflammation than human small intestine (p. 92)
I.H.R. Hundscheid[1], J. Grootjans[1], B. Boonen[1], J.G. Bloemen[1], K. Lenaerts[1], C.H.C. Dejong[1], M.F. Von Meyenfeld[1], G.L. Beets[1], W.A. Buurman[1], [1]Dept. of Surgery, NUTRIM School for Nutrition, Toxicology & Metabolism, Maastricht University Medical Center, Maastricht, The Netherlands

14.06 Pregnane X Receptor stimulation reduces NF-kappa B mediated cytokine expression in intestinal biopsies from inflammatory bowel disease patients (p. 93)
J.J. Deuring[1], T. van den Berg[1], E.J. Kuipers[1], M.P. Peppelenbosch[1], C. de Haar[1], C.J. van der Woude[1*], [*]These authors contributed equally to this work, [1]Erasmus Medical Centre, Gastroenterology and Hepatology, Rotterdam, The Netherlands*

14.18 **Invited Speaker**
Endoplasmatic reticulum stress and inflammation
Prof. dr. G.R. van den Brink, Dept of Gastroenterology and Hepatology, Academic Medical Center Amsterdam.

15.00 Theepauze en ALV Nederlandse Vereniging voor Hepatologie

DEGH-Meeting **Baroniezaal**

Voorzitters: G. Bouma en C.C. Paulusma

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

Theme **Bile physiology, signaling and therapy**

15.30 Identification of a novel FXR response element, Human FXR induces SHP expression through direct binding to an LRH-1 binding site, independent of the presence of an IR-1 and LRH-1 (p. 94)

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

15.42 Effects of bile acid receptor agonists INT-747 and INT-777 on estrogen deficiency-related post-menopausal obesity and hepatic steatosis (p. 95)

M.C. de Oliveira[1,2], C.L. Salgueiro[2], E.L. Ishii-Iwamoto[2], I.C. Gaemers[1], R.J.P. Oude Elferink[1], [1]Tytgat Institute for Liver and intestinal Research, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Laboratory of Biological Oxidations, Dept. of Biochemistry, University of Maringá, Maringá, Brazil

15.54 Activation of nuclear receptor FXR by oral chenodeoxycholic acid in patients with Crohn's colitis, potential therapeutic consequences for inflammatory bowel disease (p. 96)

F.D.M. van Schaik[1], R.M. Gadaleta[1,2], F.G. Schaap[3], S.W.C. van Mil[2], P.D. Siersema[1], B. Oldenburg[1], K.J. van Erpecum[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, [2]Dept. of Metabolic Diseases, University Medical Center Utrecht, [3]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

16.06 MicroRNA profiles in graft preservation solution are prognostic for biliary strictures after liver transplantation (p. 97)

C.J. Verhoeven[1], W.R.R. Farid[1], P.E. de Ruiter[1], J. de Jonge[1], J. Kwekkeboom , H.J. Metselaar[2], H.W. Tilanus[1], G. Kazemier[1] and L.J.W. van der Laan[1], [1]Depts. of Surgery and [2]Gastroenterology & Hepatology Erasmus MC - University Medical Center, Rotterdam, The Netherlands

16.18 Reduced FGF19 level in bile and decreased FGF19 expression in the gallbladder of patients with primary sclerosing cholangitis (p. 98)

S.J.L.B. Zweers[1], A. Shiryaev[2], T.H. Karlsen[2], P.L.M. Jansen[1,3], F.G. Schaap[1], [1]Tytgat Institute for Intestinal and Liver Research, Academic Medical Center, Amsterdam, The Netherlands, [2]Norwegian PSC Research Center, Clinic for Specialized Medicine and Surgery, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [3]Dept. of Hepatology and Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands

16.30 Bile acid-preconditioning protects HepG2.rNTCP cells against bile acid-induced apoptosis (p. 99)
E.M. Verhaag, G. Karimian, M. Buist-Homan, H. Moshage and K.N. Faber, Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

16.42 ATP8B1 and ATP11C deficiency affect taurocholate and glucose uptake in Caco-2 cells (p. 100)
V.A. van der Mark, D.R. de Waart, K.S. Mok, H.R. de Jonge, R.P.J. Oude Elferink, C.C. Paulusma, Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

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

Nederlandse Vereniging voor Gastroenterologie — Brabantzaal

Voorzitters: H.M. van Dullemen en J.E. van Hooft

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

15.30 Diagnostic scoring systems for autoimmune pancreatitis are complementary and correctly identify the majority of patients at initial presentation, without the need for histology (p. 101)
J. Buijs[1], M.J. van Heerde[1], B.E. Hansen[1, 2], K. Biermann[3], F.P. Vleggaar[4], M.A. Brink[5], E.J. Kuipers[1,6], H.R. van Buuren[1], M.J. Bruno[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [2]Dept. of Public Health, Erasmus University Medical Center, Rotterdam, [3]Dept. of Pathology, Erasmus University Medical Center, Rotterdam, [4]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, [5]Dept. of Gastroenterology, Meander Medical Center, Amersfoort, [6]Dept. of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

15.40 Comparable efficacy of low and high dose induction corticosteroid treatment in autoimmune pancreatitis (p. 102)
J. Buijs[1], M.J. van Heerde[1], B.E. Hansen[1, 2], K. Biermann[3], F.P. Vleggaar[4], M.A. Brink[5], E.J. Kuipers[1,6], M.J. Bruno[1], H.R. van Buuren[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [2]Dept. of Public Health, Erasmus University Medical Center, Rotterdam, [3]Dept. of Pathology, Erasmus University Medical Center, Rotterdam, [4]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, [5]Dept. of Gastroenterology, Meander Medical Center, Amersfoort, [6]Dept. of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

15.50 Surgical treatment of choledochal cysts in children and adults. a single-center experience in 83 patients (p. 103)
Y. El-Massoudi, M. Bieze, J. de Wilde, O.R.C. Busch, D.J. Gouma, T.M. van Gulik, AMC, The Netherlands

16.00 Outcomes of liver resection for hepatocellular adenoma and focal nodular hyperplasia, results of a prospective trial (p. 104)

M. Bieze[1], Youssef El-Massoudi[1], J. Verheij[2], S.S.K.S. Phoa[3], O.R.C. Busch[1], D.J. Gouma[1], T.M. van Gulik[1], [1]Dept. of Surgery, Academic Medical Center, [2]Dept. of Pathology, Academic Medical Center, [3]Dept. of Radiology, Academic Medical Center, The Netherlands

16.10 Prospective evaluation of the incidence and prevalence of exocrine pancreatic insufficiency in patients with irresectable pancreatic adenocarcinoma (p. 105)

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

16.20 Tumor progression after preoperative portal vein embolization (p. 106)

L.T. Hoekstra[1], K.P. van Lienden[2], A. Doets[1], O.R.C. Busch[1], D.J. Gouma[1], T.M. van Gulik[1], [1]Dept. of Surgery, Academic Medical Center, Amsterdam, [2]Dept. of Radiology, Academic Medical Center, Amsterdam, The Netherlands

16.30 PET/CT using ^{18}F-fluoromethylcholine to detect hepatocellular carcinoma and assess extent of the disease (p. 107)

M. Bieze[1], H.J. Klumpen[2], J. Verheij[5], S.D. Hemelrijk[1], U.H.W. Beuers[3], P.S.L. Jansen[3], S.S.K.S. Phoa[4], Y. El Massoudi[1], T.M. van Gulik[1], R.J. Bennink[6], [1]Dept. of Surgery, Academic Medical Center, [2]Dept. of Medical Oncology, Academic Medical Center, [3]Dept. of Hepatology, Academic Medical Center, [4]Dept. of Radiology, Academic Medical Center, [5]Dept. of Pathology, Academic Medical Center, [6]Dept. of Nuclear Medicine, Academic Medical Center, The Netherlands

16.40 The diagnostic value of the double duct sign in patients with a periampullary lesion (p. 108)

J.C.E.M. ten Berge[1], M. Suker[1*], M.J. Bruno[2], J.W. Poley[2], S. Spronk[3], R.S. Dwarkasing[4], K. Biermann[5], C.H.J. van Eijck[1], [1]Erasmus University Medical Center, Dept. of Surgery, Rotterdam, [2]Erasmus University Medical Center, Dept. of Gastroenterology and Hepatology, Rotterdam, [3]Erasmus University Medical Centre, Dept. of Radiology and Dept. of Epidemiology, Rotterdam, [4]Erasmus University Medical Centre, Dept. of Radiology, Rotterdam, [5]Erasmus University Medical Centre, Dept. of Pathology, Rotterdam, The Netherlands * Both authors attributed equally*

16.50 Factors determining long-term survival after HIPEC (p. 109)

B. Mirck[1], S.C. Bruin[1], Dr. M.L.F. van Velthuysen[2], Dr. V.J. Verwaal[1], [1]Chirurgische oncologie, Nederlands Kanker Instituut - Antoni van Leeuwenhoek Ziekenhuis, [2]Pathologie, Nederlands Kanker Instituut - Antoni van Leeuwenhoek Ziekenhuis, The Netherlands

Plenaire sessie — Brabantzaal

17.00 **Frieda den Hartog Jager Lecture**
'30 jaar (erfelijk) darmkanker onderzoek'
Dr. F.M. Nagengast, maag-darm-leverarts,
Universitair Medisch Centrum St. Radboud, Nijmegen

President Select (plenaire sessie) — Brabantzaal

Voorzitters: J.Ph. Kuijvenhoven en C.J.J. Mulder

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

17.30 Contrast Enhanced abdominal Ultrasound in IBD. Comparison with Ileo-colonoscopy and MR Enterography (p. 110)
C.S. Horjus[1,3], R. Bruijnen[2], L. Roovers[1], D.J. de Jong[3], F.B.M. Joosten[2], M.J.M. Groenen[1], P.J. Wahab[1], [1]Dept. of Gastroenterology, Rijnstate Hospital, Arnhem, [2]Dept. of Radiology, Rijnstate Hospital, Arnhem, [3]Dept. of Gastroenterology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

17.45 Myosin Vb controls the apical localization and activation of ezrin in human enterocytes, which is inhibited in Microvillus Inclusion Disease (p. 111)
H. Dhekne[1], N-H Hsiao[1], E.H.H.M Rings[2], S.C. D. van IJzendoorn[1,] Department of [1]Cell Biology, section Membrane Cell Biology, and [2]Pediatrics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

18.00 Transanal endoscopic microsurgery, a retrospective multicenter analysis of patients with a pT2/pT3 cN0M0 rectal carcinoma (p. 112)
K.L.J Rademakers[1], J. Heemskerk[1], M. Maas[2], P.G. Doornebosch[3], T.M. Karsten[4], E.J. Derksen[5], L.P.S. Stassen[2], C. Rosman[6], G.L. Beets[2], E.J.R. de Graaf[3], J.W.A. Leijtens[1], [1]Dept. of surgery Laurentius Hospital Roermond, [2]Dept. of surgery Maastricht University Medical Centre, [3]Dept. of surgery IJsselland Hospital Capelle a/d IJssel, [4]Dept. of surgery Reinier de Graaf Gasthuis Delft, [5]Dept. of surgery Slotervaart Hosptial Amsterdam, [6]Dept. of surgery Canisius Wilhelmina Hospital Nijmegen, The Netherlands

18.15 Radiofrequency ablation combined with endoscopic resection for barrett's esophagus with early neoplasia in 132 patients. Results of a prospective European multicenter study (EURO-II) (p. 113)
K.N. Phoa[1], R.E. Pouw[1], R. Bisschops[2], O. Pech[3], K. Ragunath[4], B.L. Weusten[5], B. Schumacher[6], B. Rembacken[7], A. Meining[8], H. Messmann[9], E. Schoon[10], L. Gossner[11], J. Mannath[4], C. Seldenrijk[5], M. Visser[1], A. Lerut[2], T. Rosch[12], S. Seewald[12], F. ten Kate[1], C. Ell[3], H. Neuhaus[6], J.J. Bergman[1], [1]Academic Medical Center, Amsterdam, The Netherlands, [2]University Hospitals, Leuven, Belgium, [3]Dr. Horst-Schmidt-Kliniken, Wiesbaden, Germany, [4]Wolfson Digestive Diseases Centre, Nottingham, United

Kingdom, [5]St Antonius Hospital, Nieuwegein, The Netherlands, [6]Evangelisches Krankenhaus Dusseldorf, Dusseldorf, Germany, [7]The General Infirmary at Leeds, Leeds, United Kingdom, [8]Technical University of Munich, Munich, Germany, [9]Klinikum Augsburg, Augsburg, Germany, [10]Catharina Hospital, Eindhoven, Netherlands, [11]Klinikum Karlsruhe, Karlsruhe, Germany, [12]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany

18.30 Einde programma, congresborrel in expositiehal.

Symposium MDL-oncologie **Auditorium**

Voorzitter: C.J.J. Mulder en C. van Enckevort

Themasymposium:
'Activiteiten van de MDL-arts binnen de MDL-oncologie':

13.00 Normering van de MDL-oncologie, huidige en toekomstige stand van zaken
Dr. A. Cats, MDL-arts, Antoni van Leeuwenhoekhuis, Amsterdam

13.30 Multidisciplinair samenwerken, wat en wie komt daar voor kijken?
Dr. K.M.A.J. Tytgat, MDL-arts, AMC, Amsterdam

14.00 Chemotherapie door MDL-arts in de dagelijkse praktijk
Dr. G.H. de Groot, MDL-arts, Rode Kruis Ziekenhuis, Beverwijk

14.30 Palliatieve zorg door de MDL-arts
Dr. V.M.C.W. Spaander, MDL-arts

15.00 Einde symposium

Sectie Neurogastroenterologie en Motiliteit **Auditorium**

Voorzitters: A.J. Bredenoord en R.M.J.G.J. van den Wijngaard

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

15.30 The relation between stress, microscopic inflammation and visceral sensitivity in patients with irritable bowel syndrome (p. 114)

*B. Braak[1, *], T. K. Klooker[1, *], M. M. Wouters[2], O. Welting[3], C.M. van der Loos[4], O. I. Stanisor[3], S. van Diest [3], R. M. van den Wijngaard[3] and G. E. E. Boeckxstaens[1,2,5], [1]Department of Gastroenterology and Hepatology, AMC, Amsterdam, The Netherlands, [2]Translational Research Center for Gastrointestinal Disorders, University Hospital Leuven, Catholic University Leuven, Leuven, Belgium, [3]Tytgat Institute of Liver and Intestinal Research, AMC, Amsterdam, The Netherlands, [4]Dept of Pathology, AMC, Amsterdam, The Netherlands, [5]Dept of Gastroenterology, University Hospital Leuven, Catholic University Leuven, Leuven, Belgium [*] Both authors participated equally and sharing first authorship*

15.40 Cholinergic anti-inflammatory pathway in Post-Operative Ileus: role of the spleen and intestinal innervation (p. 116)

L.M.M. Costes[1], J. van der Vliet[1], M.A. Nolte[2], S.H.W. van Bree[1], G.E. Boeckxstaens[3], C. Cailotto[1], Tytgat Institute for Liver and Intestinal Research, AMC, Amsterdam[1], Dept of Hematology, Sanquin, Amsterdam[2], Dept Gastroenterology, University Hospital Leuven, Belgium[3]

15.50 Esophageal electrical tissue impedance spectroscopy can detect esophageal permeability changes in gastroesophageal reflux disease during upper endoscopy (p. 117)

P.W. Weijenborg[1], W.O.A. Rohof[1], L.M.A. Akkermans[2], P.D.P. Lundin[3], A.J.P.M. Smout[1], A.J. Bredenoord[1], [1]Dept. of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Surgery, University Medical Centre, Utrecht, The Netherlands, [3]Clinical Development, AstraZeneca R&D, Mölndal, Sweden

16.00 Sensation of stasis is poorly correlated to impaired esophageal bolus transport (p. 118)

A. Bogte[1], A.J. Bredenoord[2], J. Oors[2], P.D. Siersema[1], A.J.P.M. Smout[2], [1]Gastrointestinal Research Unit, Department of Gastroenterology and Hepatology, University Medical Center, Utrecht, [2]Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherlands.

16.10 Effect of Transoral Incisionless Fundoplication on the occurrence of transient lower esophageal sphincter relaxations (TLESRs) in GERD patients (p. 119)

N.*F. Rinsma[1], D.W. Bruls[1], B.F. Kessing[1], N.D. Bouvy[2], A.A.M. Masclee[1], J.M. Conchillo[1], [1]Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [2]Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands*

16.20 Esophagogastric junction (EGJ) distensibility in GERD patients as measured with an endoscopic functional luminal imaging probe: correlation with endoscopic and pH-impedance reflux parameters (p. 120)

F.G. Smeets[1], N.D. Bouvy[2], G.H Koek[1], A.A.M. Masclee[1], J.M. Conchillo[1], [1]Division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, [2]Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

16.30 Gastric belching and supragastric belching are two distinct pathophysiological entities: A study using combined high-resolution manometry and impedance monitoring (p. 121)

B.F. Kessing, A.J. Bredenoord, A.J.P.M. Smout, Department of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, Amsterdam, The Netherlands

16.40 Clinical examination remains more important than anorectal function tests in patients with constipation to identify treatable conditions (p. 122)

T.J. Lam[1], C.J. Mulder[1], R.J.F. Felt-Bersma[1], [1]Department of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

16.50 Long term course of perianal and anorectal complications in IBD-patients: a single centre inceptive cohort analysis (p. 123)

T.J. Lam[1], A.A. van Bodegraven[1], C.J.J. Mulder[1], R.J.F. Felt-Bersma[1], [1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

17.00 Einde abstractsessie

Voor de Frieda den Hartog Jager lezing en de aansluitende President Select kunt u zich begeven naar de Brabantzaal

Voorzitters: H. Braat en C.J.J. Mulder

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

13.00 Fecal immunochemical test results in different stages of colorectal cancer. A colonoscopy controlled study (p. 124)

I. Ben Larbi[1], S.T. van Turenhout[1], F.A. Oort[1], J.S. Terhaar sive Droste[1], R.W.M. van der Hulst[2], P. Scholten[3], R.J.L.F. Loffeld[4], A.C.T.M. Depla[5], V.M.H. Coupe[6], A.A. Bouman[7], G.A. Meijer[8], C.J.J. Mulder[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [4]Gastroenterology and Hepatology, Zaans Medical Center, Amsterdam, [5]Gastroenterology and Hepatology, Slotervaart Hospital, Amsterdam, [6]Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [7]Clinical Chemistry, VU University Medical Center, Amsterdam, [8]Pathology, VU University Medical Center, Amsterdam, The Netherlands

13.10 Gender disparity in colonic tumorigenesis depends on male hormone tumor promotion, not female hormone protection (p. 125)

J. Heijmans[2], J.M. Amos-Landgraf[1*], M.C.B. Wielenga[2], V.Muncan[2], W.F. Dove[1], G.R. van den Brink[2], [1]McArdle Laboratory for Cancer Research, and Laboratory of Genetics, University of Wisconsin School of Medicine and Public Health, Madison, [2]Tytgat intstitute for Liver and Intestinal Research and Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands *these authors contributed equally*

13.20 Lumican and Versican predict good outcome in stage II and III colon cancer (p. 126)

M. de Wit[1], E.JTh Belt[2], P.M Delis-van Diemen[1], B. Carvalho[1], V.M.H. Coupé[3], H.B.A.C. Stockmann[4], H. Bril[5], J.A.M. Belien[1], R.J.A. Fijneman[1], G.A. Meijer[1], [1]Dept. of Pathology, [2]Dept. of Surgery, [3]Dept. of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, [4]Dept. of Surgery and [5]Pathology, Kennemer Gasthuis, Haarlem, The Netherlands

13.30 Incidence and potential causes for metachronous colorectal cancer. A 10-year retrospective survey (p. 127)

C. le Clercq[1], M. Bouwens[1], R. Riedl[2], G. Beets[3], B. Winkens[4], W. Hameeteman[1], A. Masclee[1], S. Sanduleanu[1], [1]Division of Gastroenterology and Hepatology, Dept. of Internal Medicine, [2]Dept. of Pathology, [3]Dept. of Surgery, and [4]Dept. of Methodology and Statistics, Maastricht University Medical Center, The Netherlands

13.40 Potential Benefits of Proton Pump Inhibitor Use on Acute Coronary Syndromes. Results of a Decision Analysis (p. 128)

N.L. de Groot[1], H.G.M. van Haalen[1], B.M.R. Spiegel[2-4], A. Lanas[5], L. Laine[6], J. Jaspers Focks[7], P.D. Siersema[1], M.G.H. van Oijen[1,4], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Division of Gastroenterology and Hepatology, Veterans Affairs Greater Los Angeles Health Care system, Los Angeles, CA, [3]Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, CA, [4]University of California Los Angeles/Veterans Affairs Center for Outcomes Research and Education (CORE), Los Angeles, CA, [5]University of Zaragoza Medical School, Aragón Health Research Institute (IIS Aragón), CIBERehd, Zaragoza, Spain, [6]Division of

Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles (CA), USA, [7]Dept. of Cardiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

13.50 Potentially reversible risk factors for peptic ulcer bleeding in average-risk users of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin (ASA) (p. 129)

C.W. Ho[1], Y.K. Tse[2], J.Y.L.Ching[2], P.K. Cheong[2], C. Kee[2], A.O.Y. Chan[2], Y.Chan[2], F.K.L. Chan[2], [1]Dept. Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands, [2]Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong, China

14.00 Use of prophylactic gastroprotective therapy in patients with nonsteroidal anti-inflammatory drugand aspirin- associated ulcer bleeding (p. 130)

C.W. Ho[1], Y.K. Tse[2], J.Y.L. Ching[2], C.J.J. Mulder[1], B. Wu[2], F.K.L. Chan[2] ,[1]Dept. Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands, [2]Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong, China

14.10 Upper gastrointestinal hemorrhage. Missed opportunities for prevention? (p. 131)

M.J. Temming[1], W.L. Curvers[1], D.J. van Leeuwen[1,2], [1]Dept. of Gastrointestinal and Liver Diseases, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands, [2]Dartmouth Medical School, Hanover NH, USA

14.20 Hyoscine N-butylbromide does not improve polyp detection during colono-scopyA double-blind randomized placebo-controlled clinical trial (p. 132)

F. ter Borg[1], E.J.M. de Brouwer[1], M.E.L. Arbouw[2], W.C. van der Zwet[3], M.A. van Herwaarden[1], M. Ledeboer[1], F.G.A. Jansman[2], [1]Dept. of Gastroenterology, Deventer Hospital, [2]Dept. of Clinical Pharmacy, Deventer Hospital, [3]Dept. of Clinical Statistics, Deventer Hospital, The Netherlands

14.30 Remotely controlled, small intestinal release of 99mTc-pertechnetate using an ingestible electronic device. the IntelliCap (p. 133)

P.J. van der Schaar[1,2], H. Broekhuizen-de Gast[3], J.F.W. Nijssen[3], N. van Lelyveld[1], H. Zou[4], J. Shimizu[4], F. Dijksman[5], C. Wanke[5], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center, Utrecht, [2]Dept. of Gastroenterology, St Antonius Ziekenhuis, Nieuwegein, [3]Dept. of Nuclear Medicine, University Medical Center, Utrecht, [4]Medimetrics, Philips Research, Briarcliff Manor NY, USA, [5]Medimetrics, Philips Research, Eindhoven, The Netherlands

14.40 **MLDS-project**
Correction of hepatosteatosis by hydrophobic iminosugars modulating glycol sphingolipid metabolism (p. 134)

J.M. Aerts[1], F.Bietrix[1], E. Lombardo[1], C. Vrins[1], R. Ottenhof[1], J.A. Aten[2] , A.K Groen[3] [1]Department of Medical Biochemistry & [2]Department of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, [3]Present address: Department of Pediatrics, University Medical Center Groningen, Groningen, The Netherlands

14.50 **MLDS-project**
A randomized sham-controlled trial of left lateral body positioning and acid suppression for infantile gastroesophageal reflux: A concept test for efficacy of reflux inhibition in infants (p. 135)
C.M. Loots, S. Kritas, M.P. van Wijk, L. McCall, L. Peeters, P. Lewindon, R. Bijlmer, R. Haslam, J. Tobin, M.A. Benninga, G. Davidson, T.I. Omari, Academic Medical Hospital Amsterdam / Emma Childrens Hospital, Amsterdam.

15.00 Theepauze

Nederlandse Vereniging voor Gastroenterologie — Parkzaal

Voorzitters: R.J.F. Felt-Bersma en A.A.M. Masclee

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

15.30 Surgery for Anterior Cutaneous Nerve Entrapment Syndrome. A double blind randomised placebo controlled trial (p. 136)
O.B. Boelens, M.R. Scheltinga, S. Houterman, R.M. Roumen, Maxima Medisch Centrum Instituut, The Netherlands

15.40 Sexual abuse history in GI-Illness, how do gastroenterologists deal with it? Results of a Dutch survey (p. 137)
M.P.J. Nicolai[6], H.H. Fidder[1], J.J.H. Beck[2], M.D. Bekker3, H. Putter [4], R.C.M. Pelger[6], M.F. van Driel[5], H.W. Elzevier[6], [6]Dept. of Urology, Leiden University Medical Center, [1]Dept. of Gastroenterology, Utrecht University Medical Center, [3]Dept. of Surgery, Haaglanden Medical Center, [4]Dept. of Medical statistics, Leiden University Medical Center, [5]Dept. of Urology, University Medical Center Groningen, [2]Dept. of Urology, Zuwe Hofpoort Woerden & St. Antonius Nieuwegein, The Netherlands

15.50 Lymfocytic and collagenous colitis have a different clinical course, experience from a single-center 10 year cohort of 125 patients (p. 138)
M. van der Lugt[1], J. van Baarlen[3], M.G. Russel[1], G. van Olffen[1], J. Kolkman[1,2], [1]Medisch Spectrum Twente, Enschede, [2]University of Groningen, Groningen, [3]Pathology, Laboratory of Pathology East Netherlands, Enschede, The Netherlands

16.00 Should screening for latent tuberculosis infection be repeated after travel to tuberculosis endemic areas in patients treated with TNF-alpha inhibitor therapy? (p. 140)
R.W. Hofland[1], M.A.M.T. Verhagen[1], R. Huisman[2], A. Bossink[3], [1]Dept. Gastroenterology Diakonessenhuis Utrecht, [2]Dept. Rheumatology, Diakonessenhuis Utrecht, [3]Dept. Pulmonology, Diakonessenhuis Utrecht, The Netherlands

16.10 Over a quarter of the general adult population experiences gastrointestinal symptoms influencing health-related quality of life. results of 50,000 questionnaires (p. 141)

M.M. Tielemans[1,2], J. Jaspers Focks[1], L.G.M. van Rossum[1], J.B.M.J. Jansen[3], R.J.F. Laheij[2], M.G.H. van Oijen[2], [1]Radboud University Nijmegen Medical Centre, Nijmegen, [2]University Medical Centre Utrecht, Utrecht, [3]Elkerliek Hospital, Helmond, The Netherlands

16.20 New insight into dynamics of plasma Intestinal Fatty Acid Binding Protein as a marker for epithelial damage in human small intestinal ischemia-reperfusion (p. 142)

D.H.S.M. Schellekens[1], J. Grootjans[1], J.P.M. Derikx[1], S.A.G.W. Dello[1], A.A. van Bijnen[1], R.M. van Dam[1], C.H.C. Dejong[1], W.A. Buurman[1], Dept. of Surgery, Maastricht University Medical Center and Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht, The Netherlands

16.30 Moderate dosage of ethanol increases small and large intestinal permeability in healthy volunteers (p. 143)

E. Elamin[1,2, 3], D. Jonkers[1, 2, 3], F. Troost[1, 2, 3], J. Dekker[1, 4], A. Masclee[1, 2, 3], [1]Top Institute Food and Nutrition (TIFN), Wageningen, [2]Division of Gastroenterology-Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, Maastricht, [3]School for Nutrition, Toxicology and Metabolism of Maastricht University Medical center, [4]Dept. of Animal Sciences, Wageningen UR, Wageningen, The Netherlands

16.40 HLA-DQ genotype distribution in Type 1 Diabetes Mellitus patients with concomitant Celiac Disease (p. 144)

S.F. Bakker[1], M.E. Tushuizen[1], J.B.A. Crusius[2], S. Simsek[3], C.J.J. Mulder[1], B.M.E. von Blomberg[4], [1]Dept. of Gastroenterology and Hepatology, VU University Medical Center, Laboratory of Immunogenetics, [2]Dept. of Pathology, VU University Medical Center, [3]Dept. of Internal Medicine, Medical Center Alkmaar, [4]Dept. of Medical Immunology, VU University Medical Center, The Netherlands

16.50 Can the systemic compartment contribute to barrier disruption in diarrhea predominant IBS patients? (p. 145)

S. Ludidi, E. Elamin, H.J. Pieters, P. Bours, E. Schaepkens, J.M. Conchillo, D.M. Jonkers, A.A. Masclee, Dept. of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Centre+, Maastricht, The Netherlands

17.00 Einde abstractsessie, voor de Frieda den Hartog Jager lezing kunt u zich begeven naar de Brabantzaal

Sectie Gastrointestinale Endoscopie — Brabantzaal

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

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

08.30 Clinical impact of autofluorescence imaging on the endoscopic treatment for early Barrett's neoplasia. A prospective assessment of 371 patients (p. 146)

D.F. Boerwinkel[1], W.L. Curvers[1], M.A. Kara[1], M. Visser[2], S.L. Meijer[2], J.A. Holz[3], M.C. Aalders[3], J.J. Bergman[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Centre Amsterdam, [2]Dept. of Pathology, Academic Medical Centre Amsterdam, [3]Dept. of Biomedical Engineering and Physics, Academic Medical Centre Amsterdam, The Netherlands

08.40 Prospective long-term follow-up after radiofrequency ablation for Barrett's esophagus with high-grade dysplasia and/or early cancer (p. 147)

K.Y.N. Phoa[1], R.E. Pouw[1], F.G.I. van Vilsteren[1], C.M.T. Sondermeijer[1], F.J.W. Ten Kate[2], M. Visser[2], S.L Meijer[2], M.I. van Berge Henegouwen[3], B.L.A.M. Weusten[4], R.C. Mallant-Hent[5], E. Schoon[6], J.J.G.H.M. Bergman[1], [1]Gastroenterology, Academic Medical Center, Amsterdam, [2]Pathology, Academic Medical Center, Amsterdam, [3]Surgery, Academic Medical Center, Amsterdam, [4]Gastroenterology, St Antonius hospital, Nieuwegein, [5]Gastroenterology, Flevo hospital, Almere, [6]Gastroenterology, Catharina-ziekenhuis, Eindhoven, The Netherlands

08.50 A prospective multicenter study to identify predictive markers for initial treatment response after circumferential radiofrequency ablation for Barrett's esophagus with early neoplasia (p. 148)

F.G.I. van Vilsteren[1], L. Alvarez Herrero1[1,2], R.E. Pouw[1], D. Schrijnders[1], C.M. Sondermeijer[1], R. Bisschops[3], J.M. Esteban[4], A. Meining[5], H. Neuhaus[6] , A. Parra-Blanco[7], O. Pech[8], Krish Ragunath[9], B. Rembacken[10], B.E. Schenk[11], M. Visser[12], F.J.W. ten Kate[12], J.B. Reitsma[13], B.L.A.M. Weusten[1,2], E.J. Schoon[14], J.J.G.H.M. Bergman[1], [1]Academic Medical Center, Amsterdam, Netherlands, [2]St Antonius Hospital, Nieuwegein, Netherlands, [3]University Hospital Gasthuisberg, Leuven, Belgium, [4]Hospital Clínico San Carlos, Madrid, Spain, [5]Klinikum rechts der Isar München, Germany, [6]Evangelisches Krankenhaus Düsseldorf, Germany, [7]Hospital Universitario Central de Asturias, Oviedo, Spain, [8]Dr.-Horst-Schmidt-Kliniken Wiesbaden, Germany, [9]Queens Medical Centre Nottingham, United Kingdom, [10]Nuffield Hospital Leeds, United Kingdom, [11]Isala Klinieken Zwolle, The Netherlands, [12]Pathology, Academic Medical Center, Amsterdam, Netherlands, [13]Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, Netherlands, [14]Catharina Hospital Eindhoven, The Netherlands

09.00 Simplifying radiofrequency ablation of Barrett's esophagus. a randomized multicenter trial comparing three different treatment regimens for circumferential ablation using the HALO^{360} System (p. 149)

F.G.I. van Vilsteren[1], L. Alvarez Herrero[2], R.E. Pouw[1], N. Phoa[2], C.M.T. Sondermeijer[1], G. van Lijnschoten[3], C.A. Seldenrijk[4], M. Visser[5], M.I. van Berge Henegouwen[6], B.L.A.M Weusten[2], E.J. Schoon[7], J.J.G.H.M. Bergman[1], [1]Gastroenterology, Academic Medical Center, Amsterdam Gastro-enterology, St Antonius Hospital, Nieuwegein, [3]Pathology, Catharina Ziekenhuis Eindhoven, [4]Pathology, St Antonius Hospital, Nieuwegein, [5]Pathology, Academic Medical Center, Amsterdam, [6]Surgery, Academic Medical Center, Amsterdam, [7]Catharina Ziekenhuis Eindhoven, The Netherlands

09.10 A multicenter randomized trial comparing two ablation regimens for focal radiofrequency ablation of Barrett's mucosa using the HALO^{90} system (p. 150)

F.G.I. van Vilsteren[1], L. Alvarez Herrero[2], R.E. Pouw[1], N. Phoa[1], C.M.T. Sondermeijer[1], M. Visser[3], F.J.W. Ten Kate[3], M.I. van Berge Henegouwen[4], B.L.A.M Weusten[2], E.J. Schoon[5], J.J.G.H.M. Bergman[1], [1]Gastroenterology, Academic Medical Center, Amsterdam, [2]Gastroenterology, St. Antonius Hospital, Nieuwegein, [3]Pathology, Academic Medical Center, Amsterdam, [4]Surgery, Academic Medical Center, Amsterdam, [5]Catharina Hospital Eindhoven, The Netherlands

09.20 Safety of simultaneous use of endoscopic resection and radiofrequency ablation. Evaluation of two variants of "single step" treatment in an esophageal porcine model (p. 151)

L. Alvarez Herrero[1, 2], F.G.I. van Vilsteren[2], M. Visser[3], M.I. van Berge Henegouwen[4], J.J.G.H.M. Bergman[2], B.L.A.M. Weusten[1,2], [1]Dept. of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept. of Pathology, Academic Medical Center, Amsterdam, [4]Dept. of Surgery, Academic Medical Center, Amsterdam, The Netherlands

09.30 Does Lugol's staining prevent stenosis formation induced by radiofrequency ablation of oesophageal squamous epithelium? A study in a porcine model (p. 152)

D. Schölvinck[1,2], L. Alvarez Herrero[1], M. Visser[3], J.J.G.H.M. Bergman[2], B.L.A.M. Weusten[1,2], [1]Dept. of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept. of Pathology, Academic Medical Center, Amsterdam, The Netherlands

09.40 Predictors of mortality in patients with esophageal adenocarcinoma in a large Dutch population-based cohort (p. 153)

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

09.50 Botulin and steroid injection directly after widespread endoscopic resection do not prevent severe stenosis in an esophageal porcine model (p. 154)

L. Alvarez Herrero[1,2], M. Visser[3], M.I. van Berge Henegouwen[4], J.J.G.H.M. Bergman[2], B.L.A.M. Weusten[1], [1]Dept. of Gastroenterology and Hepatology, St Antonius hospital, Nieuwegein, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [3]Dept. of Pathology, Academic Medical Center, Amsterdam, [4]Dept. of Surgery, Academic Medical Center, Amsterdam, The Netherlands

10.00 Safety of Endoscopic Removal of Self-expandable Stents after Treatment of Benign Esophageal Diseases (p. 155)

E.E. van Halsema[1], L.M. Wong Kee Song[2], T.H. Baron[2], P.D. Siersema[3], F.P. Vleggaar[3], G. Ginsberg[4], P. Shah[4], D.E. Fleischer[5], S.K. Ratuapli[5], P. Fockens[1], G. Rando[6], A. Repici[6], J.E. van Hooft[1], [1]Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Gastroenterology & Hepatology, Mayo Clinic, Rochester, Minnesota, USA, [3]Gastroenterology & Hepatology, University Medical Center Utrecht, The Netherlands, [4]Gastroenterology & Hepatology, Hospital of the University of Pennsylvania, Philadelphia, USA, [5]Gastroenterology & Hepatology, Mayo Clinic, Scottsdale, Arizona, USA, [6]Digestive Endoscopy, Istituto Clinico Humanitas, Rozzano (Milan), Italy

10.10 Peroral Endoscopic Myotomy (POEM) for the treatment of achalasia. preliminary feasibility and safety results (p. 156)

T. Verlaan[1], A.J. Bredenoord[1], Th. Roesch, S. Eberl[2], P. Fockens[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Anesthesiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [3]Dept. of Interdisciplinary Endoscopy, University Hospital Eppendorf, Hamburg, Germany

10.20 Treatment of GERD patients with Transoral Incisionless Fundoplication leads to a significant reduction in reflux symptoms and objective reflux parameters at six and 12 months follow up (p. 157)

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

10.30 Koffiepauze

Sectie Gastrointestinale Endoscopie — Brabantzaal

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

Nederlands, spreektijd 07 minuten, discussietijd 03 minuten

11.00 A cost study of covered transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic treatment for secondary prevention of gastro-oesophageal variceal bleeding (p. 158)

I.L. Holster[1], S. Polinder[2], A. Moelker[3], H. van Buuren[1], E.J. Kuipers[1,4], Depts. of [1]Gastroenterology and Hepatology, [2]Public health, [3]Radiology, and [4]Internal Medicine, Erasmus MC University Medical Centre, The Netherlands

11.10 EUS-guided drainage is an effective treatment for the majority of symptomatic peripancreatic fluid collections (p. 159)

H.T. Künzli[1], M.G.H. van Oijen[1], R. Timmer[2], M.P. Schwartz[3], B.J. Witteman[4], B.L. Weusten[2], P.D. Siersema[1], F.P. Vleggaar[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, [2]Depts. of Gastroenterology St. Antonius Hospital Nieuwegein, [3]Meander Medical Center Amersfoort, [4]Gelderse Vallei Hospital Ede, The Netherlands

11.20 Growth rate of pancreatic neuroendocrine tumors in MEN1 syndrome, an EUS surveillance study (p. 160)

C. Cottone[1], G.D. Valk[2], M.G. van Oijen[1], P.D. Siersema[1], F.P. Vleggaar[1], Dept. of Gastroenterology and Hepatology[1], Dept. of Internal Medicine[2] , University Medical Center Utrecht, Utrecht, The Netherlands

11.30 Visible light spectroscopy in diagnosis of chronic gastrointestinal ischemia, results of a cohort study (p. 161)

A. Sana[1], L.M.G. Moons[1], B. E. Hansen[1,2], P. Dewint[1], D. van Noord[1], P.B.F. Mensink[1], Ernst J. Kuipers [1,3], Depts. of Gastroenterology and Hepatology[1], Center for Medical Decision Sciences[2], Internal Medicine[3], Erasmus MC – University Medical Center, Rotterdam, The Netherlands

11.40 Real-time in vivo imaging of early mucosal changes during ischemia-reperfusion in human jejunum (p. 162)

J. Grootjans[1], W. Hameeteman[2], A.A. Masclee[2], R.M. van Dam[1], W.A. Buurman[1], C.H.C. Dejong[1], [1]Dept. of Surgery, Maastricht University Medical Center, [2]Dept. of Gastroenterology, Maastricht University Medical Center, The Netherlands

11.50 Impact of Colonoscopy in CT-Detected Colonic Wall Thickening (p. 163)

K. van Boxtel, E.T.P. Keulen, M.J.L. Romberg-Camps, H.M.J.M. Verhoeven, L.G.J.B. Engels, Dept. of Gastroenterology, Orbis Medical Centre, Sittard-Geleen, The Netherlands

12.00 High adenoma detection rate in first degree relatives of patients with serrated polyposis syndrome. a prospective study (p. 164)

Y. Hazewinkel[1], J.J. Koornstra[2], K.S. Boparai[1], T.A.M. van Os[3], K.M.A.J Tytgat[1], P. Fockens[1], E. Dekker[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, [3]Dept. of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands

12.10 Colonoscopy performed by nurse endoscopists is associated with high patient satisfaction (p. 166)

P.G. van Putten[1], R. Massl[1], E.W. Steyerberg[2], A.J.P. van Tilburg[3], J.Y.L. Lai[4], R.J.J. de Ridder[5], J.T. Brouwer[6], R.J. Verburg[7], J. Alderliesten[8], E.J. Schoon[9], M.E. van Leerdam[1], Ernst J. Kuipers[1,10], [1]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [2]Erasmus University Medical Center, Dept. of Public Health, Rotterdam, [3]Dept. of Gastroenterology and Hepatology, Sint Franciscus Gasthuis, Rotterdam, [4]Dept. of Gastroenterology, Groene Hart Ziekenhuis, Gouda, [5]Division of Gastroenterology-Hepatology, Dept. of Internal Medicine, Maastricht University Medical Center, Maastricht, [6]Dept. of Gastroenterology and Hepatology, Reinier de Graaf Medical Center, Delft, [7]Dept. of Gastroenterology, Medisch Centrum Haaglanden, Den Haag, [8]Dept. of Gastroenterology, Albert Schweitzer hospital, Dordrecht, [9]Dept. of Gastroenterology, Catharina Hospital, Eindhoven, [10]Dept. of Internal Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

12.20 Malignant colonic polyps are not benign. Outcome and guideline adherence after endoscopic or surgical treatment (p. 167)

F.E. Beumer[1], M.G. Havenith[2], J. van Baarlen[3], G.A. Patijn[4], J.J. Kolkman[5], J. Vecht[1], [1]Dept. of Gastroenterology & Hepatology, Isala clinics, Zwolle, [2]Dept. of Pathology, Isala clinics, Zwolle, [3]Dept. of Pathology, Medisch Spectrum Twente, Enschede, [4]Dept. of Surgery, Isala clinics, Zwolle, [5]Dept. of Gastroenterology & Hepatology, Medisch Spectrum Twente, Enschede, The Netherlands

12.30 Lunchpauze

Voorzitters: S. Sanduleanu en F. Vleggaar

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

08.30 Risk factors for lymph node metastasis in 342 surgically treated patients with early gastric cancer confined to the upper submucosal layer (Sm1) (p. 168)
Y-K. Sung[2], K-M Kim[3], B-H Min[2], J-H Lee[2], S. Kim[4], T.S. Sohn[4], J-H Noh[4] , R.E. Pouw[1], Y-N. Choi[1], Y. Hazewinkel[1], J.J. Bergman[1], J.J. Kim[2], [1]Dept. of Gastroenterology, Samsung Medical Center (SMC), Seoul, South Korea, [2]Dept. of Surgery, SMC, Seoul, South Korea, [3]Dept. of Pathology, SMC, Seoul, South Korea, [4]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

08.40 Long-term survivors of esophageal cancer in The Netherlands (p. 169)
P. Bus[1], V.E.P.P. Lemmens[2,3], M.G.H. van Oijen[1], G.J. Creemers[4], G.A.P. Nieuwenhuijzen[4], J.W.P.M. van Baal[1], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, [2]Comprehensive Cancer Center South (CCCS), Eindhoven, [3]Dept. of Public Health, Erasmus Medical Center, Rotterdam, [4]Catharina Hospital, Eindhoven, The Netherlands

08.50 Familial clustering of Barrett's esophagus and esophageal adeno-carcinoma in The Netherlands (p. 170)
R.E. Verbeek[1], L.F. Spittuler[1], A. Peute[1], M.G.H. van Oijen[1], F.J. ten Kate[2], J.R. Vermeijden[3], A. Oberndorff[4], J.W.P.M. van Baal[1], P.D. Siersema[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Pathology, University Medical Center Utrecht, [3]Dept. of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, [4]Dept. of Gastroenterology and Hepatology, Diakonessenhuis, Utrecht, The Netherlands

09.00 Electrical stimulation of the lower esophageal sphincter in patients with gastroesophageal reflux disease is technically feasible and results in a decrease in symptoms (p. 171)
B.F. Kessing[1], M.I. van Berge-Henegouwen[2], M.P. Schijven[2], A.J.P.M. Smout[1], A.J. Bredenoord[1], [1]Dept. of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, Amsterdam, [2]Dept. of Surgery, Academic Medical Center Amsterdam, Amsterdam, The Netherlands

09.10 High enzyme activity UGT1A1 or low activity UGT1A8 and UGT2B4 genotypes increase esophageal cancer risk (p. 172)
P. Dura[1], J. Salomon[1], R.H.M. te Morsche[1], H.M.J. Roelofs[1], J.O. Kristinsson[1], T. Wobbes[2], B.J.M. Witteman[3], A.C.I.T.L. Tan[4], J.P.H. Drenth[1], W.H.M. Peters[1], [1]Dept. of Gastroenterology and [2]Surgery, Radboud University Medical Center, Nijmegen, [3]Dept. of Gastroenterology, Hospital Gelderse Vallei, Ede, [4]Dept. of Gastroenterology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

09.20 Rapidly increasing incidence of eosinophilic esophagitis in a nationwide cohort (p. 173)
B.D. van Rhijn[1], J. Verheij[2], A.J.P.M. Smout[1], A.J. Bredenoord[1], [1]Dept. of Gastroenterology & Hepatology, [2]Dept. of Pathology, Academic Medical Center, Amsterdam, The Netherlands

09.30 Short- vs. long-term value of prognostic factors in colon and rectal cancer. A population based study (p. 174)

V.K. Dik[1], V.E. Lemmens[2,3], M.G.H. van Oijen[1,4], P.D. Siersema PD[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Eindhoven Cancer Registry, Comprehensive Cancer Center South (IKZ), Eindhoven, The Netherlands, [3]Dept. of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands, [4]Division of Digestive Diseases, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

09.40 Cochrane Review. Helicobacter pylori eradication for pre-malignant lesions of the gastric mucosa (p. 175)

A.C. de Vries[1], I.L. Holster[1], E.J. Kuipers[1,2], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

09.50 hsTRAIL/Apo2L-Induced Apoptosis in Enteropathy-Associated T-Cell Lymphoma (p. 176)

M. Radersma[1], L.R. de Baaij[1], N.J. Hijmering[2], C.J.L.M. Meijer[2], C.J.J. Mulder[1], S.A.G.M. Cillessen[2], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Pathology, VU University Medical Center, Amsterdam, The Netherlands

10.00 Primary colorectal cancer with unresectable synchronous metastases. Chemotherapy first? (p. 177)

M. Radersma[1,2], S.M.M. de Castro[2], B.A. van Wagensveld[2], W.F. van Tets[2], B.C. Vrouenraets[2], [1]Dept. of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Dept. of Surgery, Sint Lucas Andreas Hospital, Amsterdam, The Netherlands

10.10 Low yield of advanced neoplasia within six years after negative colonoscopy. A population-based study (p. 178)

I. Ben Larbi[1], A.J. Buth[1], N. Akdemir[1], R.W.M. van der Hulst[2], P. Scholten[3], H.A.R.E. Tuynman[4], G.A. Meijer[5], C.J.J. Mulder[1], J.S. Terhaar sive Droste[1], [1]Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, [2]Gastroenterology and Hepatology, Kennemer Gasthuis, Haarlem, [3]Gastroenterology and Hepatology, Sint Lucas Andreas Hospital, Amsterdam, [4]Gastroenterology and Hepatology, Medical Center Alkmaar, [5]Pathology, VU University Medical Center, Amsterdam, The Netherlands

10.20 The rising incidence of esophageal adenocarcinoma is not accompanied with an increase in mortality. Results of a population-based cohort study (p. 179)

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

10.30 Koffiepauze in de expositiehal

Sectie Kinder-MDL **Auditorium**

Voorzitters: R.H.J. Houwen en H-J. Verkade

Symposium Galgangatresie

11.00 Pathogenese
Prof. M. Davenport, Consultant Paediatric Surgeon, King's College Hospital, London

Prognose, korte en lange termijn:
Dr. W. de Vries, anios Kindergeneeskunde, Wilhelmina Kinderziekenhuis, Utrecht

Resultaten van OLT bij kinderen:
Prof. dr. H-J. Verkade, kinderarts MDL, Beatrix Kinderziekenhuis, Groningen

Transitie naar volwassen zorg:
Dr. R.A. de Man, MDL-arts, Erasmus MC, Rotterdam

12.30 Einde symposium, lunchbuffet in expositiehal

Sectie Kinder-MDL **Auditorium**

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

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

14.00 The human leukocyte antigen DQ B1*02 is more frequent in patients with tissue-transglutaminase antibody levels U100 U/Ml (p. 180)
A. Mubarak[1], E. Spierings[2], V.M. Wolters[1], R.H.J. Houwen[1], Depts. of Paediatric [1]Gastroenterology and [2]Immunology, University Medical Center Utrecht, The Netherlands

14.10 Long term follow-up of gut-directed hypnotherapy versus standard care in children with functional abdominal pain or irritable bowel syndrome (p. 181)

A.M. Vlieger[1], J.M.T.M. Rutten[2], A.M.A.P. Govers[1], C. Frankenhuis[2], M.A. Benninga[2], [1]St Antonius Hospital Nieuwegein, Dept. of Pediatrics, [2]Academic Medical Center Amsterdam, Dept. of Pediatrics, The Netherlands

14.20 **MLDS-project**
Long term effects of cognitive behavior therapy for the treatment of children with functional abdominal pain. Results of a randomized controlled trial (p. 182)

S.M.C. van der Veek[1], H.H.F. Derkx[2], E. de Haan[3], M.A. Benninga[2] & F. Boer[1], [1]Academisch Medisch Centrum Amsterdam, afdeling Kinder- en Jeugdpsychiatrie, [2]Emma Kinderziekenhuis AMC, [3]Academisch Medisch Centrum Amsterdam, afdeling Kinder- en Jeugdpsychiatrie en Universiteit van Amsterdam, afdeling pedagogische wetenschappen, The Netherlands

14.30 Completion of toilet training in children with defecation disorders and concomitant symptoms of autism spectrum disorders (p. 183)

B. Peeters[1], M.A. Benninga[1], I.L.J. Noens[2], [1]Dept. of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands, [2]Parenting and Special Education Research Unit, Katholieke Universiteit Leuven, Leuven, Belgium

14.40 Predicting NAFLD in severely obese children and adolescents. Non-invasive prediction rules and novel biomarkers lack sufficient diagnostic accuracy (p. 184)

B.G.P. Koot[1], O.H. van der Baan-Slootweg[2], A.E. Bohte[3], A.J. Nederveen[3], M.P. Merkus[4], P.L.M. Jansen[5], J. Stoker[3], M.A. Benninga[1], [1]Dept. of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital/Academic Medical Centre Amsterdam, [2]Childhood Obesity Centre Heideheuvel, Hilversum, [3]Dept. of Radiology, Academic Medical Centre Amsterdam, [4]Clinical Research Unit, Academic Medical Centre, Amsterdam, The Netherlands, [5]Dept. of Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

14.50 Gluten challenge in the diagnosis of celiac disease (p. 185)

N. van Rheenen[1], R.H.J. Houwen[1], F.J.W. ten Kate[2], A. Mubarak[1], Depts. of Paediatric [1]Gastroenterology and [2]Pathology, University Medical Center Utrecht, The Netherlands

15.00 Increased IL-21, but not IL-17A production in the small intestine is characteristic for pediatric Celiac Disease (p. 186)

M.A. van Leeuwen[1], D.J. Lindenbergh-Kortleve[1], L.F. de Ruiter[1], H.C. Raatgeep[1], R.R. de Krijger[2], M. Groeneweg[3], J.C. Escher[1], J.N Samsom[1], [1]Dept. of Pediatric Gastroenterology, Erasmus Medical Centre-Sophia Children's Hospital, Rotterdam, [2]Dept. of Pathology, Erasmus Medical Centre, Rotterdam, [3]Dept. of Pediatrics, Maasstad Hospital, Rotterdam, The Netherlands

15.10 Rectal examination in children. Digital versus transabdominal ultrasound (p. 187)

R. Burgers[1, 2], T.P.V.M. de Jong[1, 2], M.A. Benninga[1], [1]Pediatric Gastroenterology, Emma Children's Hospital, AMC, Amsterdam, Netherlands, [2]Pediatric Urologic Center, University Children's Hospital UMC Utrecht/AMC Amsterdam, The Netherlands

15.20 The value of defecography in the diagnostic and therapeutic management in defecation disorders in children (p. 188)

S.M. Mugie[1,3], G. Bates[2], J. Punati[1], C. Di Lorenzo[1], H. Mousa[1], [1]Division of Pediatric Gastroenterology, Nationwide Children's Hospital, Columbus, OH, [2]Dept. of Radiology, Nationwide Children's Hospital, Columbus, OH, [3]Division of pediatric gastroenterology, AMC/Emma Children's Hospital, Amsterdam, The Netherlands

15.30 Disease phenotype at diagnosis in paediatric Crohn's disease. 5-year analyses of the EUROKIDS registry (p. 190)

C.I. de Bie[1], A. Paerregaard[2], S. Kolacek[3], F.M. Ruemmele[4], S. Koletzko[5], J.M.E. Fell[6], J.C. Escher[1], and the EUROKIDS Porto IBD Working Group of ESPGHAN, [1]Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, [2]Hvidovre University Hospital, Copenhagen, Denmark, [3]Children's Hospital Zagreb, Zagreb, Croatia, [4]Hôpital Necker-Enfants Malades, Paris, France, [5]Dr. von Haunersches Kinderspital, Ludwig-Maximilians-Universität, Munich, Germany, [6]Chelsea and Westminster Hospital, London, United Kingdom

15.40 Huishoudelijke vergadering Sectie Kinder MDL

DEGH-Meeting **Baroniezaal**

Voorzitters: K.N. Faber en J.C. Fernández-Checa

ZonMw

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

Theme **Disease mechanism and therapy**

09.00 Albumin is a neuroprotective agent for bilirubin-induced auditory brainstem dysfunction in Gunn rat pups (p. 191)

A.B. Schreuder[1], A.C. Rice[2], J. Vanicova[3], L. Vitek[3,4], S.M. Shapiro[2], H.J. Verkade[1], [1]Pediatric Gastroenterology and Hepatology, Dept. of Pediatrics, Center for Liver, Digestive, and Metabolic Diseases, Beatrix Children's Hospital- University Medical Center Groningen, University of Groningen, The Netherlands, [2]Dept. of Neurology, Virginia Commonwealth University, Richmond, Virginia, USA, [3]Institute of Clinical Biochemistry and Laboratory Diagnostics, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, [4]4th Dept. of Internal Medicine, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

09.12 Inhibition of MRP1 attenuates liver fibrosis in vitro and in vivo (p. 192)

A.U. Rehman, B. Mikus, H. Moshage and K.N. Faber, Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, The Netherlands

09.24 How computer simulations of fatty-acid beta-oxidation help to elucidate metabolic disease mechanisms (p. 193)

K. van Eunen[1,2], S. Simons[1], A. Gerding[1], G. den Besten[1,2], N. Touw[1], D-J. Reijngoud[1,2], A.K. Groen[1,2] and B.M. Bakker[1,2], [1]Dept. of Pediatric, Center for Liver, Digestive and Metabolic Disease, University Medical Center Groningen, Groningen, [2]Netherlands Consortium for Systems Biology, Amsterdam, The Netherlands

09.36 Role of NLRP3 in obesity-induced liver steatosis and inflammation (p. 194

A.A.A. Adam[1], P.J. Bakker[2], G.W.J. Teske[2], I.C. Gaemers[1,3], J.C. Leemans[2,3], [1]Tytgat institute for liver and intestinal research and [2]Pathology, AMC. Amsterdam, The Netherlands, [3]Last authors

09.48 **Invited speaker**
Mitochondrial cholesterol in liver diseases
Professor J.C. Fernández-Checa, groupleader at the Liver Unit and Instituto del investigaciones Biomédicas de Barcelona (IIBB), Spain and visiting research professor of Pathology at the University of Southern California in Los Angeles, U.S.A.

10.30 Koffiepauze

DEGH-Meeting **Baroniezaal**

Voorzitters: J. Raes en A.A. te Velde

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

Theme **G&H disease gene identification & functional analysis**

11.00 Immunochip-based analysis of 72.000 individuals identifies 50 novel IBD loci, refining definitions of disease pathways (p. 195)

R.K.Weersma[1] on behalf of the International IBD Genetics Consortium, [1]Dept. of Gastroenterology and Hepatology, University of Groningen and University Medical Center Groningen, The Netherlands

11.12 Genome wide analysis identifies mitotic recombination as cause of somatic loss of heterozygosity in cysts from polycystic liver disease patients (p. 196)

M.J. Janssen[1], R. Pfundt[2], J.P.H. Drenth[1], [1]Dept. of Gastroenterology & Hepatology, [2]Dept. of Human Genetics Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

11.24 HSPA6 is a prominent cigarette smoke-induced gene residing in a UC susceptibility locus and protects against cytokine-induced apoptosis (p. 197)

A. Regeling[1], F. Imhann[1], T. Blokzijl[1], H.H. Volders[1], J.A.L. Visser[1], V.W. Bloks[2], K.N. Faber[1], G. Dijkstra[1], [1]Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, [2]Dept. of Pediatrics, University Medical Center Groningen, The Netherlands

11.36 Cigarette smoke is an environmental factor that reduces innate immune functions especially in individuals with the CD-associated risk variant ATG16L1-T300A (p. 198)

A. Regeling, H.H. Volders, T. Blokzijl, E.M.J. van der Logt, H.H.J. Geuken, K.N. Faber, G. Dijkstra, Dept. of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, The Netherlands

11.48 **Invited Speaker**
The gut microbiome in health and IBD
Prof. J. Raes, group leader at the VIB Department of Structural Biology Free University Brussel, Belgium

Postersessie DEGH — Meierij Foyer

12.30 De postersessie van de DEGH vindt plaats tussen 12.30 en 13.30 uur. Tijdens deze sessie worden de posters voor de posterprijzen geselecteerd. Voor het posterprogramma zie pagina 51.

13.30 Vervolg DEGH-programma.

Sectie Inflammatoire Darmziekten (IBD) — Brabantzaal

Voorzitters: G. Dijkstra en G.R.A.M. d'Haens

14.00 Genetische factoren bij IBD: betekenis voor de kliniek, nu en in de toekomst
Dr. R.K. Weersma, MDL-arts, UMC Groningen

14.25 Huidige pathofysiologische inzichten: wat gaat ons dit opleveren?
Dr. G. Bouma, MDL-arts, VU medisch centrum, Amsterdam

Vrijdag 23 maart 2012

14.50 **Oprichting Sectie Inflammatoire Darmziekten (IBD)**
voorgezeten door voorzitter D.J. de Jong en secretaris B. Oldenburg
van voormalige werkgroep IBD van de NVGE

Vervolg programma

Voorzitters: G. Dijkstra en G.R.A.M. d'Haens

15.05 Is Top Down en tight control de juiste strategie bij alle Crohn patiënten in de toekomst? Heterogeniciteit in ziekte ernst in het IBD-Zuid-Limburg cohort.
Dr. M.J. Pierik, MDL-arts, Maastricht UMC

15.30 Anti-TNF behandeling en monitoring in de praktijk
Dr. C.I.J. Ponsioen, MDL-arts, AMC, Amsterdam

15.50 Vragen en uitslag stemming bestuursleden sectie IBD

16.00 Einde programma

Voorzitters: D. Jonkers en S.W.C. van Mil

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

Theme **G&H-Immunology**

14.00 Adrenergic modulation of inflammatory dendritic cells (p. 199)
L.E.J. Nijhuis[1], B.J. Olivier[1], F.W. Hilbers, W.J. de. Jonge[1], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands

14.12 Effects of corticosteroids on interferon-α signaling and inhibition of hepatitis C infection by plasmacytoid dendritic cells (p. 200)
P.E. de Ruiter, P.P.C. Boor, Q. Pan, J. de Jonge, H.J. Metselaar, G. Kazemier, H.W. Tilanus, J. Kwekkeboom, L.J.W. van der Laan, Depts. of Surgery and Gastroenterology & Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

14.24 Conditional activation of intestinal Hedgehog signaling inhibits the Interferon response (p. 201)
N.V.J.A. Büller[1], W.A. van Dop[2], A. Uhmann[3], P.E. Ver Loren van Themaat[4], J. Heijmans[1], D.W. Hommes[5], V. Muncan[1], H. Hahn[3], G.R. van den Brink[1, 2], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [3]Institute of Human Genetics, Georg August University of Göttingen, Germany, [4]Max Planck Institute for Plant Breeding Research, Cologne, Germany, [5]Dept. of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

14.36 Rapamycin inhibits innate and adaptive immune functions of human plasmacytoid dendritic cells (p. 202)
P.P.C. Boor[1], S. Mancham[1], L.W.J. van der Laan[2], H.J. Metselaar[1], J. Kwekkeboom[1], Depts. of [1]Gastroenterology and Hepatology, and [2]Surgery, Erasmus MC-University Medical Centre, Rotterdam, The Netherlands

14.48 The formation of tertiary lymphoid tissue in colitis is under neuronal control (p. 203)
B.J. Olivier[1], C. Cailotto[1], J. van der Vliet[1], F. Hilbers[1], G.E. Boeckxstaens[2], W.J. de Jonge[1,4], R.E. Mebius[3,4], [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept. of Gastroenterology, University Hospital Leuven, Leuven, Belgium, [3]Dept. of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands [4]These Authors contributed equally

15.00 Abstract and poster prizes

Vrijdag 23 maart 2012

15.15 Ledenvergadering Sectie Experimentele Gastroenterologie

sectie experimentele gastroenterologie

Abstract Meeting NESPEN — Zaal 80

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

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

09.30 Fall incidents decrease after short-term oral nutritional intervention in malnourished elderly patients: a randomized controlled trial (p. 204)

F. Neelemaat[*1] , *P. Lips*[2] , *J.E. Bosmans*[3] , *A. Thijs*[4] , *J.C. Seidell*[3] , *M.A.E. van Bokhorst-de van der Schueren*[1], [1]*Departments of Nutrition and Dietetics, Internal Medicine and EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam,* [2]*Department of Internal Medicine, Section Endocrinology and EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam,* [3]*Department of Health Sciences and EMGO Institute for Health and Care Research, Faculty of Earth and Life Sciences, VU University, Amsterdam,* [4]*Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands*

09.40 The bioelectrical impedance phase angle as indicator of undernutrition and adverse clinical outcome in cardiac surgical patients (p. 205)

M. Visser[1, 2], *L.M.W. van Venrooij*[1, 3], *D.C.M. Wanders*[4], *R. de Vos*[5], *W. Wisselink*[2], *P.A.M. van Leeuwen*[2], *B.A.J.M. de Mol*[1], [1]*Department of Cardiothoracic Surgery, Academic Medical Center University of Amsterdam, Amsterdam,* [2]*Department of Surgery, VU University Medical Center, Amsterdam,* [3]*Department of Dietetics, Academic Medical Center University of Amsterdam, Amsterdam,* [4]*Institute of Health Sciences, Faculty Earth and Life Sciences, VU University, Amsterdam,* [5]*Department of Clinical Epidemiology and Biostatistics, Academic Medical Center University of Amsterdam, Amsterdam, The Netherlands*

09.50 A 60% reduction in hospital admission rate of patients on home parenteral nutrition after introduction of taurolidine catheter locking: a follow-up of nearly 200.000 days (p. 206)

E.D. Olthof[1], *G. Huisman de Waal*[1], *R. Vissers*[1], *G.J.A. Wanten*[1], [1]*Intestinal Failure Unit, Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, The Netherlands*

10.00 Use of parenteral nutrition in critically ill cardiovascular patients is related to higher mortality (p. 207)

P.J.M. Weijs[1,2], *S.N. Stapel*[1], *S.D.W. de Groot*[2], *A. Girbes*[1], *A. Beishuizen*[1], [1]*Department of Intensive Care Medicine,* [2] *Department of Nutrition and Dietetics, VU University Medical Center, The Netherlands*

10.10 Coffee and tea consumption is not associated with colorectal cancer risk: results of a large prospective population-based cohort study (p. 208)

V.K. Dik[1], M.G.H. Van Oijen[1,2], C.S.P.M. Uiterwaal[3], C.H. Van Gils[3], F.J.B. Van Duijnhoven[4,5], P.D. Siersema[1], H.B. Bueno-de-Mesquita[1,4], [1]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands, [2]Division of Digestive Diseases, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, [3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, [4]National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, [5]Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands

10.20 Prospective evaluation of the prevalence of fat-soluble vitamin deficiencies and decreased bone mineral density in chronic pancreatitis (p. 209)

E.C.M. Sikkens[1], D.L. Cahen[1], E.J. Kuipers[1], M.J. Bruno[1], [1]Department of Gastroenterology, Erasmus University Medical Center, Rotterdam, The Netherlands

10.30 Severe weight loss before radiotherapy is a major prognostic factor for survival in patients with head and neck cancer (p. 210)

J.A.E. Langius[1], S. Bakker[1], D.H.F. Rietveld[2], H.M. Kruizenga[1], J.A. Langendijk[3], P.J.M. Weijs[1], C. René Leemans[4], [1]Dept. of Nutrition and Dietetics, Internal Medicine, [2]Radiation Oncology, VU University Medical Center, Amsterdam, [3]Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, [4]Otolaryngology/Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands

10.40 Koffiepauze en ontvangst netwerksymposium frontroom Parkzaal
NESPEN members, research dietitians and nurse practitioners

NESPEN **Zaal 80**

Symposium nutritional assessment,
do's and don'ts in clinical nutrition

Chair: Dr. G. Ligthart-Melis and Dr. G. Wanten

11.00 Introduction and goals of symposium
(Platform research dietitians and nurse practioners)
Dr. M.A.E. van Bokhorst – de van der Schueren

Vrijdag 23 maart 2012

11.10 Nutritional assessment in dietetic research
Professor Marinos Elia, of the University of Southampton's Institute of Human Nutrition and Developmental Origins of Health and Disease Division of the School of Medicine

11.50 Discussion

Short presentations of research dietitians and nutritionists on their studies in relation to body composition, body function and energy expenditure

(7 minutes presentation / 3 minutes discussion)

12.00 Handgrip strength and self reported weight in the perioperative outpatient clinic
Liesbeth Haverkort, VUmc/AMC

12.10 Fat free mass in pediatric patients
Peter Weijs, VUmc / Hogeschool van Amsterdam

12.20 Resting energy expenditure in head and neck cancer patients
Jacqueline Langius, VUmc Amsterdam

12.30 Body composition in patients with rheumatoid arthritis: two sides of the coin
Nicole Konijn, VUmc / Wageningen University

12.40 Screening and treatment of malnutrition in infants
Joanne Oliemans, Erasmus MC, Rotterdam

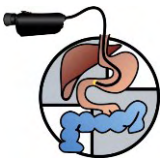
12.50 Refeeding in clinical practice, a research protocol
Sandra Visser, Medisch Centrum Alkmaar

13.00 Presentation of translated website malnutrition steering group
Marian van Bokhorst, malnutrition steering group

13.10 Cora Jonkers, secretary NESPEN
What have we learned today, where do we want to go?

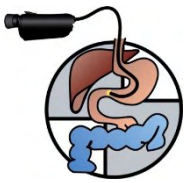
13.15 Networking lunch

Programma V &VN MDL **Diezezaal**



10.00	Opening door de voorzitter *Mevr. P. Bol, voorzitter V&VN MDL, Meander Medisch Centrum, Amersfoort*
10.00	Endo-SPONGE *Dr. C.M. Bakker, MDL-arts, Atrium MC, Heerlen*
10.20	Ileus in de palliatieve fase *Dr. A. De Graeff, internist-nefroloog, Universitair Medisch Centrum Utrecht*
10.40	GIST patiënten, een zorg apart *Mevr. E. van Arem-de Haas, Contactgroep GIST Nederland-België*
11.10	Multidisciplinaire richtlijn 'stoornissen in het gebruik van alcohol' *Drs. E. van der Schrieck-de Loos, **C**entraal **B**egeleidings **O**rgaan, Utrecht*
11.30	Voeding bij PDS *Mevr. U. Harkema, zelfstandige diëtistenpraktijk, Breukelen*
11.50	Algemene Ledervergadering *Mevr. P. Bol, voorzitter V&VN MDL*
12.15	Lunchbuffet in de Kempenhal

Programma Endoscopieverpleegkundigen — Diezezaal



Voorzitter: P. Bol

13.50 Communicatie met analfabeten, allochtone patiënt
Drs. H. Akol, MDL-arts, Meander Medisch Centrum, Amersfoort

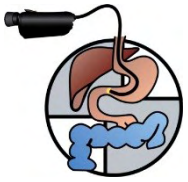
14.10 Stand van zaken verpleegkundig endoscopisten
Mevr. W. Kok, verpleegkundig endoscopist, Medisch Centrum Alkmaar

14.40 Evidence based bloedingen
Dr. R.J.J. de Ridder, MDL-arts, Maastricht UMC

15.00 Advanced imaging
Dr. E.J. Schoon, MDL-arts, Catharina Ziekenhuis Eindhoven

15.30 Einde programma

Programma Leververpleegkundigen — Zaal 52



Voorzitter: A. Nijmeijer

13.50 Hepatitis B: De Nieuwe Richtlijn!
Dr. E. Buster, MDL-arts i.o., Albert Schweitzer ziekenhuis, Dordrecht

14.10 Hepatitis E: Een zorg van de toekomst?
Dr. R.A. de Man, MDL-arts, Erasmus MC, Rotterdam

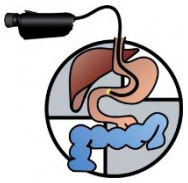
14.40 Hepatitiscentra / Levercentra: De Toekomst?
Dr. P. Honkoop, MDL-arts, Albert Schweitzer ziekenhuis, Dordrecht

15.00 Hepatitis C: Update in behandelingsmogelijkheden
Prof. dr. J.P.H. Drenth, MDL-arts, Universitair Medisch Centrum St. Radboud, Nijmegen

15.30 Einde programma

Programma IBD verpleegkundigen — Zaal 55

Beroepsvereniging van zorgprofessionals
Maag Darm Lever



Voorzitter: A. de Heer

13.50 TOPIC: de eerste resultaten en implicaties voor de praktijk
Dr. D.J. de Jong, MDL-arts, Universitair Medisch Centrum St. Radboud, Nijmegen

14.20 The Price of IBD
Drs. M. van der Valk, arts-onderzoeker, Universitair Medisch Centrum Utrecht

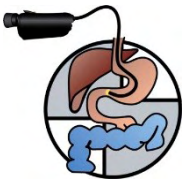
14.40 Faecestransplantatie
Drs. N. Rossen, arts-onderzoeker, Academisch Medisch Centrum, Amsterdam

15.00 Calprotectine, een toegevoegde waarde?
Drs. J.M. Jansen, MDL-arts, Onze Lieve Vrouwe Gasthuis, Amsterdam

15.30 Einde programma

Programma voedingsverpleegkundigen **Zaal 51**

Beroepsvereniging van zorgprofessionals
Maag Darm Lever



Voorzitter: W. Kuin

13.50 Voeding bij Brickeroperaties
Dhr. R. Snelders, diëtist i.o.

14.10 DRIFT: the Dutch Registry of Intestinal Failure and Transplantation
Drs. A.M.C. Roskott, chirurg i.o., Martini Ziekenhuis, Groningen

14.40 Onderzoek ervaringen neussonde
Mevr. N. Tijdeman, in kader van Afstudeerproject TU Delft

15.00 Hydratatie in de geriatrie
Dr. W. Janssens, geriater, Universitair Ziekenhuis, Gent

15.30 Einde programma

Theme **Cell Biology and Metabolism –** Chair: D. Jonkers and S.W.C. van Mil

1. ER stress in Paneth cells of inactive Crohn's disease patients with ATG16L1 mutations

J.J. Deuring[1], M.P. Peppelenbosch[1], E.J. Kuipers[1], C. de Haar[1] , C.J. van der Woude[1*], [*]These authors contributed equally to this work , [1]Erasmus Medical Centre, Gastroenterology and Hepatology, Rotterdam, The Netherlands*

2. The role of cell division orientation in liver development

C.L. Slim[1], F. Lazaro-Dieguez[2], D. Cohen[2], L. Penning[3], H. Toussaint[3], A. de Bruin[3], D. Hoekstra[1], A. Muesch[2], S.C.D. van IJzendoorn[1], [1]Dept of Cell Biology, Section of Membrane Cell Biology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, [2]Dept of Developmental & Molecular Biology, Albert Einstein College of Medicine, New York, USA [3] Faculty of Veterinary Medicine, Dept of Pathobiology, Utrecht University, Utrecht, The Netherlands

3. Targeting specific FXR isoforms in the bile acid biosynthetic pathway

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

4. Renal NKCC2 transporter triggers enhanced urinary ammonia excretion during induced hyperammonemia: a novel target of therapy for hepatic encephalopathy?

L. Mpabanzi[1,2,3], D. Dhar[2] , C.H.C. Dejong[1], R. Jalan[3], S.W.M. Olde Damink[1,2], [1]Dept of Surgery, Maastricht University Medical Centre, and NUTRIM School of Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands, [2]Hepato-Pancreato-Biliary and Liver Transplant Surgery, Royal Free Hospital, University College London, London, UK, [3]Liver Failure Group, UCL Hepatology, Royal Free Hospital, University College London, United Kingdom

5. Somatic inactivation in polycystic liver SEC63 germline carriers occurs through loss of heterozygosity

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

Theme **Metaplasia and Cancer –** Chair: G. Bouma and C.C. Paulusma

6. Toll-Like Receptor 4 activation may promote development of esophageal adenocarcinoma in Barrett's esophagus through induction of COX2 (p. 00)

R.E. Verbeek[1], P.D. Siersema[1], P. Bus[1], F.J. ten Kate[2], K. Fluiter[3], R.F. Souza[4], F.P. Vleggaar[1], J.W.P.M. van Baal[1], [1]Dept. of Gastroenterology and Hepatology, [2]Dept. of Pathology, University Medical Center Utrecht, [3]Dept. of Neurogenetics, Academic Medical Center, University of Amsterdam, The Netherlands, [4]University of Texas Southwestern Medical Center, Dallas, Texas

7. Stool proteomics reveals new candidate biomarkers for colorectal cancer screening

L.J.W. Bosch[1], M. de Wit[2], G. Oudgenoeg[2], A.C. Hiemstra[1], S. Mongera[1], S.R. Piersma[2], T.V. Pham[2], N.C.T. van Grieken[2], J.S. Terhaar sive Droste[2], F.A. Oort[3], S.T. van Turenhout[3], I. Ben Larbi[3], C.J.J. Mulder[3], B. Carvalho[1], C.R. Jimenez[2], R.J.A. Fijneman[1], G.A. Meijer[1], [1]Dept of Pathology, VU University Medical Center, Amsterdam, [2]Dept of Medical Oncology, VU University Medical Center, Amsterdam, [3]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

8. MicroRNAs as biomarkers for the response on chemoradiotherapy in esophageal cancer

E.L.A. Toxopeus[1], W.R.R. Farid[1], K. Biermann[2], H.W. Tilanus[1], B.P.L. Wijnhoven[1] , L.J.W. van der Laan[1], Depts of [1]Surgery and [2]Pathology, Erasmus MC – University Medical Centre, Rotterdam, The Netherlands

9. Tumor-infiltrating regulatory T cells favor tumor development by suppressing local tumor-specific T cell responses in primary and metastatic liver cancer

A. Pedroza-Gonzalez[1], C. Verhoef[2], J.N.M. IJzermans[2], M.P. Peppelenbosch[1], J. Kwekkeboom[1], H.L.A. Janssen[1], D. Sprengers[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Surgery, The Netherlands

10. Retinoic acid metabolism in Barrett's esophagus, duodenum and normal esophagus

A. Lind[1,2], L. Koenderman[2], J.G. Kusters[3], T. Konijn[4], R. Mebius[4], Peter D. Siersema[1], [1]Gastroentertology and Hepatology, UMC Utrecht, [2]Respiratory medicine, UCM Utrecht, [3]Microbiology, UMC Utrecht, [4]Immunology, VU medical Center, The Netherlands

Theme **Immunology 1 – Chair:** J.P.H. Drenth and R.K. Weersma

11. Immunological changes in IBD patients clinically responding to low-dose naltrexone treatment

C. de Haar[1], C. van der Ent[1], M.P. Peppelenbosch[1], C. Janneke van der Woude[1], [1]Dept of Gastroenterology & Hepatology, Erasmus MC, Rotterdam, The Netherlands

12. Serum IP-10 levels correlate with virus load in hepatitis C infected chimpanzees and evidence for novel IL-28B polymorphism

B.E. Verstrepen[1,2], N.G. de Groot[1,3], Z.M.A. Groothuismink[4], E.J. Verschoor[2], R.A. de Groen[4], W.M. Bogers[2], H.L.A. Janssen[4], P. Mooij[2], R.E. Bontrop[3], G. Koopman[2], A. Boonstra[4], [2]Dept of Virology, Biomedical Primate Research Centre, Rijswijk, [3]Dept of Comparative Genetics and Refinement, Biomedical Primate Research Centre, Rijswijk, [4]Dept. of Gastroenterology and Hepatology, Erasmus MC University Hospital, Rotterdam, The Netherlands [1] both authors contributed equally to this work

13. Cytokine induced colonic epithelial barrier dysfunction is mediated by cholinergic receptors by an nf-kb independent mechanism

S. Dhawan[1], F.W. Hilbers[1], L.E.M. Willemsen[3], I.H. Hiemstra[2], J.M.M. den Haan[2], W.J. de Jonge[1], [1]Tytgat Institute for Liver and Intestinal Diseases, Academisch Medisch Centrum, Amsterdam, [2]Dept. of Molecular Cell Biology and Immunology, VU University Medical Centre, Amsterdam, [3]Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

14. Functional and genetic alterations of the intestinal barrier in compensated cirrhotic patients

K.E. Pijls[1], D.M.A.E. Jonkers[1], H. de Vries[1], E. Schaepkens[1], A.A.M. Masclee[1], G.H. Koek[1], [1]Dept of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Center, The Netherlands

Theme **Immunology 2 – Chair:** K.N. Faber and A.A. te Velde

15. Histone deacetylase dependent regulation of cytokine secretion in murine and human macrophages

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16. Optimizing induction of CD8+ regulatory T cells by allogeneic human plasmacytoid dendritic cells

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17. Suppressive macrophage phenotype is regulated via retinoic acid in the intestines

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18 Hepatitis B virus infection activates Kupffer cells

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Determination of the HER-2 status in esophageal adenocarcinoma: HER-2/neu is associated with survival

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Amplification of the human epidermal growth factor receptor-2 gene (HER-2) is usually accompanied by HER-2/neu protein over-expression. This is described in various human tumors, including esophageal cancer. However, the prognostic significance of HER-2/neu protein expression and gene amplification in esophageal adenocarcinoma (EAC) is unclear. Aim of this study was to evaluate the percentage, agreement and prognostic value of HER-2/neu protein and gene amplification in a large and homogenous population with adenocarcinoma. A tissue micro array (TMA) was constructed comprising tumor cores of 154 patients with EAC. The HER-2/neu gene amplification status was assessed by silver-enhanced in situ-hybridization (SISH) technique.
Immunohistochemical staining (HER-2/neu specific antibody) and scoring was according to the HercepTest™ which ranges from 0 (negative) to 3+ (intense staining). Estimated 5 year overall survival was 33%. HER-2/neu protein over-expression was detected in 14.2% (21/148) and HER-2/neu gene amplification in 19.1% (29/152) of patients. All patients with 3+ staining, 33.3% of patients with 2+ staining and 9.5% of patients with negative or 1+ staining showed gene amplification. Overall concordance between protein expression and gene amplification was 87%. HER-2/neu over-expression was significantly associated with lymph node metastasis (p=.037, chi-square test) and with distant recurrence of disease (p=.048). HER-2/neu gene amplification was associated with advanced T-stage (p=.012), lymph node metastasis (p=.004) and with distant recurrence (p=.040). In univariate analysis HER-2/neu protein over-expression was significantly associated with poor cancer specific (CSS) and overall survival (OS) (HR 1.896; 95% CI 1.096-3.278; p=.022 and HR 1.915; 95% CI 1.143-3.210; p=.014, Cox proportional regression analysis). HER-2/neu gene amplification was associated with CSS (HR 1.673; 95% CI 1.027-2.726; p=.039). In multivariate analyses T-stage (HR 3.247; 95% CI 1.522-6.928; p=.002), grade of tumor differentiation (HR 2.424; 95% CI 1.479-3.973; p=.000) and HER-2/neu protein expression (HR 1.929; 95% CI 1.039-3.582; p=.038) were independent prognostic factors for poor OS.
In conclusion, HER-2/neu protein over-expression was seen in 14.2% and gene amplifications in 19.1% of patients. HER-2/neu protein expression seems a better prognosticator than gene amplification. Moreover, results emphasize the need to examine HER-2/neu gene amplification status in all patients, because a proportion with low HER-2/neu protein levels showed gene amplification. These patients might also benefit from trastuzumab (HER-2/neu specific inhibition) therapy.

The influence of young age on outcome in oesophageal cancer

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The increased incidence of oesophageal cancer, especially in the younger age group, should encourage early diagnosis. The perceived rarity and poor prognostic outcome of oesophageal cancer in this group is based on retrospective studies. The aim of this study was to review the clinicopathological characteristics and outcome after surgery of patients aged 50 years and younger with oesophageal cancer. Prospectively maintained database records of all patients diagnosed with oesophageal carcinoma and treated with curative intent over a 22-year period (1990-2011) in a single institution were analyzed. Patients aged 50 years and younger at diagnosis (n=163) were compared with those over 50 years (n=1151) with respect to clinicopathological stage and oncological outcomes. Younger patients had less co-morbidites ($p<0.001$). There were no differences in location of the tumour, histology, tumour grade and TNM-stage. In both groups, 37% of the patients underwent neoadjuvant chemo(radio)therapy. Fifty-three percent of the older patients had one or more non-surgical complications vs. 42% in the younger-aged group ($p=0.012$). The 30-day mortality was 4.3% for patients over 50 compared to 1.0% for younger patients ($p=0.021$). While 5yr overall survival was significantly better for the younger patients as compared to the elderly (41% vs. 31%, $p<0.001$), median disease-specific and disease-free survival did not differ between both groups (36 vs. 29 months, $p=0.106$ and 49 vs. 28 months,$p=0.079$ respectively). Multivariate analysis revealed that independent factors related to the difference in overall survival included age, co-morbidity, surgical complications, tumour grade, resection margin and disease stage.
Conclusions: A considerable proportion of oesophageal cancer patients are diagnosed aged less than 50 years. No phenotypic tumour differences were noted between the groups and disease-specific survival is similar to the older cohort.

Surgical treatment of gastric GIST in the imatinib era

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The introduction of the tyrosine kinase inhibitor imatinib (Glivec) has profoundly changed the treatment of gastrointestinal stromal tumours (GISTs). Neo-adjuvant imatinib treatment is strongly advised in patients with locally advanced or marginally resectable disease, where the risk of incomplete resection, tumour spill or significant postoperative morbidity is high. In metastatic GIST imatinib is considered treatment of primary choice, followed by secondary surgery in responding patients. In this study, the outcome of patients who were operated for a gastric GIST with or without neo-adjuvant imatinib was investigated. All patients surgically treated for a gastric GIST at our institute in the past twelve years (1999-2011) were included in this retrospective study. Patient, tumour, and treatment characteristics were retrieved from written and electronic patient files. A series of 48 patients was identified: 18 patients were treated with primary surgery (group 1) and 30 patients received imatinib prior to surgery (group 2). The median tumour size was 5.0 cm (range 1.5-19 cm) in group 1, and 13.5 cm (range 3.0-29 cm) in group 2. Most patients had local disease, but one patient in group 1 and seven patients in group 2 had metastatic GIST. Neo-adjuvant treatment led to a 25% reduction in tumour size ($p < 0.001$). Complete resection (RO) was achieved in all patients in group 1, and 27 patients (90%) in group 2. Wedge, partial and total gastric resection was required in 7 (39%), 10 (56%) and none of the patients (0%) in group 1, against 3 (10%), 13 (43%) and 4 patients (13%) in group 2. Multiple organ resection was performed in 1 patient (5%) in group 1, and in 10 patients (34%) in group 2. Postoperative complications (0% in group 1 and 20% in group 2; $p= 0.043$), were all transient with one complication in group 2 necessitating a re-intervention. Stratified for extent of resection, there was no significant difference in complication rate ($p= 0.226$). At a median follow-up of 30 months, 2 patients (11%) in group 1 and 5 patients (17%) in group 2 had recurrent or progressive disease. This was seen exclusively in patients with R1 or R2 resection or tumour spill during the operation. Five patients died of GIST. Median survival was not yet reached in either group.

Conclusions: In this surgical series of gastric GIST patients, neo-adjuvant imatinib led to a significant reduction in tumour size, with a non-significant increase in postoperative complication rate. Considering the larger tumour size of patients in group 2, with a historical poor prognosis, imatinib proved its value in our series in achieving a longer progression free and overall survival.

Safety of epirubicin, cisplatin and capecitabin chemotherapy in patients with resectable oesophageal or gastro-oesophageal junction adenocarcinoma outside clinical trials

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Introduction: In this retrospective study an analysis was performed of safety and feasibility for perioperative epirubicin, cisplatin and capecitabine (ECC) chemotherapy in a population based patient group with resectable oesophageal and GOJ adeno-carcinoma. Our goal was to compare safety and efficacy in our cohort to the MAGIC trial study population. Methods: The clinical data from 93 consecutive patients, treated with perioperative ECC for resectable oesophageal or GOJ adenocarcinoma were analysed. All patients had a least 1 month follow up since the last ECC dose. Source data verification of all grade 3, 4, and 5 adverse events was performed by two independent observers, Results: Chemotherapy treatment using ECC was found to result in more than expected toxicity however this did not affect the rate of curative intent surgery. The most frequently reported toxicities were grade 3 and 4 thromboembolic (16.2%) and cardiovascular (7.5%) events. Often these toxic effects resulted in early discontinuation of chemotherapy treatment. A medical history of cardiac- and vascular disease was independently associated with discontinuation of preoperative chemotherapy in binary regression analysis. A medical history of cardiac disease alone was independently associated with the occurrence of grade 3 and higher adverse events (p: 0.049). Despite the difficult delivery of the planned therapy and its toxicity, our preliminary efficacy data suggest that this treatment strategy is effective with a pCR rate of 8%.
Conclusion: This is the first study that evaluated the administration of 6 cycles of ECC based perioperative chemotherapy in a homogeneous population of patients with oesophageal adenocarcinoma outside clinical trials. The regimen appeared more toxic than reported in mixed series of patients with oesophageal and gastric cancer.

End-to-end cervical esophagogastric anastomoses require a higher number of endoscopic stricture dilations compared with end-to-side anastomoses after esophagectomy

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Cervical anastomotic leakage and benign stricture formation occur frequently after esophagectomy. Surgical anastomotic techniques might influence outcome.The objective of this study is to analyze the influence of end-to-end (ETE) versus end-to-side (ETS) hand-sewn esophagogastric anastomosis in patients who underwent an esophageal resection with gastric conduit reconstruction. A total of 390 consecutive patients were analyzed, with 112 ETE and 278 ETS anastomoses after esophagectomy and gastric tube reconstruction. No significant differences were found for in hospital mortality for ETE 5 (4%) versus ETS 16 (6%) anastomoses (p=0.61); anastomotic leakage rates, ETE 21 (18%) versus ETS 58 (21%; p=0.50). A higher incidence of anastomotic strictures was seen in ETE 48 (42%) compared with ETS 89 (32%) anastomoses (p=0.04). In contrast, the group with ETS anastomoses had a significantly higher rate of pneumonia, 77 (28%) versus 18 (16%; p=0.01). In multivariate analysis, none of these differences remained significant. However, the number of endoscopic dilations required for patients with an ETE anastomosis continued to be significantly higher. A median of 11 (7-17) dilations were necessary in patients with a benign anastomotic stricture in the ETE group, compared with a median of 4 (2-8) dilations per patient with a benign anastomotic stricture in the ETS group (p<0.001).
In conclusion, the technique of anastomosis is not significantly related to mortality, anastomotic leakage, stricture formation, and hospital stay. However, patients with ETE anastomoses require significantly more dilations compared with patients with ETS anastomoses.

Increase in brown adipose tissue activity in morbidly obese subjects after bariatric surgery

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Increasing energy expenditure by the stimulation of heat production in brown adipose tissue (BAT) is a potential target to treat obesity. We earlier demonstrated that BAT activity is inversely related to body fat percentage, which suggests increasing BAT activity could prevent or treat obesity. It is unknown whether BAT can be recruited in adult humans. Here we observed BAT activity in morbidly obese subjects before and after weight loss induced by bariatric surgery. Ten morbidly obese subjects were studied before and one year after bariatric surgery. After the application of a personalized cooling protocol for optimal non-shivering thermogenesis, BAT activity was determined using ^{18}F-fluoro- deoxyglucose positron-emission-tomography and computed-tomography (FDG-PET-CT). In the morbidly obese state, only two out of 10 subjects showed active BAT. One year after surgery five subjects had active BAT. BAT activity increased and BAT was present in additional anatomical locations. After weight loss, BAT-positive subjects had significantly higher non-shivering thermogenesis (NST) compared to BAT-negative subjects ($P<0.05$).
Conclusions: After weight loss the presence of BAT increased. Here we show for the first time that BAT can be recruited in adult humans. In addition, we demonstrate that BAT thermogenesis may be important in human energy balance. Therefore, BAT recruitment can be a therapeutic target in the prevention and treatment of the metabolic syndrome.

Failure to record a family history of familial cancer in patients' notes is associated with early stage colorectal cancer

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Background: Lynch syndrome associated colorectal cancer (CRC) usually presents at a relatively young age. The Revised Bethesda Guidelines advise screening for Lynch syndrome in patients diagnosed with CRC and a positive family history (FH) of CRC and related cancers. Recording of FH of CRC and related cancers in young patients diagnosed with CRC is known to be insufficient; however, the extent of non-recording is unknown. Identification of factors associated with the failure to record the FH may improve adherence to the Revised Bethesda Guidelines. Aim: To evaluate whether a FH of CRC and related cancers was recorded in patients' notes and to identify factors associated with insufficient recording of the FH in patients with CRC who are 60 years or younger. Methods: In one university and two general hospitals, all patients diagnosed with CRC at an age of 60 or younger between 1999 and 2008 with an electronic medical record were included. All electronic medical records were evaluated for a recorded FH of CRC and other Lynch syndrome associated cancers. Patient- and tumor characteristics were retrieved from the Dutch Comprehensive Cancer Centre (IKNL) and the Dutch Pathological Archive (PALGA). Multivariate analysis was performed using the binary logistics module of PASW Statistics version 17. Results: A total of 1,421 patients diagnosed with CRC aged 60 years or younger were included of which 710 had an electronic medical record. FH was not recorded in 294/710 (41%) patients. Multivariate analysis showed that from 1999 to 2008, recording of a FH of CRC and related cancers improved with an odds ratio (OR) of 1.09 (95%CI 1.03-1.16) per year. In addition, early stage (stage 0 to II) CRC was associated with the failure to record the FH (OR 1.55, 95%CI 1.14-2.12). Other factors, including younger age at diagnosis (OR 0.99, 95%CI 0.97-1.01), male gender (OR 1.16, 95%CI 0.85-1.57), proximal tumor localization (OR 1.15, 95%CI 0.82-1.61), poor differentiation grade (OR 0.97, 95%CI 0.64-1.46) and mucinous histology (OR 0.89, 95%CI 0.56-1.40) were not associated with the failure to record FH of CRC and other Lynch syndrome associated cancers.
Conclusion: A FH of CRC and other Lynch syndrome associated cancers was not recorded in more than 40% of patients who presented with CRC aged 60 years or younger. Recording of the FH improved gradually over the years. As early stage CRC was found to be associated with the failure to record FH, this suggests that particularly advanced stage CRC makes physicians, patients or both aware that the detected CRC may have a relationship with a FH of CRC and related cancers.

Barriers to genetic testing for Lynch syndrome

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Lynch syndrome (LS) is a genetic predisposition for colorectal carcinoma, endometrial cancer and other malignancies and is caused by inherited germ mutations in mismatch repair (MMR) genes. Despite the fact that genetic testing and targeted surveillance can have a major impact on cancer survival, the uptake of genetic testing by family members of LS carriers is far from complete. The objective of this study therefore was to investigate barriers to genetic testing for LS. For this study, 177 individuals tested for LS between 2003-2008 at a tertiary center, were invited by phone and mail to participate. Furthermore, they were asked to approach non-tested family members to participate in this survey study. A questionnaire was sent to all family members who consented to participate, addressing motivation, Hospital Anxiety and Depression scale (HADS), cancer worry scale, family dynamics, and risk knowledge. Tested and non-tested family members were compared using the Fisher's exact test and Mann-Whitney U test. In total 129/177 tested (73%, 39% male) and 16/38 non-tested (42%, 38% male) family members from 40 LS families completed the questionnaire. Median age of tested family members was higher than non-tested family members (59 vs 38 yrs; p=0.007). There were no differences between tested and non-tested family members in anxiety, cancer worry scores and risk knowledge on LS-associated cancer risks. Regarding family communication, there were no differences in timing and communication tools for communicating the diagnosis of LS in the family. However, tested family members knew significant more first degree relatives (FDR) (median: 2 vs 1 FDR; p=0.004) and second degree relatives (SDR) (median: 2 vs 1 SDR, p=0.05) with cancer than non-tested family members. The most important reasons for genetic testing for LS were: 1) availability of surveillance programmes for LS (61%), 2) to end insecurity regarding LS diagnosis (47%), 3) fear for cancer (22%). The three most important reasons for declining genetic testing were: 1) problems with life insurance and mortgage (50%), 2) being happy with life as it is (44%), and 3) not experiencing any physical complaints (37%).
In conclusion, although the number of included non-tested family members is limited, the most important barriers for genetic testing in LS are not related to anxiety, cancer worry, or impaired risk knowledge, but to the personal situation and the limited contact with family members affected by cancer. Anticipated problems with life insurance and mortgage are important to abstain from genetic testing. Younger age and knowing fewer family members with cancer influence the urge to be tested.

Patients with Lynch-compatible colorectal cancer without identifiable germ mutation do not have a positive family history of Lynch syndrome

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Lynch Syndrome (LS), caused by mismatch repair (MMR) gene germ mutations, predisposes to various malignancies including colorectal cancer (CRC). The molecular hallmark is microsatellite instability (MSI). However in some CRC patients with a tumor tissue profile compatible with LS, a germ mutation can not be confirmed. The aim of this study was to identify clinical and familial characteristics of these patients.In a population based study, CRC patients ≤70 years were prospectively included. Tumor specimens were analyzed for microsatellite instability (MSI), immunohistochemical MMR protein expression, and MLH1-promoter methylation. Patients with tumors likely caused by LS were advised to undergo germ mutation analysis. Patients were classified as either LS, LS compatible; LS tumor profile without identifiable germ mutation, sporadic MSI, or sporadic microsatellite stable (MSS) CRC. Family history of randomly selected sporadic CRC patients was collected by questionnaires. Pathological and familial data were compared using Fisher's exact test and Mann Whitney U. In this study, a total of 1117 CRC patients (57% males, median age 61yrs) were included. Compared to sporadic CRC patients (N=998, 58% males, median age 61yrs), patients with LS compatible tumors (N=11, 82% males, median age 58yrs) more often had right-sided tumors (21% vs 82%; p=0.001) and poorly differentiated adenocarcinoma (45% vs 7%; p=0.02) than sporadic CRC patients. Comparing LS compatible patients with sporadic MSI-H cases (N=71, 28% males, median age 64yrs) and LS patients (N=26, 62% males, median age 56 yrs), no differences were found in location, histology and TNM stage and MSI-H features. Family history questionnaires were returned by 130 patients with sporadic CRC. Comparing patients with LS compatible tumors and sporadic CRC, no differences were found in first degree family members with CRC (0% vs 14%, p= 0.36) and fulfilment of Bethesda guidelines (18% vs 14%, p=0.36). However, 46% of LS patients had one or more first degree family members with CRC, compared to none of the patients with LS compatible tumors (p=0.009). Furthermore, 18% of patients with LS compatible tumors fulfilled Bethesda guidelines, compared to 72% of LS patients (p=0.004).
In conclusion, LS compatible tumors are often located right sided and more often poorly differentiated compared to sporadic CRC. Patients with LS compatible tumors have less often a family history of CRC than LS patients and do not differ from sporadic CRC patients regarding family history of CRC and fulfilment of Bethesda guidelines. Further molecular studies are needed to reveal the molecular mechanism in LS compatible tumors.

Aspirin use is associated with lower stage CRC at diagnosis compared to non users

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Several recent publications have suggested a chemopreventive effect of low dose aspirin on colorectal cancer (CRC) development. We hypothesized that aspirin may lead to a lower incidence of CRC due to an increased incidence of bleeding as detected by iron deficiency anemia or hematochezia, from advanced colonic neoplasia which may result in an earlier presentation and consequently to earlier stage CRC at diagnosis. As survival is directly related to stage of CRC, aspirin may ultimately result in a prolonged survival. The purpose of this study was to determine whether the use of aspirin is associated with an earlier stage CRC at the time of diagnosis and may prolong survival. We performed a retrospective cohort study, using a health insurance database in the Netherlands which was linked to the National Pathology Database to identify patients older than 40 years who were diagnosed with CRC between 2001 and 2005. We compared the stage of CRC (according to the TNM classification) and 4-year mortality between aspirin users and non users by using logistic regression analysis. In total 4,218 consecutive patients were diagnosed with CRC in the study period. The mean age was 70 (SD 11) years and 48% was male. A total of 252 (6%) patients used aspirin during or before the time of CRC diagnosis. Patients using aspirin compared to non users were older (mean age 75 years, SD 9 and 70 years, SD 11, respectively, $p<0.01$) and more often male (51% and 48%, respectively, $p=0.27$). Patients using aspirin were more often diagnosed with stage II CRC compared to non-users (46% and 39%, respectively, OR 1.36, $p=0.02$). All other stages were not statistically significantly different, although there was a trend towards a lower stage III CRC in aspirin users compared to non users (31% and 36%, respectively, OR 0.80, $p=0.10$). Four-year mortality was significantly higher in aspirin users compared to non users (17% and 11%, respectively, OR 1.71, $p<0.02$).
Conclusions: Aspirin use was associated with a higher incidence of stage II CRC and a trend towards a lower incidence of stage III. This effect may be due to an increased incidence of symptomatic bleeding from advanced colonic neoplasia caused by aspirin. However despite earlier stage of CRC at diagnosis, aspirin use was associated with a higher mortality rate compared to non users which may be due to patients' characteristics such as older age and cardiovascular conditions requiring use of aspirin.

Metachronous colorectal neoplasia after adenoma removal: a multivariate analysis of risk factors for non-advanced and advanced neoplasia

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To ensure efficient use of resources, surveillance colonoscopy should be targeted at patients who will benefit most from the procedure, i.e. those at highest risk for metachronous neoplasia. Internationally, surveillance guidelines are based on the advanced characteristics and multiplicity of adenomas. Evidence for how these factors relate to each other and to other risk factors, such as older age, male gender and proximal location, is sparse.The aim of the study was to determine the most important risk factors and their associated relative risks for metachronous colorectal neoplasia, in a representative cohort of adenoma patients.We used the Dutch nationwide histopathology registry to select newly diagnosed adenoma patients from 1988 to 2002 from 10 hospitals throughout the Netherlands. We excluded patients with a history of CRC or CRC at index colonoscopy, hereditary colorectal cancer syndromes or IBD. Electronic medical records were reviewed up to December 1, 2008 for follow-up data. Patient characteristics (gender and age) and adenoma characteristics (number, size, location, villousness and grade of dysplasia) at index colonoscopy were considered as potential risk factors for metachronous colorectal neoplasia at first follow-up. Advanced colorectal neoplasia was defined as advanced adenoma or CRC. We performed a multinomial logistic regression analysis to simultaneously assess relative risks (odds ratios (OR (95% CI)) for non-advanced and advanced colorectal neoplasia. Adjustment is made for bowel preparation, reach of the colonoscope and surveillance interval. The analysis included 2,990 adenoma patients (55% male, mean age 61 (SD 10) years). At a median surveillance interval of 24 months, 826 (28%) patients had any metachronous colorectal neoplasia, 145 (5%) had advanced adenoma(s) and 26 (0.9%) had cancer. Risk factors for metachronous non-advanced colorectal neoplasia were male gender (OR 1.4 (1.1–1.6)), number of adenomas (OR ranging from 1.4 (1.1–1.8) for 2 adenomas to 2.6 (1.5–4.3) for ≥5 adenomas), and proximal location (OR 1.2 (1.0–1.5)). For metachronous advanced colorectal neoplasia these were male gender (OR 1.6 (1.1–2.2)), age (OR 1.3 (1.1–1.5) per 10 years older), number of adenomas (OR ranging from 1.7 (1.1–2.5) for 2 adenomas to 3.3 (1.5–7.1) for ≥5 adenomas), large size (≥10mm) adenoma (OR 2.1 (1.5–3.0)), and proximal location (OR 1.8 (1.2–2.6)).
Conclusions: Next to multiplicity and size, older age, male gender and proximal location were important risk factors for metachronous advanced colorectal neoplasia. This implies that more detailed combinations of risk factors should be considered for better tailored surveillance guidelines.

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Gastrointestinal carcinomas of Peutz-Jeghers syndrome patients: a further look

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Peutz-Jeghers syndrome (PJS) is a rare disease, caused by inactivating germ mutations in the LKB1 tumour suppressor gene. PJS patients are at high risk for cancer at a young age, including cancers in the gastrointestinal (GI) tract. However, little is known about the mechanism of PJS-associated carcinogenesis. Therefore, the aim of this study was to investigate the involvement of several candidate genes and molecular pathways in PJS-associated GI cancers. Patients diagnosed with a primary malignancy of the GI tract (i.e. oesophagus, stomach, small bowel, colorectum, pancreas, liver and biliary tract) were selected from a Peutz-Jeghers syndrome database (n=144, 49% males). All patients had a definite diagnosis of PJS, defined by diagnostic criteria recommended by the WHO, a proven LKB1 mutation, or both. Clinical data of cases were collected, characteristics of the carcinomas were described, and available FFPE tissue slides were immunostained for β-catenin, P53 and phospho-S6 (a downstream target of mTOR). Twenty-eight of the 144 patients (19%, 64% males) from 20 families developed 30 GI malignancies; 8 colorectal (27%), 7 pancreatic (23%), 4 small intestinal (13%), 4 gastric (13%), 2 biliary (7%), 2 ampullary (7%) and 3 adenocarcinomas of the digestive tract not further specified (10%). Median age at diagnosis of first cancer was 44 years (IQR 35-57). Two patients were diagnosed with two primary GI carcinomas. Three (10%) malignancies were discovered during surveillance, all carcinomas in situ (one colorectal and two gastric lesions). Twenty-three patients (82%) deceased at a median age of 54 years (IQR 36-61); 19 (68%) of whom had died as a direct cause of GI cancer. Of these 23 patients, median survival after GI cancer diagnosis was 6 months (IQR 1-18). Of 16 carcinomas FFPE tissue was available for molecular analysis. Nuclear β-catenin was detected in 3/5 (60%) primary intestinal carcinomas. Overexpression of P53 was observed in 7/16 (44%) carcinomas, and a total absence of P53 was observed in one (6%) sample. All available samples showed heterogeneous expression of pS6, in which epithelial expression was more pronounced compared to the stromal component in 9/14 (64%) cases.

Conclusion: Gastrointestinal cancer often affects PJS patients already at a young age. Alterations in Wnt/b-catenin signaling and in P53 are observed in a subset of PJS carcinomas, while activation of mTOR signaling seems to be altered in the majority of these carcinomas, predominantly in the epithelial compartment. These results suggest that treatment with mTOR inhibitors may be beneficial in the anti-cancer treatment of PJS patients.

Pancreatic cancer risk in Peutz-Jeghers patients; results of a large Dutch cohort study and implications for surveillance

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Although Peutz-Jeghers syndrome (PJS) is thought to be associated with an increased pancreatic cancer (PC) risk, estimates of this risk differ widely. This hampers counseling of PJS patients and the development of optimal screening strategies. We therefore aimed to determine the risk of developing PC in a large cohort of Dutch PJS patients.All patients included in this cohort study had a definite diagnosis of PJS as defined by diagnostic criteria recommended by the WHO, a proven LKB1 germ mutation, or both. Patients were followed prospectively between January 1995 and July 2011; clinical data from the period before 1995 were collected retrospectively. All patients with a diagnosis of PC were identified. As screening of the pancreas can also lead to the detection of other malignancies in the pancreatic region, we also selected patients diagnosed with distal cholangiocarcinoma or ampullary carcinoma. To ascertain the diagnosis, clinical, radiological and histological data was reviewed by experts of all relevant disciplines. In inconclusive cases, immunohistochemical staining was performed. Cumulative risks were calculated using Kaplan-Meier analysis and relative risks using Poisson regression analysis. We included 144 PJS patients (49% males) from 61 families, accounting for 5640 person years of follow-up. Seven PJS patients (6 males) from 7 families developed PC at a median age of 54 years (IQR 36-62 years), 6 of whom had ductal adeno-carcinoma and one acinar cell carcinoma. All 7 patients were symptomatic at the time of presentation with advanced stage disease. The median survival after diagnosis was 5 months (IQR 3-17 months). Additionally, 2 cases of distal cholangiocarcinoma and 2 cases of ampullary carcinoma were diagnosed (3 males) at a median age of 55 years (IQR 44-69). The cumulative PC risk was 23% (95% CI 4.1;41.3) by the age of 70 years (Figure). Compared to the general population the PC risk was significantly increased (HR 76.2, $p<0.001$). The cumulative risk for developing PC, distal cholangiocarcinoma or ampullary carcinoma was 29% (95% CI 10.4;47.6) by the age of 70 years (Figure).
Conclusion: Patients with Peutz-Jeghers syndrome are at very high risk for developing cancer in the pancreatic region, including pancreatic cancer, with a cumulative risk of 29% by the age of 70 years. This very high risk and the notion that early detection of these malignancies or its precursors will hopefully lead to an improved survival, make PJS patients good candidates for screening. This screening should be performed with annual endoscopic ultrasonography (EUS) and/or MRI within well-defined research protocols. The impact of such an approach on survival of these patients remains to be demonstrated.

Prospective evaluation of psychological impact of pancreatic cancer surveillance in high-risk individuals

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The success of pancreatic cancer (PC) surveillance depends to a large extent on the commitment of participants to adhere to the repeated follow-up investigations. Though the results of our recently conducted retrospective study showed that the burden of PC surveillance is acceptable, a prospective assessment was warranted to document the mental and psychological impact of PC screening. We aimed to investigate possible changes in cancer worries and levels of anxiety and depression in high-risk individuals participating in a PC surveillance program.Eligible for this prospective questionnaire study were high-risk individuals participating in our multicenter nationwide endoscopic ultrasonography (EUS)-MRI-based PC-surveillance study. High-risk individuals were those with a strong family history of PC or carriers of PC-prone gene mutations. Questionnaires, administered both before (pretest) and after (posttest) the base PC screening investigations, assessed concerns about developing cancer (Cancer Worry Scale), and levels of anxiety and depression (Hospital Anxiety and Depression scale). Of the 54 high-risk individuals, 47 (87%) completed both the pretest and posttest questionnaires (38% male, mean age= 52 yr., range 20-74 yrs.). Of these, 44 participated in the PC screening and 3 declined. All participants underwent both EUS and MRI. Prior to undergoing PC screening, 36% of the participants reported being fearful about undergoing EUS, whereas 5% was fearful about the MRI. After screening, 2.3% of all participants feared the next EUS ($p<.001$) and 2.3% the next MRI. The mean level of depression was significantly higher prior to screening as compared to after screening ($p<.001$). However, the number of participants with clinical levels of anxiety and/ or depression was low (n=5) and remained stable over time. Prior to, as well as after screening the most frequently reported worries were about the possibility of developing cancer themselves (29% at both time points) and the chance that relatives would develop cancer (19% and 21%, respectively). The 3 individuals who did not undergo screening indicated that they were not very fearful of the MRI or EUS. They also had low levels of anxiety, depression and cancer worries.
Conclusion: The results of this prospective study indicate that: (1) the expected burden of EUS is higher than the actual experienced burden; and that (2) mean levels of anxiety, depression and cancer worries are not significantly influenced by participating in the PC screening program. This finding is of great importance for this group that is at high risk of developing pancreatic cancer and might benefit from participation in a life-long repeated PC surveillance program.

Chromosomal aberrations implicated in colorectal adenoma to carcinoma progression as markers of high risk colorectal adenomas

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Background: Advanced adenomas are considered as an important intermediate endpoint for colorectal cancer (CRC) screening. Still the majority of these lesions do not progress to cancer. Hence, using this intermediate endpoint in evaluation of screening programs may lead to an overestimation of the effect of screening. Underlying genomic alterations like chromosomal instability charecteristic of colorectal adenoma to carcinoma progression (gains of 8q, 13q, 20q and losses of 8p 15q, 18q) may more precisely mark high risk adenomas. Previously, we have shown that presence of two or more of these particular chromosomal alterations was associated with malignant progression. Aim: To evaluate the prevalence of chromosomal aberrations implicated in colorectal adenoma to carcinoma progression in advanced and non-advanced colorectal adenomas. Materials and methods: The prevalence of DNA copy number gains and losses of 8q, 13q, 15q, 18q, 20q, 8p and 17p was determined in 65 advanced and 58 non-advanced adenomas using multiplex ligation-dependent probe amplification (MLPA). Adenomas ≥1.0 cm, with any villous features (i.e. tubulovillous or villous adenoma) or high-grade dysplasia were called advanced adenomas, while tubular adenomas, <1.0 cm and with low-grade dyplasia were called non-advanced adenomas.Results: In 18% of advanced adenomas showed two or more cancer associated chromosomal aberrations compared to 2% in the non-advanced adenomas. Significantly more copy number gains of 13q and 20q and loss of 17p were found in advanced adenomas compared to non-advanced adenomas (22% vs 2%; 14% vs 2% and 11% vs 0; p=0.013, p=0.001 and p=0.013, respectively). None of the DNA copy number changes studied was independently associated with the histological subtypes of advanced adenomas. Significantly more copy number gains of 13q and 20q and losses of 17p and 18q were found in adenomas >1.0 cm compared to adenomas <1.0 cm(17% vs 3%; 27% vs 3%; 13% vs 1% and 10% vs 0; p= 0.007, p<0.001, p=0.045, p=0.022 & p=0.015, respectively).
Conclusion: 18% of the advanced adenomas and 2% of the non-advanced adenomas showed two or more CRC associated chromosomal aberrations. These findings are consistent with the hypothesis that the morfological parameters used to classify adenomas lack specificity as an intermediate endpoint in colorectal cancer screening.

Heterozygous knockout of ß-catenin in Apc1638N mice prevents gastrointestinal tumor formation but predisposes for mammary lesions

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Apc-driven tumor formation in patients and Apc mutant mouse models is generally attributed to increased levels of ß-catenin signaling. We and others have proposed that a specific level of ß-catenin signaling is required to successfully initiate tumor formation, and that each tissue selects for different dosages of signaling. This is nicely illustrated by the different tumor phenotypes displayed by different Apc mutant mouse models. ApcMin mice have relatively high levels of ß-catenin signaling and develop intestinal tumors at high multiplicity (>100). Animals carrying the hypomorphic Apc1638N mutation, associated with intermediate ß-catenin signaling, characteristically develop intestinal tumors at lower multiplicity (<10) and in parallel show a high susceptibility for extra-intestinal tumor types such as cysts and desmoids. The Apc1572T mouse model, associated with lower levels of ß-catenin signaling, is free of intestinal tumors but instead develops mammary tumors with high penetrance. This indicates that intestinal tumors are associated with higher levels of ß-catenin signaling than cysts and desmoids, which in turn are associated with higher ß-catenin signaling than mammary tumors. Although the concept of ß-catenin signaling dosage and its impact on tumor growth among tissues is gaining acceptance, it has not been formally proven. In addition, alternative explanations for Apc-driven tumor formation have been proposed.To obtain direct evidence that different tumor phenotypes are the result of different ß-catenin levels, we crossed Apc1638N mice with heterozygous ß-catenin knockout mice, thereby reducing their ß-catenin levels. All Apc1638N control mice (n=19) developed gastrointestinal tumors (3.1 ± 1.5 per animal). However, all Apc1638N mice with heterozygous knockout of ß-catenin (n=21) revealed complete absence of gastrointestinal tumors. Incidence of other Apc1638N-associated lesions was strongly reduced as well, including desmoids (8.6 ± 3.0 to 0.2 ± 0.4 in females, 61.4 ± 14.4 to 19.1 ± 8.1 in males) and cysts (5.6 ± 3.8 to 0.4 ± 0.6 in females, 29.8 ± 19.5 to 2.4 ± 1.5 in males). Interestingly, 7 out of 14 female mice with heterozygous ß-catenin knockout now developed mammary tumors (1-2 per mouse), which are rarely observed in Apc1638N mice. Taken together, reducing ß-catenin levels in Apc1638N phenocopies tumor predisposition typically observed in Apc1572T mice. We hereby provide in vivo evidence that by simply reducing ß-catenin levels, tumors develop in different tissues. This clearly demonstrates the central role of ß-catenin dosage to dictate tissue-specific tumor predisposition in the setting of Apc-driven cancer.

Rock-inhibitors reduce the induction of Epithelial-to-Mesenchymal Transition, migration and invasionin SMAD4 deficient colorectal cancers caused by Bone Morphogentic Protein Signaling

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Introduction: The ability of cancer cells to invade and metastasize is dependend on the induction of Epithelial-to-Mesenchymal Transition (EMT). SMAD4 mutations in colorectal cancer (CRC), an essential component of canonical SMAD-dependent Bone Morphogenetic Protein (BMP) signaling, have been correlated with poor survival. We have previously shown that activation of the BMP pathway in SMAD4 negative cell lines induces EMT markers, migration and invasion as well as the cell migration pathways p38MAPK, JNK, RHO-Rock and BRAF-ERK. By identifying through which of these pathways EMT is induced, we might find a new therapeutic option for the prevention of metastases in SMAD4- negative CRC's. Aims & Methods: Our aim was to investigate whether the induction of EMT by activation of non-canonical BMP signaling acts through one of the migration pathways. We treated both SMAD4 negative and SMAD4 positive cell lines with inhibitors specific for these pathways and induced EMT by activation of the BMP pathway by transfecting a plasmid encoding BMPRII. The effect of the inhibitors on EMT was evaluated by qRT-PCR for E-cadherin and Vimentin and by migration and invasion assays. We also treated SMAD4 negative cell with BMP ligands to examine the connection between the BMP pathway and the RHO-Rock pathway by immunoblotting for Rock and it's downstream targets. Results: Inhibition of Rock, but not p38, JNK and ERK abolishes the induction of EMT seen upon activation of BMP signaling in SMAD4 negative cancers. Activation of the BMP pathway in SMAD4 negative cell lines increases the expression Rock and it's downstream targets p-LIMK and p-cofilin. Furthermore, the increased cell migration and invasion caused by the activation of the BMP pathway in SMAD4 negative cell lines, which does not occur in SMAD4 positive cell lines, is inhibited by Rock inhibition.
Conclusion: BMP pathway activation in SMAD4-negative cancer cells induces EMT, increased migration and invasion. Our data suggest that this occurs through activation of the RHO-Rock pathway. The RHO-Rock pathway is a well-known activator of migration. Rock-inhibitors could be a new promising therapeutic option in preventing metastases in patients with SMAD4-negative CRC, since inhibitors of Rock have shown to be safe for use in patients.

Bone Morphogentic Protein 4 signaling alters microRNA-145 expression in the esophagus

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Barrett's esophagus (BE) is a metaplastic condition of the distal esophagus, characterized by the replacement of normal squamous epithelium (SQ) by columnar epithelium. Bone Morphogenetic Protein 4 (BMP4) signaling is one of the signaling routes involved in BE development, capable of inducing ID2 and SOX9 expression. In stem cells, BMP4 expression has been found to correlate with microRNA (miRNA)-145 expression. miRNA-145 is known to be highly expressed in BE compared to SQ; however, its function in the esophagus is largely unknown. Therefore we aimed to investigate the effect of miRNA-145 overexpression and knockdown in the esophagus and to determine whether miRNA-145 expression is affected by BMP4 signaling in the esophagus.In situ hybridization (ISH) was performed on BE and SQ tissues obtained from 10 patients. To induce overexpression and knockdown, miRNA-145 precursor and/or inhibitor were transfected into a esophageal (HET1A) and a Barrett's (BAR-T) epithelial cell line. Q-RT-PCR was performed to determine GATA6 (transcription factor, capable of regulating BMP4 expression), BMP4, ID2 and SOX9 expression. In addition, Western blot analysis was performed to determine BMP4 pathway activation by examining ID2 protein expression and Smad 1/5/8 phosphorylation. Finally cells were incubated with recombinant human BMP4 to activate signaling. At several time points, RNA was isolated and Q-RT-PCR was performed to determine ID2, GATA6 and miRNA-145 expression.ISH confirmed an increased expression of miRNA-145 in BE compared to SQ, with BE showing moderate to strong miRNA-145 expression, while it was mainly expressed in the basal cell layer in SQ. miRNA-145 overexpression in HET-1A and BAR-T cells resulted in decreased GATA6, BMP4, ID2 and SOX9 mRNA expression. In addition ID2 protein expression and Smad 1/5/8 phosphorylation was decreased, suggesting no BMP4 pathway activation. These effects were not observed when miRNA-145 expression was knocked down. BMP4 incubation of HET-1A and BAR-T cells for 1, 2 and 5 hours showed an increased GATA6 and ID2 expression, which was decreased when cells were incubated with BMP4 for 24 hours. On the contrary, miRNA-145 expression was decreased following BMP4 incubation for 1, 2 and 5 hours, but increased after 24 hours of BMP4 incubation.
Conclusion: miRNA-145 overexpression in the esophagus results in inactivation of the BMP4 signaling, with decreased expression of BMP4 and molecules associated with the BMP4 pathway, whereas activation of the BMP4 signaling pathway initially decreases miRNA-145 expression but over time increases miRNA-145 expression. These results suggest that miRNA-145 and BMP4 have mutual effects in the esophagus.

Enhanced tumor growth after portal vein embolization in a rabbit VX2 tumor model

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The aim of this study was to assess tumor growth after portal vein embolization (PVE) in a rabbit hepatic tumor model. Preoperative PVE is employed to increase future remnant liver (FRL) volume through induction of hepatocellular regeneration. This intervention, however, potentially increases tumor size because of growth factor and cytokine release in the regenerating liver. Tumor progression may therefore render the patient unresectable after PVE. New Zealand White rabbits were allocated to a PVE group or a control group (n=5/group). Two weeks after transcapsular implantation of a VX2 carcinoma, PVE was performed with particles and coils or the liver was only mobilized (control). CT volumetry was performed on days 3, 7, 10, and 14 post-PVE.
Hepatocellular proliferation rate, tumor growth rate (TGR), and liver damage parameters were assessed before PVE, and on 1, 3, 7, 10, and 14 days post-PVE. Portography films performed directly after embolization and on day 14 post-PVE showed complete portal occlusion in all PVE-rabbits. TGR was increased in both groups, with a significantly larger increase in the PVE-group over time (day 14: mean 34.4±4.3mL/day vs sham: 24.1±7.2mL/day). The hypertrophy response and proliferation rate in the non-embolized liver lobe were significantly higher in the PVE group, which was confirmed by liver to body-weight index assessment. There was transient, minimal increase in liver damage parameters after PVE, which returned to base values within 7 days. Tumor growth (TGR) was significantly increased after PVE in the rabbit tumor model over time compared to the control group. This finding supports the notion that PVE potentially enhances tumor growth.

Clarifying the role of the HLA in Ulcerative Colitis by extensive finemapping of a Dutch cohort

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Genetic susceptibility is known to make a major contribution to the pathogenesis of ulcerative colitis (UC). Several genome-wide association (GWA) studies have been performed to identify the genetic risk factors contributing to UC risk. By far the strongest genetic risk locus for UC seems to be the HLA region. Due to the extended and complex linkage disequilibrium structure within the HLA region it has been extremely difficult to pinpoint the associated epitopes. Data from GWA studies do not supply sufficient coverage of this highly variable region to determine which HLA epitopes confer individual disease risk. Data from other diseases such as rheumatoid arthritis suggest that HLA does not only contribute to disease risk in general, it can also determine disease phenotypes: such as age of onset and disease severity. The aim of this study was to determine which HLA haplotypes at the different epitopes are associated with disease risk and with sub-phenotypes such as early-onset disease. 781 UC cases and 1500 controls from the Netherlands were genotyped by a customized GWAS chip (ImmunoChip) including ~200.000 markers.

It is especially designed to fine-map genomic regions relevant to immune-related diseases and includes over 17.000 SNPS to fine-map the HLA region. In order to derive exact HLA haplotype data from the genotypes we use an especially designed imputation method called HLA-IMP (https://oxfordhla.well.ox.ac.uk/hla/) that calculates the haplotypes in the classic HLA epitopes; we intend to extend this imputation to genetic variation in the HLA region beyond the classic epitopes. We perform a binary logistic regression and a conditional analysis to calculate the contribution of the different haplotypes to UC risk. We then use a multivariate regression analysis to detect phenotype-specific risk variations in the HLA region. We observe a very strong risk effect for HLA-DRB1*0103 and 0104 ($p = 5.3x10^{-4}$, OR 3.2 (CI 1.7-6.2) and $p = 5.9x10^{-4}$, OR 3.8 (CI 1.8-8.5) resp.) and a strong protective effect for HLA-DRB1*0901 (p = 0.004, OR 0.30 (CI 0.14-0.68). Previous studies have shown that HLA-DRB1*1502 and HLA-DRB1*0103 increase the risk for UC, whereas HLA-DR4 and HLA-DR6 have a protective effect on UC. In our cohort these haplotypes are present, but do not seem to be significantly associated to disease risk.

Conclusions: for the first time, deep analysis of the HLA loci is possible. Here, we report important newly identified roles for DRB1*0104 and HLA-DRB*0901 in UC. Analyses are still ongoing whilst algorithms for imputation are being developed and ImmunoChip data calling is being refined.

Once-daily versus twice-daily mesalazine (Pentasa®) for active ulcerative colitis: Efficacy results from MOTUS, a multicentre, controlled, randomised, investigator-blinded study

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Objectives: In ulcerative colitis (UC), compliance with 5ASA is poor with a significantly increased risk of recurrence (5-fold) in non-compliant patients. Data show that less frequent dosing may positively impact compliance. PODIUM demonstrated non-inferiority, and superiority (p=0.02), of once-daily (OD) vs twice-daily (BID) Pentasa® granules for the maintenance of remission in UC. The objective of MOTUS was to show non-inferiority of OD Pentasa® 2g sachet prolonged release granules (new concentrated formulation) vs standard BID dosing for the induction of remission in active UC. Methods: Patients with active mild-to-moderate UC were randomised to 5ASA granules 4g/d: 2x 2g OD or 1x 2g BID. All patients also received 5ASA enema (1g/d) for 4 weeks. Primary endpoint: clinical and endoscopic remission at week 8 (UC-DAI score ≤1). Secondary endpoints: clinical remission at weeks 4, 8, 12 (normal stool frequency, no bloody stools, no active disease by physician's global assessment); mucosal healing at week 8 (UC-DAI endoscopic mucosal appearance score ≤1). Statistical data are from intent-to-treat (ITT) and per-protocol (PP) analyses, Cochran-Mantel-Haenszel test used to show non-inferiority of OD vs BID. Results: 206 patients enrolled (OD n=102; BID n=104). Primary endpoint, remission at week 8, was met: 5ASA 4g OD was non-inferior to BID (ITT analysis 52.1% [52/101] vs 41.8% [42/101], difference 10.4%, 95% CI -3.4 to 24.1; PP analysis 61.0% [48/79] vs 48.3% [37/77], difference 12.8%, 95% CI -2.7 to 28.2). The lower limit of the two-sided 95% CI of the difference in remission rate was -3%, within the pre-specified non-inferiority margin of -15%. Secondary endpoints for OD vs BID: clinical remission at weeks 4, 8, 12: 39.8% vs 27.6%; difference 12.2% [95% CI -0.9; 25.3] (p=0.07), 45.1% vs 40.8%; difference 4.4% [95% CI -9.2; 18.0] (p=0.53), 92.4% vs 79.4%; difference 12.9% [95% CI -3.7; 29.6] (p=0.13); mucosal healing at week 8 by UC-DAI sub-score ≤1: 87.5% vs 71.1% (p=0.007).
Conclusions: MOTUS showed non-inferiority of Pentasa® 4g OD vs BID in patients with active UC. The primary endpoint was met in all analysis groups. All secondary endpoints were also non-inferior (with respect to the 15% margin) for OD vs BID, with mucosal healing being significantly better with OD. The data are consistent with PODIUM (maintenance 5ASA). These studies show that OD treatment with 5ASA granules is at least as effective as BID dosing, allowing treatment to be personalised to patient preference.

Is there a difference in quality of life or costs between ulcerative colitis patients with a pouch or an ileostomy?

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Twenty percent of patients with ulcerative colitis (UC) face colectomy and therefore need to choose between restorative proctocolectomy with a pouch reconstruction or a permanent ileostomy. In order to provide patients and physicians with evidence-based information on both patient-reported outcomes and costs, we compared quality of life and total costs (healthcare costs and productivity costs) in patients with a pouch or ileostomy in a large unselected cohort with IBD patients in the Netherlands. We obtained data from the 'Cost of Inflammatory bowel disease in the Netherlands' or COIN study, a prospective web-based 3 monthly questionnaire. We included all UC patients with a pouch and ileostomy at 3 months of follow up. The questionnaires contained questions on demographics, health care costs and productivity costs. Health-related quality of life was assessed using the EQ-5D. Costs were calculated by multiplying resource use by the unit costs as determined in the Dutch guidelines for pharmaco-economic analyses for the year 2009 by Oostenbrink et al. A total of 982 UC patients completed the follow up questionnaire at 3 months, of whom 77 patients (7.8%) had a pouch (57.1% males, mean age 46.8 ± 12.4 years, mean disease duration 14.9 ± 8.8) and 53 patients (5.4%) an ileostomy (54.7% males, mean age 52.7 ± 11.3 years, mean disease duration 16.9 ± 11.5). There was no statistically significant difference in health-related quality of life: mean EQ-5D utility for pouch was 0.85 (SD 0.19), and 0.85 (SD 0.17) for ileostomy. The mean (95% CI) costs per 3 months in patients with a pouch were significantly lower as compared to patients with an ileostomy, €929 (127-1732) versus €1282 (323-2242), respectively ($p<0.01$). This was mainly due to higher healthcare costs caused by hospitalizations (2 (2.6%) versus 6 (11.3%)) among UC patients with an ileostomy as compared to UC patients with a pouch (€371 (76-666) versus €66 (27-160), $p=0.02$). Conclusion: We observed no difference in quality of life in patients with a pouch or ileostomy, but patients with a pouch had significantly lower total costs, mainly due to fewer hospitalizations.

Ulcerative colitis patients with an inflammatory response upon mesalazine cannot be desensitized: a single-blind randomized study

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Mesalazine containing agents are very important in the treatment of ulcerative colitis (UC). Intolerance to mesalazine has been described, including skin reactions, fever, pneumonitis, interstitial nephritis, and gastrointestinal symptoms. A number of case reports reported successful desensitization of patients with mesalazine intolerance. Aim of this study was to assess the number of patients who are persistently intolerant to mesalazine after single-blind rechallenge and to test the effectiveness of a rapid desensitization protocol in patients with UC with demonstrated mesalazine intolerance. It was a single-center prospective, single-blind randomized study in patients with UC who stopped mesalazine because of intolerance including mild pancreatitis, erythematous skin reactions and fever. Patients with interstitial nephritis, severe pancreatitis, broncho-spasm, bullous skin reactions or anaphylactic shock were excluded. Eligible patients underwent a skin patch test with mesalazine in white soft paraffin 0.1, 1 and 10 %, and if negative started with a single-blind randomized crossover rechallenge with 500 mg mesalazine or placebo for 1 week with a three week washout interval. Patients with symptoms upon rechallenge were admitted to the hospital for oral desensitization with an increasing dose of mesalazine (1-3 g) in 3 days. Vital signs, hypersensitivity reactions, CRP, tryptase and urine methyl histamine levels were monitored. Of the 37 UC patients who stopped mesalazine because of intolerance 8 patients participated in this study. All patients had negative patch tests, 2 patients had no symptoms upon blinded rechallenge, and 6 patients had symptoms (fever, nausea, vomiting, and diarrhea) within 2 hours upon rechallenge. Four of these 6 patients participated in the desensitization protocol and none of these patients had a successful desensitization. Upon desensitization with even a low cumulative dose (150 mg) mesalazine all 4 patients had the same reaction pattern with fever, nausea, vomiting, diarrhea and rise of CRP within 3 hours. There were no clinical signs of immediate type allergic reactions, like urticaria, bronchial obstruction or anaphylaxis. Serum tryptase and urinary-methylhistamine did not rise significantly.
Conclusions: UC patients with fever, nausea, diarrhea, vomiting and a CRP response upon mesalazine cannot be desensitized with a 3 day desensitization protocol.

Fatigue in IBD patients is associated with differences in immune parameters

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Background: Fatigue contributes to the decreased quality of life of inflammatory bowel disease (IBD) patients. The immune system plays an important role in various cases of disease-associated fatigue. As such, we were interested whether there are detectable differences in immune parameters between fatigue and non-fatigue IBD patients. In this study only patients in clinical and biological remission were included to rule out inflammation-associated fatigue. Methods: After informed consent 78 IBD patients in clinical and biological remission, defined by a normal Harvey Bradshaw Index (< 5) and Colitis activity index (< 10), normal levels of hemoglobin, iron, CRP, liver enzymes and normal kidney function were included. All patients were phenotyped according to the Montreal classification and the Checklist Individual Strength (CIS) was used to assess fatigue. Other parameters included were: Quality of life scores and medication use. We used flow cytometry on peripheral blood samples to investigate the differences in leukocyte subsets. Furthermore, serum levels of IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNFα and IFNg were measured using ELISA. Results: In total 54 fatigue patients (CIS score of ≥ 35) and 24 patients without fatigue were included. Significantly more females were included in the fatigue group compared to the non-fatigue group (69% vs. 46%; p = 0.032). The other characteristics revealed no significant differences between the groups.
Flow cytometry data showed a significant lower percentage of monocytes (5% vs. 7%; p = 0.010), higher percentage of memory T-cells (42% vs. 34%; p = 0.006) and higher percentage of neutrophils (75% vs. 68%; p = 0.043) in fatigue patients compared to non-fatigue patients. Mean serum levels of IL-5 (F: 57 pg/ml, NF: 2 pg/ml; p = 0.021) and IL-12 (F: 9 pg/ml, NF: 3 pg/ml; p = 0.003) were significantly higher in fatigue patients while IL-8 (F: 10 pg/ml, NF: 61 pg/ml; p = 0.012) was significantly lower in fatigue pts compared to NF pts. No other significant differences were seen in cytokines or leukocyte subsets profiles.
Conclusion: This study shows for the first time that there are immunological differences between fatigue and non-fatigue IBD patients in remission. The signs of immune stimulation in fatigue could represent an on-going infection or autoimmune response that occurs without any clinical or histological signs of IBD and could even be indirectly or unrelated to the IBD. Further exploration of the underlying immune effects associated with fatigue is warranted to determine potential treatment options.

Anti TNF-α therapy is a major cost driver in inflammatory bowel disease: results from the COIN study

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Inflammatory bowel disease (IBD) is associated with a high economic burden to society. It has been estimated that up to two third of the total costs of IBD are generated by productivity loss. Most costs studies, however, have been performed before the introduction of the effective but costly biological therapies. In the present study, we therefore aimed to assess the total costs of IBD in a large cohort of IBD patients and to identify the main cost drivers. Between October 1, 2010 and June 1, 2011 a total of 10,947 patients with IBD were invited to participate in the COIN study and to fill out a web-based questionnaire every 3 months during 2 years of follow up. The questionnaires included questions on demographics, healthcare costs (visits to outpatient clinic, diagnostic procedures, hospitalization, surgery and medication use) and productivity costs (work days lost due to sick leave). Costs were calculated by multiplying resource use by the unit costs as determined by the Dutch pharmaco-economic guide by Oostenbrink et al. A total of 2,554 patients completed both the base as well as 3 months of follow-up questionnaires, of which 1,304 (51%) reported to suffer from Crohn's disease (CD), 928 (36%) patients from ulcerative colitis (UC), and 322 (13%) had unspecified type of IBD. In CD the mean total costs in 3 months were €1,738, of which €1,468 (84%) were healthcare costs and €270 (16%) productivity costs. For UC costs were significantly lower (€896 total costs, €553 (60%) healthcare costs, €363 (40%) productivity costs). Overall, the single most expensive resource was medication use, mainly due to prescription of anti-TNFα therapy accounting for an average of €1,044 (71%) in CD patients and €186 (33%) in UC patients. Furthermore, 10% of the high-cost patients accounted for 40% of the total health care costs in CD and 59% in UC, respectively.
Conclusion: The traditional cost profile in IBD has changed and health care costs are now even more driven by medication costs, most importantly due to anti-TNFα therapy. Whether this is balanced by a decrease in surgery and hospital admission-related costs as suggested by recent studies, and/or resulting in a reduction of sick leave and work disability will be assessed in follow-up studies.

Parent of origin effects for IL12B and NOD2 in Inflammatory Bowel Disease

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Genome-wide association studies (GWAS) for the two main forms of inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) have identified 99 independent susceptibility loci explaining ~23% of the total genetic risk for IBD. In the post-GWAS era the challenge is to uncover the remaining so-called hidden heritability. One of the sources might be a parent of origin (POO) dependent risk per allele, named genomic imprinting. This is characterized by a consecutive activation or inactivation of one of the copies of an allele depending on the parent from which it is inherited. An epidemiological study has shown that children from mothers with CD more often get CD than children from fathers with CD, indicating the existence of such a POO effect. We are the first to test for POO effects in IBD. For DNA genotyping we used a custom-made chip, the immunochip, which contains a dense map of ~180 immune disease related loci and ~200.000 variants. In a case-control study of 1367 cases and 2098 controls of Dutch ancestry we confirmed the association of 19 of the 99 known IBD loci (p value<0.001). To test for POO effects we used a recently developed POO-likelihood-ratio model that proved successful in determining a PPO effect in type I diabetes. For this study, we tested the 28 loci that are associated with both CD and UC in 187 Dutch child parent trios in which the child suffers from either UC or CD. Additionally, we tested the three known NOD2 variants in CD trios and the UC gene BTNL2 in UC trios, since this gene is already known to be imprinted. In the analysis of the Dutch trios a significant POO effect in the IL12B locus was found (P= 0.019 OR=3.2). In the NOD2 locus the reported frame-shift mutation (rs2066847) showed a POO effect (p=0.013 OR=21.0). No significant POO effects were detected in the BTNL2 locus.

Conclusions: Very little is known on the effect of genomic imprinting in complex diseases like IBD. Here we show for the first time that there is a POO effect for IL12B and NOD2 in the Dutch population. In the post GWAS era it is of utmost importance to study new sources to identify the hidden heritability. Follow-up studies with bigger cohort sizes and preferably including different ethnicities are necessary to confirm our findings and unravel the observed maternal imprinting in IBD. Currently we are analyzing a cohort of trios of Indian descent. We will test POO effects of 10 shared risk loci between Indian UC and Caucasian UC cases.

Screening for opportunistic infections prior to TNF-alpha inhibitor treatment in Crohn's disease and the risk of severe infections

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Prior to the start of TNF-alpha inhibitor treatment in patients with inflammatory bowel disease (IBD), screening for opportunistic infections should be performed according to international guidelines and consensus statements. It is of interest to know whether healthcare providers indeed adhere to these guidelines and whether this affects the occurrence of serious infections. In this study we investigated the actual screening practice and assessed the absolute risk of opportunistic and serious infections in a cohort of patients with Crohn's disease (CD) on infliximab (IFX) or adalimumab (ADA). A multicenter retrospective cohort study was conducted in three university medical centres. CD patients in whom IFX or ADA was administered between 2000 and 2011 were included. Conventional screening was defined as performing at least a tuberculin skin test (TST) or a chest X-ray (CXR), for detection of tuberculosis (TB). Extended screening comprised conventional screening and one or more tests for detection of viral pathogens. Patients were followed from the start of IFX or ADA until three months after stop, death or end of follow-up (June 1st, 2011). Our primary endpoints were infections and serious infections, requiring or prolonging admission, threatening life or leading to death.A total of 639 patients with Crohn's disease were included (mean age 34, SD 12; 36% male), the majority receiving IFX (95%). In total, 487 (76%) patients underwent screening, with conventional screening being performed in 371 patients (58%) and extended screening in 116 patients (18%). Four percent (n=15) of screened patients tested TST positive, of whom two showed signs of pulmonary TB on CXR. Active infection with CMV or EBV was found in 5 (4%) of the extendedly screened patients. During a median follow-up of 2.0 years (range 3 months–10 years), a total of 96 infections were detected in 85 (13%) patients, corresponding with 5.7 infections per 100 patient-years (PY) of follow up. Serious infections were encountered in 28 patients (4%, 1.7/100PY), including 3 cases of TB. Two patients (0.3%) died of infectious complications. No statistically significant differences were found between screened and unscreened patients in prevalence of infections (15% vs. 13%) and serious infections (6% vs. 4%). Furthermore, extension of screening did not significantly reduce the risk for overall (10% vs. 14%) or serious (3% vs 4%) infections.
Conclusion: Only three-quarters of CD patients underwent screening prior to TNF-alpha inhibitor use. However, this does not result in an increased prevalence of opportunistic or serious infections in unscreened patients.

Extensive screening for opportunistic infections prior to biological therapy in patients with Crohn's disease is not cost-effective

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The use of tumor necrosis factor (TNF)-α inhibitors in patients with Crohn's disease is associated with rare but potentially serious opportunistic infections. Therefore, an extensive consensus-based screening strategy prior to starting TNF-α inhibitors has been developed by Viget and colleagues. Since the overall risk of serious opportunistic infections is limited, we studied whether an adapted version of this extensive screening strategy is cost-effective compared to conventional screening. A Markov model was constructed to compare extensive screening (serological tests for hepatitis B and C infection, human immunodeficiency virus and tuberculin skin test and/or an interferon-g release assay) with conventional screening (chest X-ray and/or tuberculin skin test) for a base-case adult patient with luminal Crohn's disease receiving TNF-α inhibitors. In the Markov model, patients were followed over 3-month time intervals in which they could migrate between a series of healthstates following a list of input variables, all based on published literature. Direct medical costs were assessed and discounted for from a healthcare perspective. The primary outcome was the incremental cost-effectiveness ratio, with an incremental cost-effectiveness ratio (ICER) below €20,000 being considered to be cost-effective (following national guidelines). One-way sensitivity analyses were performed over wide ranges of probability and cost estimates to test the robustness of our model. In the base-case patient, the ICER of extensive screening compared with conventional screening was €263,939 to gain 1 additional quality-adjusted life-year (QALY), which is far above the threshold of cost-effectiveness. The ICER for extensive screening was most sensitive to changes in the overall detection rate at screening, and the overall occurrence rate of overt infections while on TNF-α inhibitors. Extensive screening was only cost-effective if total extensive screening costs were less than €272 (compared to €666 in base-case). Extensive screening became more effective, but not cost-effective, if the overall detection rate was below 6%, or overall occurrence of infection on TNF-α inhibitors was below 0.3%.
Conclusion: Extensive screening for potentially serious infections before the start of treatment with TNF-α inhibitors in patients with luminal Crohn's disease is not cost-effective. This may become cost-effective if screening costs are largely reduced. The extent of screening should be tailored to patient-specific risks of contracting infections during treatment with TNF-α inhibitors.

Impact of nasojejunal, jejunostomy and parenteral feeding after pancreatico-duodenectomy

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European nutritional guidelines recommend routine use of enteral feeding after pancreaticoduodenectomy (PD) whereas American guidelines do not. Data on the efficacy and, especially, complications of the various feeding strategies after PD are scarce. The aim of this study was to compare the efficacy and complications of routine feeding after PD by nasojejunal tube (NJT), jejunostomy tube (JT) or total parenteral nutrition (TPN). We performed a retrospective monocenter cohort study in 144 consecutive patients who underwent PD during a period wherein the routine post-PD feeding strategy changed twice. Patients not receiving nutritional support (n=15) were excluded. Complications were graded according to the Clavien-Dindo classification and the International Study Group of Pancreatic Surgery (ISGPS) definitions. Analysis was by intention-to-treat. Primary endpoint was the time to resumption of normal oral intake. 129 patients undergoing PD (111 pylorus preserving) were included. 44 patients (34%) received enteral nutrition via NJT, 48 patients (37%) via JT and 37 patients (29%) received TPN. Groups were comparable with respect to base characteristics, Clavien ≥II complications (P=0.99), in-hospital stay (P=0.83) and mortality (P=0.21). There were no differences in time to resumption of normal oral intake (primary endpoint; NJT/JT/TPN: median 13, 16 and 14 days, P=0.15) and incidence of delayed gastric emptying (P=0.30). Duration of enteral nutrition was shorter in the NJT- compared to the JT- group (median 8 vs. 12 days, P=0.02). Tube related complications occurred mainly in the NJT-group (34% dislodgement). In the JT-group, relaparotomy was performed in three patients (6%) because of JT-leakage or strangulation leading to death in one patient (2%). Wound infections were most common in the TPN group (NJT/JT/TPN: 16%, 6% and 30%, P=0.02). In a multivariable logistic regression analysis, adjusting for differences in age, gender, BMI, year of procedure and surgeon, there was no difference between the three strategies in the rate of morbidity or mortality.
Conclusions: None of the analysed feeding strategies was found superior with respect of time to resumption of normal oral intake, morbidity and mortality. Each strategy was associated with specific complications. Nasojejunal tubes dislodged in a third of patients, jejunostomy tubes caused few but potentially life-threatening bowel strangulation and TPN doubled the risk of infections.

How to further lower the complication rate after laparoscopic cholecystectomy

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Postoperative complications occur in grossly 10% of all patients undergoing laparoscopic cholecystectomy. With increasing subspecialisation of surgeons complication rates may be lowered by identifying cholecystectomies at risk for complications and subsequent planning of these patients to be operated on by a specialized surgeon. The aim of this multicenter, retrospective study was to identify independent risk factors for a complicated postoperative course after laparoscopic cholecystectomy for symptomatic bile stone disease. Furthermore we seeked to point out which type of complication was associated with which risk factor, in order to be able to anticipate on specific postoperative complications in selected patients.Two retrospective databases of two major teaching hospitals in the Netherlands were combined. The main outcome parameters were occurrence of major complications, mortality and length of hospital stay. Independent risk factors for the development of complications were analysed using uni- and multivariate analysis and the distribution of complications over these risk factors was assessed. A Total of 2634 patients were included in the database. The overall complication rate was 8.8%. Independent risk factors for postoperative complications were older age, acute cholecystitis, previous ERCP and conversion to open cholecystectomy. Length of surgery was not an independent risk factor. Acute cholecystitis was a risk factor for any complication except biliary injury, previous ERCP was mainly associated with cystic duct leakage. Of these risk factors the only one that can be influenced is conversion to open cholecystectomy. The overall conversion rate was 4.6%. The complication rate in converted patients increased to 21.3% versus 6.9% in patients in whom the procedure was finished laparoscopically ($p<0.0001$). Pneumonia was the most frequently encountered complication after conversion. The median duration of hospital admission was also significantly longer in converted patients: six versus two days ($p<0.0001$). The overall mortality rate was 0.4% and did not differ between the two groups. Patients with complicated gall stone disease have an increased risk of subsequent complicated surgery. Also, conversion to open cholecystectomy is associated with increased postoperative morbidity and a significantly longer hospital stay. High risk cases should therefore be planned to undergo surgery in the hands of a laparoscopiccally skilled surgeon, and if a less experienced surgeon considers converting, consultance of a laparoscopic surgeon should be considered.

Single port transanal surgery vs. transanal endoscopic microsurgery for rectal tumours: a case-control study

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Single port transanal surgery (SPTS) is a novel technique for the resection of rectal lesions, which are eligible for Transanal Endoscopic Microsurgery (TEM). Instrumental simplicity, similarity to laparoscopy and standard lithotomy positioning in SPTS may reduce patients' stay in the operating theatre, thereby improving cost-effectiveness of the procedure. We aimed to compare the in-theatre stay of patients undergoing SPTS and TEM during the initial clinical utilization of SPTS.Consecutive candidates for TEM who presented between April and September 2011 were operated via SPTS, using the SSL Access System (Ethicon Endo-surgery, Cincinnati, OH, USA) and standard laparoscopic instruments. Patients undergoing SPTS were matched with patients who had undergone TEM from 2006 – 2010 (using a rigid rectoscope with stereoscopic view and dedicated instruments (Wolf GmbH, Knittlingen, Germany)) in a 1:2 ratio. Controls were matched for lesion size (<20 vs. ≥20 cm^2), distance ab ano (<7.5 vs. ≥7.5 cm), rectal quadrant (posterior vs. non-posterior) and benign vs. malignant disease. All procedures were performed by a single surgeon with limited expertise in SPTS (13 cases) and extensive experience in TEM (>500 cases). Primary outcome was in-theatre stay including anesthesia induction, instrument preparation and patient positioning. Secondary outcomes included procedure time and conversion rate.Twenty-two patients (mean age 72 ± 12 years; 15 (68%) males) undergoing SPTS were included. Rectal lesions (55% adenoma, 18% polypectomy scar, 5% rectal stenosis, 14% T1 carcinoma, 9% T2) were located at a mean distance of 7.7 ± 4.5 cm ab ano and on the anterior, posterior, left lateral, right lateral and circumferential rectal walls in 36, 9, 14, 36 and 5% respectively. Median surface of resection specimens was 11 cm^2 (IQR 7-33 cm^2). Patients were matched to 44 controls who underwent TEM. Median in-theatre time was 76 minutes (IQR 57 – 106) in SPTS and 71 minutes (IQR 60 – 91) in TEM (p=.923). Median procedure time was 35 minutes (IQR 22-59) for SPTS and 33 minutes (IQR 23 – 49) for TEM (p=.698). Three SPTS procedures (14%) were converted to conventional TEM due to port dislodgement; 1 to anterior resection because of oncological considerations and 1 to transanal excision because of tumour prolapse. No conversion occurred in TEM procedures (P=.003). SPTS was technically feasible in 86% of patients who presented with lesions otherwise eligible for TEM. Efficiency was similar despite the limited experience with SPTS. For surgeons who routinely perform conventional TEM, SPTS might prove a technically simpler and more cost-effective technique.

Transanal Endoscopic Microsurgery: colorectal surgeons' learning curve

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Transanal endoscopic microsurgery (TEM) is a key technique in minimally invasive rectal surgery. TEM is technically demanding and various training programs exist. However, the learning curve of colorectal surgeons who commence with TEM is unknown. We aimed to evaluate the outcomes of colorectal surgeons' first series of TEM procedures and to assess whether outcomes improved with increasing experience.The first 32 TEM procedures of 4 colorectal surgeons, who completed a dedicated TEM training program, were analyzed. Patient, lesion and procedure characteristics were collected. Procedures were ranked chronologically per surgeon. Multivariate regression analysis was performed to identify independent predictors of conversion rate, postoperative complications, recurrence, procedure time and hospitalization length.Four colorectal surgeons performed 128 procedures (mean patient age 71 ± 12 years, 48% males, ASA classification 1/2/3 in 30/55/9%). Rectal lesions (adenoma / carcinoma / other in 76/20/4%, 21% recurrent lesions) had a median size of 13 cm^2 (IQR 6-23). Mean distance ab ano was 6.8 ± 4.0 cm. Lesions were located on the posterior, anterior, left and right lateral rectal wall in 47, 20, 19 and 15%. Resections were performed with three-dimensional (3D) stereoscope in 94 cases (73%) and 2D in 34 cases. Peritoneal breech occurred in 6 cases (5%). 86 resections (67%) were histopathologically radical (R0) and 42 were irradical or unsure (R1/Rx). Conversion (overall conversion rate 8%) was predicted by lesion size (OR 1,046 per cm^2, 95% confidence interval (CI) 1,016 – 1,075). Postoperative complications (14% overall, 12% surgical) were independently associated with peritoneal breech (overall OR 7,133 (95% CI 1,317 – 38,624), surgical OR 9,167 (95% CI 1,662 – 50,562)). Recurrence (11%) was independently associated with 3D vs. 2D instruments (OR 0,123 (95% CI 0,035 – 0,435). Procedure time (median 90 minutes (IQR 60-90)) was dependent upon the individual surgeon (P<.001), lesion size (B 2,173 (95% CI 1,745 – 2,601)) and peritoneal breech (B 71,075 (95% CI 19,939 – 122,211). Hospitalization (median 5 days (IQR 4-7)) was independently associated with patient age (B 0,129 (95% CI 0,047 – 0,211)), lesion size (B 0,069 (95% CI 0,019 – 0,119)), distance ab ano (B 0,277 (95% CI 0,013 – 0,542)) and peritoneal breech (B 18,137 (95% CI 11,659 – 24,615)). Chronological procedure rank did not predict any of the outcomes. Achieved outcomes correspond with previous literature of TEM in an early phase. As increasing experience was not associated with improved outcomes, the learning curve of TEM may extend beyond 32 cases in colorectal surgeons.

Prevention of parastomal hernias and incisional hernias in old stoma wounds: a pilot study

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Every year, thousands of stomas are created in patients. Part of them are definitive, others serve as a temporary diverting stoma. Frequently (30-50%), parastomal hernias and incisional hernias in old stoma wounds develop. These hernias bring along highly elevated risks of complications: one out of three of these patients will develop an incarceration of the hernia content, or will experience pain, esthetic complaints and limitations in daily activities warranting surgical hernia repair. Thus, prevention of parastomal and incisional hernias is of great importance. As a pilotstudy, in 10 patients receiving a temporary diverting stoma, a parastomal mesh (polyester with a collagen coating) was placed intraabdominally and fixated with absorbable tackers. At the time of stoma reversal, a laparoscope was inserted through a trocar in the old mid scar. The abdomen and mesh were closely observed and systemattically evaluated for adhesions. After closing the trocar site, the stoma was reversed. At this time, a piece of the mesh was obtained for histological evaluation. Furthermore, the cross-cut in the mesh was closed with non-absorbable sutures. Patients are followed up for a maximum of 12 months after stoma reversal. After a mean time of 6.8 (2.25-14.0) months, all 10 patients had their stoma reversed. None of the patients showed a parastomal herniation during the follow up, nor at the time of stoma reversal. One patient developed strong adhesions, due to incorrect placement of the tackers. No other serious complications have been observed. By now, after a mean follow-up time of 9.8 (4.75-12.0) months, none of the patients have developed an incisional hernia in their old stoma wound. Prophylactic intraabdominal placement of a parastomal mesh, is a safe and feasible technique to prevent parastomal herniation and incisional hernias in old stoma wounds. Care has to be taken to correctly place the tackers, to prevent complications.

Treatment of chronic presacral sinus after low anterior resection with preoperative radiotherapy for rectal cancer

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The incidence of chronic presacral sinus after low anterior resection (LAR) lies between 1-5%. Secondary complications such as fistula formation, ureteral obstruction, fasciitis, osteomyelitis and malignant transformation may occur.Aim of this study was to determine patient and treatment characteristics of symptomatic chronic presacral sinus with corresponding clinical outcome.In a retrospective cohort study, 18 patients with a presacral sinus persisting for at least 12 months were included. All patients underwent pre-operative radiotherapy (short course in 15, chemoradiotherapy in 3 patients) for the primary tumor. Patients were treated for chronic presacral sinus between January 2005 and December 2011 at the Academic Medical Centre, of whom 11 were referred. Primary outcome was healing rate and median time to healing of the pre-sacral sinus. Secondary outcome parameters were definitive ostomy rate, total number of reinterventions, necessity of resection of the rectal stump and effect of filling of the cavity with well vascularized tissue on healing rate.The median follow up was 56 months (range 21-135). During follow-up, fistulas arising from the sinus were observed in 9 (50%) patients: 5 along the piriformis muscle, 1 vaginal, 1 perineal,1 ureter and small bowel. Hydronephrosis due to fibrosis around the distal ureter was observed in 3 (17%) patients, Healing rate was 8/18 after a median time to healing of 48 months (range 23-93). Median number of therapeutic interventions (surgical, radiological, endoscopic) for presacral sinus was 6 (range 1-44). At final follow-up, 7 patients had still a colo-anal or colorectal anastomosis. Healing of the sinus occurred in 3 of these 7 patients after a new pull through anastomosis in 2 patients and by prolonged fecal diversion during 33 months in 1 patient. End-colostomy was constructed in 11 patients. Additional intersfincteric resection of the rectal stump was performed in 9 of these 11 patients and filling of the pre-sacral sinus with omentoplasty (N=7) or rectus abdominis muscle flap (N=1) was performed in 8 of these 11 patients. The sinus healed in 5 of the 11 patients with end-colostomy after both rectal resection and filling of the sinus.
Conclusion: In this retrospective series a new anastomosis after presacral sinus was feasible in some cases. When continuity was no longer feasible, healing of the chronic presacral sinus was accomplished after breakdown of the anastomosis with end-colostomy in combination with thorough debridement of the sinus and fistulas, complete filling of the sinus with well vascularized tissue and intersfincteric resection of the rectal stump.

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Binnen de gastroenterologie uit zich dit in geneesmiddelen die, zeker bij de behandeling van chronische aandoeningen, niet alleen effectief zijn maar vooral ook bijdragen aan het verbeteren van de kwaliteit van leven, zodat de patiënt zo normaal mogelijk kan leven.

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FERRING PHARMACEUTICALS

Cholinergic anti-inflammatory pathway in DSS-induced colitis

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The cholinergic anti-inflammatory pathway (CAIP) is a recently identified endogenous anti-inflammatory mechanism modulating the immune system to dampen inflammation and reduce collateral tissue damage. We previously demonstrated activation of the CAIP by subtle inflammation of the small intestine in a model of postoperative ileus (POI). To what extent this pathway is also activated during colitis remains however unknown. Therefore, we evaluated vagal activation upon DSS-induced colitis with cFos expression, a marker for neuronal activation, in the dorsal motor nucleus of the vagus nerve (DMV) at different time points of DSS exposure. Moreover, selective vagal denervation of the proximal part of the colon was performed to investigate the anti-inflammatory role of the vagal innervation of the colon. C57/Bl6 mice were exposed to DSS in drinking water for 7 consecutive days. Mice were sacrificed at day 1, 3 and 7 days. The group of mice exposed to 7 days of DSS was divided into 2 experimental groups: mice who underwent vagal denervation of the colon (Cx) and a sham-operated group. At sacrifice, the brain was collected for cFos expression and colonic tissue was collected to determine the expression of pro- and anti-inflammatory cytokines. Mice exposed to 7 days of DSS exhibited a significant increase in the disease index activity (shortened colon length, inflammatory and diarrhea scores) and a decreased body weight. The inflamed colons showed an increased expression of IL-6, TNFα, IL1β compared to control mice. Colonic inflammation did not significantly increase cFos expression in the DMV in mice exposed to DSS for 1, 3 and 7 days (as ERK another neuronal activation marker). Despite the lack of vagal activation in the brain stem, selective denervation of the proximal part of the colon enhanced the expression of pro-inflammatory cytokines compared to sham-operated mice (IL-6 (0.0026±0.001 vs. 0.0081±0.003; mean ± S.E.M, $p<0.05$, IL1β (0.014±0.008 vs. 0.053±0.017, $p<0.05$). Interestingly, a significant increase of FoxP3 mRNA levels in inflamed colon was found in denervated (2.7±0.9 vs. 5.5±1 E-04, $p<0.05$) compared to sham-operated mice. In the present study, DSS-induced colonic inflammation, mainly affecting the mucosa, did not trigger endogenous activation of CAIP as described during intestinal muscularis inflammation in POI. This striking data suggest that CAIP activation may rely more on the anatomical location of the inflammation. Interestingly, despite the lack of endogenous vagal activation, vagal denervation of the colon enhanced inflammation in DSS exposed mice, further confirming the role of the CAIP in mucosal immune homeostasis.

Ischemia-induced mucus barrier loss and bacterial penetration are rapidly counteracted by increased goblet cell secretory activity in human and rat colon

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Ischemia/reperfusion (IR) of the colon is a frequently observed event in clinical practice carrying high morbidity. The high morbidity is associated with intestinal barrier function loss, leading to bacterial translocation and severe inflammation. In the colon, an important first line of defense against intruding pathogens is the mucus layer, which is produced by goblet cells. In this study, we investigated consequences of colon IR on the mucus layer and goblet cells, in a newly developed human and rat experimental IR model. In 10 patients, a small part of colon that had to be removed for surgical reasons was isolated and exposed to 60 minutes of ischemia with 0, 30 or 60 minutes of reperfusion (60I, 30R and 60R, respectively). Tissue not exposed to IR served as control. In rats, colon was exposed to 60I, 60I30R, 60I120R or 60I 240R (n=7 per group). Human and rat tissue was either snap-frozen, fixed in glutaraldehyde for electron microscopy (EM), fixed in formalin or fixed in methacarn fixative to preserve the mucus layer. qPCR was performed for MUC2, IL-6, IL1-β and TNF-α. The mucus layer and goblet cells were assessed using PAS/Alcian Blue (AB) or immunohistochemistry for MUC2/Dolichos biflorus agglutinin (DBA). Bacteria were studied using EM and fluorescent in situ hybridization (FISH) for bacterial rRNA. Neutrophil influx was studied using Myeloperoxidase staining.PAS/AB and MUC2/DBA staining revealed breaches in the mucus layer at 60 minutes of ischemia. This was accompanied by penetration of bacteria into the normally sterile crypts, as observed in EM and FISH, which induced massive release of goblet cell granules. During reperfusion, increased goblet cell secretory activity led to expulsion of bacteria from the bottom of the crypts towards the crypt surface. At 240 minutes of reperfusion, no bacteria were observed near the epithelium and a newly formed mucus layer provided spatial separation of intraluminal bacteria with the epithelial lining. Inflammation was limited to a slight influx of neutrophils into the lamina propria and increased expression of IL-6, IL1-β and TNF-α.In conclusion, this study provides first clues for the pathophysiology of human colonic IR. Colon ischemia is associated with breaches in the mucus layer and bacterial adherence to the epithelium. This is rapidly counteracted by increased secretory activity of goblet cells, leading to expulsion of bacteria from the crypts as well as restoration of the mucus barrier.This unique mechanism of the colon limits IR-induced bacterial penetration and inflammation.

The human colon is more resistant to ischemia-reperfusion induced tissue damage and early inflammation than human small intestine

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Small intestinal ischemia-reperfusion (IR) is a frequently occurring event carrying high morbidity and mortality. This is associated with intestinal barrier function loss, leading to bacterial translocation and severe systemic inflammation. Contrary to the severe course of small intestinal IR, colonic IR tends to have a much milder course. This is surprising, since the colonic intraluminal milieu is more pro-inflammatory. This led us to hypothesize that the human colonic epithelial barrier must be better protected to IR-induced damage compared to human small intestinal epithelium.To obtain insight in the differences in the pathophysiology of human small and large intestine IR, we developed human experimental models for small intestinal IR and colon IR. In these models we take advantage of the fact that during different types of intestinal surgery a part of the otherwise healthy intestine has to be removed for surgical reasons. Jejunal IR model: In 10 patients undergoing pancreaticoduodenectomy, a 6 centimeter segment of intestine that had to be removed, was isolated on two sides and selectively exposed to 60 minutes of ischemia followed by 0 (60I), 30 (30R) and 120 minutes of reperfusion (120R). Colonic IR model: In 10 patients undergoing left sided colonic surgery a 6 centimeter colonic segment was exposed to 60 minutes of ischemia followed by 0 (60I), 30 (30R) and 60 minutes (60R) of reperfusion, analogous to the procedure described above. In both models tissue was collected at all time points to assess morphology (hematoxylin/eosin (HE) staining), apoptosis (M30 staining) and neutrophil influx (myeloperoxidase (MPO) staining).HE staining revealed extensive damage in small intestinal villus tips at 60I whereas in the colon the epithelial lining remained intact. Apoptosis was observed in both the crypts and villi of jejunum at 30R and damaged cells were shed into the lumen, leading to barrier integrity loss. At 120R, the epithelial lining remained compromised. Interestingly, apoptosis of epithelial cells in the colon was limited to scattered cells in the surface epithelium. In addition, the epithelial barrier was not affected at 60I and during reperfusion. In with these data, neutrophil influx was only observed during small intestinal IR, whereas no neutrophjl influx was observed in colon exposed to IR.
In conclusion, we provide evidence that the human colonic epithelium is more resistant to IR then small intestinal epithelium. Future studies should be aimed at unraveling the molecular mechanisms underlying this effect.

Pregnane X Receptor stimulation reduces NF-kappaB mediated cytokine expression in intestinal biopsies from inflammatory bowel disease patients

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Mucosal detoxification of various anti-inflammatory drugs is mediated amongst others by nuclear receptors like the Pregnane X Receptor (PXR). The activation of PXR is associated with down regulation of nuclear-factor kappa-B (NF-kappaB) activity, which plays a key role in inflammation. Here, we studied whether PXR activation could reduce NF-kappaB-mediated inflammatory responses in intestinal biopsies from inflammatory bowel disease (IBD) patients. Three biopsies were taken from four different bowel locations in IBD (n=26) and control patients (n=8). Biopsies from endoscopically inflamed and non-inflamed areas were included and inflammation was histologically confirmed by an expert pathologist. The biopsies were cultured for 18 h with or without PXR activator Rifampicin (100µM). Rifampicin-induced PXR activation was verified by the mRNA expression of PXR target genes (Cyp3A4, Sult1a, MDR1) and the possible repression of NF-kappaB by the expression of its target genes (IL-8, IL-1beta, TNFalfa). In addition, the protein expression of TNFalfa and IL-8 in biopsy homogenates was measured using ELISA. The gene expression of Sult1a and MDR1 are up-regulated in all the biopsies after Rifamipcin stimulation. Furthermore, the expression of IL-8 ($p<0.001$) and IL-1beta ($p<0.01$) are 10-100 fold higher in biopsies from IBD patients than in biopsies from control patients, irrespective of disease activity. However, this elevated cytokine expression was significantly reduced after Rifampicin stimulation ($p<0.01$). This reduction is observed in all biopsies on mRNA as well as protein expression and is regardless of intestinal-location.
Conclusions: Rifampicin can activate PXR in human intestinal biopsies. Biopsies taken from IBD patients have higher NF-kappaB activity than the biopsies taken from control patients. Nevertheless, this high NF-kappaB activity could be reduced by Rifampicin, irrespective of disease type. Thus, PXR activation by Rifampicin could be used as a therapeutic approach to reduce mucosal inflammation in patients with IBD.

Identification of a novel FXR response element; Human FXR induces SHP expression through direct binding to an LRH-1 binding site, independent of the presence of an IR-1 and LRH-1

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The nuclear receptors farnesoid X receptor (FXR) and the retinoic X receptor alpha (RXRα) act as heterodimer in regulating bile salt synthesis and transport. Natural ligands for FXR and RXRα are the bile salt chenodeoxycholic acid (CDCA) and the vitamin A-derivative 9-cis retinoic acid (9cRA), respectively. Typical FXR/RXRα target genes are the bile salt export pump (BSEP/ABCB11) and the small heterodimer partner (SHP/NR0B2). FXR/RXRα binds to Inverted Repeat-1 (IR-1) sequences. Previously, we found that 9cRA inhibits binding of FXR/RXRα to the IR-1 and represses CDCA-induced BSEP transcription. In contrast, FXR-induced expression of SHP in vitro and in vivo is maintained independent of 9cRA/vitamin A. Recent data suggest that FXR may act together with the liver receptor homolog-1 (LRH-1) to induce expression of SHP. Here, we performed a detailed analysis of the FXR-mediated regulation of human SHP and established a direct binding of FXR to an LRH-1 response element independent of the IR-1 and LRH-1.
hFXR/hRXRα-transfected DLD-1, HEK293 and HepG2 cells were cultured in the presence or absence of CDCA, GW4046 (synthetic FXR ligand) and/or 9cRA. When applicable, cells were co-transfected with mLrh-1. Regulation of FXR/RXRα target genes was quantified by Q-PCR. Luciferase reporter plasmids containing deletion and site-specific mutants of a 579-bp SHP promoter element were used to locate CDCA/FXR-responsive elements. FXR-DNA interactions were analyzed by *in vitro* pull down assays.
SHP promoter elements lacking the previously identified IR-1 (-291/-279) largely maintained their activation by ligand-activated FXR, but were unresponsive to 9cRA/RXRα. SHP promoter deletion analysis revealed that FXR-mediated activation of the SHP promoter was dependent on the -122/-69 region, which contains a previously identified LRH-1 site (-78/-70). Remarkably, co-transfection of mLrh-1 did not super-induce the FXR-mediated expression of SHP. Pull down assays reveal a direct binding of FXR to the -122/-69 sequence, which was abrogated by site-specific mutations in the LRH-1 site. These mutations strongly impaired the FXR-mediated activation of the 569-bp SHP promoter that contained an intact IR-1. The minimal LRH-1 binding site was not sufficient to bind FXR.
Conclusion: We identified a novel FXR response element in the human SHP promoter that largely overlaps with a LRH-1 binding site. No synergy between LRH-1 and FXR is observed in regulation of SHP expression. These findings imply a complex interplay between FXR and LRH-1, two factors that control multiple cellular (metabolic) pathways, including bile salt and lipid homeostasis.

Effects of bile acid receptor agonists INT-747 and INT-777 on estrogen deficiency-related post-menopausal obesity and hepatic steatosis

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Menopause is a physiological state characterized by estrogen deficiency. Estrogens have important effects on body fat distribution. Estrogen deficiency can result in increased visceral adiposity and related metabolic pathologies such as chronic adipose tissue inflammation and hepatic steatosis. Recently two bile acid (BA) receptors have emerged as putative therapeutic targets for obesity and the related metabolic disorders: the nuclear farnesoid-X receptor (FXR) and the protein G coupled receptor (TGR5). FXR is involved in lipid and cholesterol homeostasis, TGR5 is implicated in energy expenditure. The aim of this study was to evaluate the effects of estrogen deficiency in metabolism and the efficacy of the novel FXR agonists INT-747 (for FXR) and INT-777 (for TGR5) as an alternative treatment for menopause pathologies. For this, female Swiss CD-1 mice (age 9-10wk, n=8/group) were ovariectomized (OVX); a group of SHAM operated mice served as controls. All mice were fed a high fat diet (HFD; 45% kcal fat) for a total of 5 weeks. For 3 groups of OVX mice the diet was supplemented with either INT-747, INT-777 or 17b-estradiol (E2) for the last 4 weeks. Bodyweight and food intake were monitored weekly. After 5 weeks mice were sacrificed and tissues were immediately harvested. At sacrifice OVX mice weighed 13% more ($p<0,001$) than SHAM mice. INT-747 and INT-777 treatment prevented bodyweight gain: bodyweight at sacrifice was 15 % and 11% less, respectively, compared to OVX mice ($p<0,001$). No significant differences were found in weekly food intake. Liver triglyceride content (TG) was measured in liver homogenates by a colorimetric assay. Liver TG were increased in the OVX group (+69% - $p=0,07$) compared with the SHAM mice, and decreased in the OVX-INT747 (-76% - $p<0,001$) and OVX-E2 (-80% - $p<0,001$) groups compared with the OVX group.
Conclusion: these results suggest that the FXR and TGR5 agonists may prevent weight gain and hepatic steatosis caused by ovariectomy. Studies on energy expenditure and gene expression in liver, adipose tissues and muscle are ongoing. Financial Support: CAPES.

Activation of nuclear receptor FXR by oral chenodeoxycholic acid in patients with Crohn's colitis: potential therapeutic consequences for inflammatory bowel disease

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The bile salt nuclear receptor Farnesoid X Receptor (FXR) is critical in preventing bacterial overgrowth and maintaining intestinal barrier. FXR activation by (semi-)synthetic agonists prevents inflammation in murine colitis models, probably by NFκB inhibition (Gut;2011;60:463-72). Patients with Crohn's colitis (CC) exhibit reduced ileal FXR target gene mRNA expression compared to patients with ulcerative colitis and controls, suggesting impaired FXR activity in CC (PLoS One 2011;6:e23745). We investigated whether pharmacological FXR activation is feasible in CC. Nine patients with quiescent CC and 12 controls were treated with the FXR ligand chenodeoxycholic acid (CDCA,15 mg/kg/day) for 8 days. Ileal FXR activation was assessed in fasting state before and each hour during 6 hours after the first CDCA dosage and after the final dosage by quantification of serum levels of FGF19 (enterokine whose expression is controlled by FXR; by ELISA). Since FGF19 induces gallbladder (GB) refilling in the mouse, we also determined GB volumes (by sonography). Ileal and cecal biopsies were obtained during colonoscopy after the last dosage, RNA was isolated, and FXR and FXR target genes expression analyzed with quantitative real time PCR. At baseline, fasting FGF19 levels did not differ between CC and controls (0.23±0.14 vs 0.21±0.11 ng/mL, mean±SD). After the first CDCA dosage, FGF19 and GB volumes initially decreased in both CC and controls (after 1 hour: FGF19 30 resp. 31% of basal and GB volume: 12 resp. 15% of basal), with subsequent progressive increases during the next 6 hours (FGF19: 537 resp. 576%; GB volume: 178 resp. 190%) without differences between both groups, and further increases at day 8. Analysis of ileal biopsies from untreated controls and from CDCA treated groups revealed that CDCA increased mRNA levels of FXR target genes IBABP (3.2 resp. 4.2 fold) and FGF19 (22 resp. 43 fold) and decreased mRNA levels of ASBT (0.46 resp. 0.58 fold) to a similar extent in CC and controls, compared to untreated controls. SHP expression was only increased in CC (2.3 fold). Regarding FXR-dependent genes implicated in antibacterial defense: ileal and cecal angiogenin 1 mRNA expression decreased (0.38 resp. 0.63 fold) in both CDCA treated groups. iNOS expression was not affected by CDCA treatment. mRNA expression of FXR and FXR target genes in cecum was much lower than in ileum, without differences between CDCA treated CC and controls.

Conclusion: Current results show that pharmacological activation of FXR is feasible in patients with CC and provide a rationale to explore the anti-inflammatory properties of pharmacological activation of FXR in these patients.

microRNA profiles in graft preservation solution are prognostic for biliary strictures after liver transplantation

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(Non)anastomotic biliary strictures after liver transplantation (LT) are common. Recently, hepatocyte and cholangiocyte-abundant microRNAs (miRNAs) have been identified as sensitive markers for liver injury in serum. The release of miRNAs during liver injury has lead to the hypothesis that they could act as potential non-invasive biomarkers in preservation solutions to predict biliary strictures in recipients after LT. The aim of this study is to investigate whether differences in the balance of hepatocyte- and cholangiocyte-derived miRNAs in graft preservation solution are prognostic of biliary strictures after LT.

Perfusate flushes from 33 consecutive liver grafts were collected at the end of cold ischemia time (CIT) and the cell-free solutions were analyzed for the presence of hepatocyte-abundant miRNAs (miR-122 and miR-148a) and cholangiocyte-abundant miRNAs (miR-30e miR-222 and miR-296) by quantitative RT-PCR. Mann-Whitney U tests and ROC-curves were generated to compare ratios of miRNAs between recipients that developed biliary strictures (n=13) versus recipients that did not (n=20).

Perfusates from grafts that developed post-LT biliary strictures contained significantly higher ratios of hepatocyte- (miR-122, miR-148a) and cholangiocyte- (miR-296, miR-30e, miR-222) specific miRNAs ($P<0.01$). ROC analysis shows that perfusates with higher ratios of hepatocyte- vs cholangiocyte-abundant miRNAs are more likely to develop biliary strictures after LT compared to perfusates with lower miRNA-ratios (AUC=0.865, P=0.0002).

Conclusion: This study demonstrates that ratios of hepatocyte vs cholangiocyte-derived miRNAs in perfusates during LT differ between grafts that develop biliary strictures and grafts that do not. Based on these ratio's, biliary strictures after LT could be predicted with high sensitivity and specificity. This non-invasive detection of specific miRNAs in preservation solution in an early phase of LT may represent a novel method to help identify liver grafts at risk of developing biliary strictures after LT.

Reduced FGF19 level in bile and decreased FGF19 expression in the gallbladder of patients with primary sclerosing cholangitis

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Human bile contains Fibroblast Growth Factor 19 (FGF19) at levels far exceeding those in the circulation (Zweers et al. Hepatology 2011; online). Apart from metabolic functions, binding of FGF19 to its receptor FGFR4 has been reported to restrain TNFa-induced NFkB signaling (Drafahl et al. PLos One 2010; 5: e14412). This anti-inflammatory action of FGF19 might be relevant for the pathogenesis of primary sclerosing cholangitis (PSC). Expression of FGF19 in gallbladder epithelium is regulated by the bile salt-activated transcription factor farnesoid X receptor (FXR) and accordingly is dependent on expression/activity of the apical sodium-dependent bile salt transporter (ASBT). In PSC there is ongoing inflammation and fibrosis of intra- and extrahepatic bile ducts. We considered the possibility that in PSC there might be a deficiency of FGF19. Therefore we studied FGF19 expression in the gallbladder and in bile of patients with PSC. Gallbladder bile (n=14 per group) and gallbladder tissue (n=4-10 per group) of PSC and non-PSC patients with various liver diseases were collected at the time of liver transplantation (LTx). FGF19 protein levels were measured by ELISA. FGF19, SHP (another FXR-target) and ASBT transcript levels were measured by RT-qPCR using mucosal epithelium-specific cytokeratin 19 as a reference gene. In gallbladder specimens of PSC patients, ASBT mRNA expression is significantly reduced (7.9 fold, P=0.03). This is accompanied by reduced expression of FGF19 and SHP mRNA in the gallbladder (2.4 fold, P=0.04 and 3.8 fold, p=0.01, respectively) and lower levels of FGF19 in LTx bile from PSC patients (8.9±7.6 vs. 22.6±25.5 ng/mL in non-PSC patients; P=0.02). FGF19 levels in LTx bile from non-PSC patients were similar to levels in gallbladder bile from patients with either gallstone disease or periampullar malignancies (22.6±25.5 vs. 21.9±13.3 ng/mL, resp.; P=0.94).
In conclusion, reduced expression of ASBT in the gallbladder of PSC patients likely results in abrogated FXR activation and reduced expression and secretion of the FXR target FGF19. Reduced FGF19 levels in bile may contribute to the ongoing inflammation and fibrosis in intra- and extrahepatic bile ducts of PSC patients.

Bile acid-preconditioning protects HepG2.rNTCP cells against bile acid-induced apoptosis

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Background: Cholestasis is characterized by accumulation of bile acids in the liver, causing hepatocyte cell death, ultimately leading to liver failure. Accumulation of bile acids in hepatocytes can damage mitochondrial membranes, induce reactive oxygen species production and activate pro-inflammatory signaling pathways. Previous research suggests that prolonged cholestasis induces adaptive changes in hepatocytes that result in resistance towards bile acid-induced cell death. Aim: Study the mechanisms how hepatocytes become resistant towards bile acid-induced apoptosis in an in vitro model of cholestatic liver disease. Methods: HepG2.rNTCP cells were preconditioned with sub-apoptotic concentrations (0,1-50 μM) of bile acids, superoxide donor menadione (10 μM) or TNF-α (10 ng/ml) followed by a challenge (200 μM, 4 hr) with the apoptosis - inducing bile acid glycochenodeoxycholic acid (GCDCA). Levels of apoptosis, necrosis and mitochondrial functioning were analyzed. Results: Preconditioning with GCDCA (10-50 μM for 24-48 h) or tauroursodeoxycholic acid (TUDCA) protected HepG2.rNtcp cells against GCDCA-induced apoptosis. In contrast, preconditioning with menadione or TNF-α strongly potentiated GCDCA-induced apoptosis. Bile acid-preconditioning did also prevent induction of GCDCA-induced necrosis and the loss of mitochondrial membrane potential by the GCDCA challenge. Inhibition of the ERK1/2 and PI3K signaling pathways attenuates the protective effect of bile acid- preconditioning.
Conclusion: Sub-toxic concentrations of bile acids improve mitochondrial fitness and protect HepG2.rNTCP cells against GCDCA-induced cell death. These data support the observation that hepatocytes become resistant towards bile acid-induced apoptosis during chronic cholestasis.

ATP8B1 and ATP11C deficiency affect taurocholate and glucose uptake in Caco-2 cells

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ATP8B1 and ATP11C are P4-type ATPases and transport phospholipids from the exoplasmic to the cytoplasmic leaflet of the membrane. ATP8B1 deficiency causes Progressive Familial Intrahepatic Cholestasis Type 1 or Benign Recurrent Intrahepatic Cholestasis type 1. Previously we showed that ATP8B1 deficient mouse hepatocytes are prone to membrane damage induced by hydrophobic bile salts with a consequent impairment of canalicular transport proteins, including the bile salt export pump. ATP8B1 deficient patients can also develop extrahepatic symptoms, including diarrhea with yet unknown etiology. Recently it was shown that ATP11C deficiency causes cholestasis in mice that resembles the cholestasis observed in ATP8B1 deficient mice. Here we sought to investigate the consequence of depletion of ATP8B1 and ATP11C on membrane protein function in intestinal Caco-2 cells. To this goal we studied bile salt and glucose transport in ATP8B1 and ATP11C depleted Caco-2 cells. In addition, we studied Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) activity in ATP8B1 depleted T84 cells. Radiolabeled taurocholate and glucose uptake was measured in cells grown in monolayers and on transwell inserts. ASBT surface expression was analyzed after surface biotinylation. CFTR function was studied in intestinal T84 cells by measuring short-circuit currents in Ussing chambers. ATP8B1 and ATP11C depleted Caco-2 cells displayed strongly reduced uptake of ASBT-dependent taurocholate (respectively 38±2% of control at 30min; $p<0.001$ and 40±1% of control at 40min; $p<0.001$). In both cell lines, impaired uptake was associated with strongly reduced membrane-associated ASBT expression without a change in ASBT mRNA. In addition, glucose uptake was significantly reduced in ATP8B1 depleted cells (73±2% of control at 4min; $p<0.001$), but, in contrast, was significantly increased in ATP11C depleted cells (133±7% of control at 4 min; $p<0.005$). Furthermore, CFTR activity was reduced in forskolin-stimulated ATP8B1 depleted T84 cells (169±39μA/cm2 vs. 213±22μA/cm2 in control cells; $p<0.05$), which was paralleled by a reduction (~40%) in CFTR protein and mRNA levels. CFTR mRNA levels were not affected in ATP11C depleted cells.

Conclusion: Our results show that ATP8B1 deficiency results in impaired glucose uptake and ASBT and CFTR activity in intestinal cells. ATP11C deficiency also results in reduced ASBT activity, however, glucose uptake is enhanced. Bile salt malabsorption provides an explanation for the diarrhea observed in ATP8B1 deficient patients. Furthermore, our data suggest a distinct role for ATP8B1 and ATP11C in the maintenance of proper membrane structure.

Diagnostic scoring systems for autoimmune pancreatitis are complementary and correctly identify the majority of patients at initial presentation, without the need for histology

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Introduction: Autoimmune pancreatitis (AIP) is a distinct type of chronic pancreatitis that may clinically mimic pancreatic cancer. Its diagnosis often proves to be challenging. Several diagnostic scoring systems are available, of which the Asian and HISORT criteria are used most frequently. Recently, novel International Consensus Diagnostic Criteria (ICDC) for AIP have been developed. The aim of this study was to investigate in a large cohort of AIP patients whether the concurrent application of all three diagnostic scoring systems provides a definite diagnosis. Methods: Patients diagnosed with AIP between May 1992 and August 2011 were enrolled. The diagnosis of AIP was made retrospectively according to the ICDC, Asian or HISORT criteria or was based on post-surgery histology, a combination of unexplained pancreatic disease, biliary disease/extrapancreatic manifestations and either response to steroids or IgG4-positive serology. Clinical data, laboratory and imaging findings, histology, response to treatment, and recurrence were studied. Scoring systems were applied using data obtained during the initial evaluation period of 6 months. Results: A total of 83 cases with AIP were included, of which 72 patients (87%) were men, with a median age at presentation of 63 years (range: 19-80). Weight loss (87%), steatorrhea (80%) and obstructive jaundice (77%) were the most frequent presenting symptoms. Extrapancreatic manifestations were observed in 65%, biliary involvement (53%) being most frequent. Serum IgG4 levels were abnormal in 78% of the patients tested. In total, 82% were treated with steroids and 99% of those responded to treatment. Disease recurrence occurred in 22% of these patients, all of them responding to repeated course of steroids with or without azathioprine. When applying the ICDC, Asian or HISORT criteria, 67 patients (81%) met the diagnostic criteria for AIP according to any of these systems. Thirteen patients (16%) met the diagnostic criteria for all three systems, 26 (30%) met criteria for two systems and 28 (34%) for one system. In 16 patients (19%) who did not fulfill any of the three scoring systems, diagnosis was based on combination of unexplained pancreatic and biliary disease/ extrapancreatic manifestations and either response to steroids or elevated IgG4. Only 2 patients (2%) had not been diagnosed until they underwent pancreatic surgery.
Conclusions: In this large cohort of AIP patients, diagnostic scoring systems for AIP proved to be complementary rather than overlapping. Four out of 5 patients were diagnosed based on clinical data obtained within the first 6 months after initial presentation, without the need for histology.

Comparable efficacy of low and high dose induction corticosteroid treatment in autoimmune pancreatitis

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Autoimmune pancreatitis (AIP) is a distinct type of chronic pancreatitis highly responsive to corticosteroids. The usually recommended dosage of prednisone for remission induction is 0.6 mg/kg/day, resulting in daily starting doses of 30 – 60 mg. This recommended dosage is largely based on empirical data and lacks scientific base. Potentially, high dose corticosteroid treatment is associated with significant side effects, particularly in a population characterised by relative advanced age, diabetes and obstructive jaundice at presentation. The rationale for high dose treatment could also be questioned considering the well-established sensitivity for corticosteroids in AIP patients. We therefore compared the efficacy of treatment and the incidence of worsening glucose tolerance in AIP patients treated with different doses of steroid induction therapy.A retrospective survey was conducted of patients diagnosed with AIP between May 1992 and August 2011. Clinical, laboratory and image findings were assessed before treatment and at 1, 3 and 6 months after starting treatment. Differences between groups treated with different initial doses of prednisone were compared using linear and logistic regression analysis.A total of 37 patients (33 males; median age 65 years) were included. The most frequent presenting symptoms included jaundice, pancreatic insufficiency, weight loss and (mild) abdominal pain. Four patients were treated with an initial dose of prednisone of 10 mg/d, 2 patients with 15 mg/d, 6 patients with 20 mg/d, 11 patients with 30 mg/d, 12 patients with 40 mg/d and 2 patients with 60 mg/d. With respect to the base characteristics including gender, age, presenting symptoms, laboratory and imaging results, there was no significant difference in administered dose of prednisone. During a clinical follow-up period of 6 months, 37/38 (97%) patients achieved clinical response. Symptomatic response after 1, 3 and 6 months of treatment was not associated with doses of prednisone. Treatment response according to imaging studies and laboratory parameters was also comparable. There was no significant difference in worsening of glucose tolerance.
Conclusions: Symptomatic, radiological and biochemical improvement was comparable for AIP patients treated with variable induction doses of prednisone. Based on these retrospective data it may be questioned whether high dose prednisone therapy is truly indicated in patients presenting with AIP.

Surgical treatment of choledochal cysts in children and adults: a single-center experience in 83 patients

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Choledochal cysts (CdC) are rare congenital dilatations of the bile ducts that are considered pre-malignant. Todani's classification is mostly used to characterize CdC; type I (extrahepatic dilatation) and IVa (extra- and intrahepatic dilatation) are most common. Type V indicates intrahepatic cysts only. Treatment consists of complete excision of the cystic dilatation with Roux-en-Y hepaticojejunostomy (HJ). For type IVa and V cysts featuring intrahepatic extension, excision combined with left or right hemihepatectomy is commonly advised. The aim of this study was 1 to evaluate presenting symptoms of patients with CdC in the pediatric and adult population.2 to evaluate outcome and complications in patients with Type IVa and V CdC, in whom excision was performed without liver resection. Medical records of 83 patients who had undergone resection of CdC were retrospectively analyzed from January 1973 to January 2011 (41 children, 42 adults; 22 male, 61 female). Children and adults had a median age of 4.6 (range 0-17) and 40 years (range 19-70), respectively, at time of surgery. Children presented with abdominal pain (75%), jaundice (63%), nausea/vomiting (39%), hepatomegaly (34%) and weight-loss (2%). Symptoms in adults were abdominal pain (100%), jaundice (17%), and weight-loss (16%). Gallstones were present in 34% of children and 14% of adults. CdC was classified as: Type I: 62 patients, Type II: 2, Type III: 2, Type IVa: 12 and Type V: 5 patients. All patients underwent extrahepatic cyst resection including 16 of 17 patients with type IVa or type V CdC with no additional hemihepatectomy. One patient with type V CdC required a left hemihepatectomy because of multiple cystic lesions and one patient with type IVa CdC was intra-operatively diagnosed with a bile duct carcinoma and underwent (R2) resection. Mean follow-up of remaining 15 patients with type IV and type V CdC treated by extrahepatic resection was 4,9 years (1-10 years). In these patients, no signs of tumor formation were detected. Postoperative morbidity was 10.8% among 42 adults and 4.8% in 41 children (recurrent cholangitis, HJ stenosis, perforation of colon after percutaneous drainage, ileus, intra-abdominal fluid collection, and wound infection). There were two postoperative deaths (mortality 2,4%): one child with type I CdC due to respiratory failure and one adult patient with type IVa CdC due to migration of a biliary stent causing portal vein injury and bleeding. Children with CdC more often presented with jaundice, gallstones and hepatomegaly. Cyst excision with biliary reconstruction is safe treatment in children and adults. Malignant transformation was not found.

Outcomes of liver resection for hepatocellular adenoma and focal nodular hyperplasia; results of a prospective trial

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Background: HCA and FNH are rare, benign liver lesions of which diagnosis and management generate confusion. Resection for HCA >5cm is recommended because of risk of bleeding and malignant transformation, whereas FNH is only resected because of symptoms. The aim of this study was to assess selection for and outcome of resection of lesions suspicious of hepatocellular adenoma (HCA) or focal nodular hyperplasia (FNH).Methods Between January 2008 and July 2011, 111 consecutive patients with suspicion on FNH or HCA >2cm based on imaging studies were included. All patients underwent pre-operative Gd-EOB-DTPA magnetic resonance (MR) imaging. Liver resections were classified as major: >3 segments, or minor: <3 segments, including laparoscopic and local excisions. Histological diagnosis was used as standard of reference. Abdominal symptoms, postoperative morbidity (Dindo/Clavien classification), mortality, and relief of symptoms were scored. Results In all 111 patients (4 male, 107 female; mean age 38years), the following preoperative diagnoses were made after MR imaging: HCA (n=44), FNH (n=59), HCA+FNH (n=4), and 4 other diagnoses. 46 patients were selected for resection because of diagnosis HCA>5cm (n=29), symptomatic FNH, or strong wish of the patient (n=15). Mean lesion size was 7,9 cm (SD 2,5; 2,5-25 cm). 28/46 patients presented with complaints. Types of resection included 36 (78%) minor (including 9 laparoscopic resections), and 10 major resections. Overall, the following postoperative complications were recorded: Grade I: 7, Grade II: 4, Grade IIIa: 2, Grade IIIb: 1, Grade IVa: 1. There was no mortality. Preoperative diagnosis was confirmed microscopically in 28/29 (97%) patients with HCA (1 hemangioma), and 15/15 (100%) patients with FNH. 26 (90%) patients with symptoms showed improved scores 3 months postoperatively.
Conclusions: Patients with suspicion on HCA or FNH were accurately diagnosed and selected for resection on the basis of MR imaging and symptoms. Most lesions (78%) required minor resection with relief of complaints in most patients (90%) with symptoms.

Prospective evaluation of the incidence and prevalence of exocrine pancreatic insufficiency in patients with irresectable pancreatic adenocarcinoma

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Weight loss in cancer patients may be caused by primary and secondary tumour effects. In pancreatic cancer, additional weight loss and malnutrition may be due to the development of exocrine pancreatic insufficiency (EPI). However, the presence of EPI is frequently overlooked, because the main focus is directed towards possible cancer treatment. So far, the frequency of EPI in pancreatic cancer is unknown. Therefore, we assessed the prevalence of EPI in patients with irresectable pancreatic adenocarcinoma. In a prospective cohort study we included all patients with irresectable pancreatic adenocarcinoma, who were referred to our tertiary referral center between March 2010 and November 2011. Patients were followed until 6 months after inclusion or death. Each month, the pancreatic function was evaluated, both exocrine (by means of a fecal Elastase-1 concentration (FEC); normal value ≥ 0.2 mg/g) and endocrine. Also, a short questionnaire was completed to search for symptoms of steatorrhea. When EPI was present, pancreatic enzyme (PE) treatment was commenced.Seventeen patients were included, of which 24% were male with a median age of 71 years (range 47-79). Three patients (18%) were inoperable based on radiological imaging. The other 14 patients (82%) were proven irresectable during diagnostic surgery, of which 10 (59%) received bypass surgery. The median tumour size was 2.7 cm (range 1.7-5.1). The tumour was located in the pancreatic head in 13 cases (77%), in the corpus area in 2 (12%), and 2 patients (12%) had an ampullary tumour. The median follow-up was 3 months (range 1-6). EPI was present at diagnosis in 12 cases (71%), of which 7 suffered from steatorrhea-related symptoms. In three additional patients (18%), EPI developed during follow-up, after a median of 1 month (range 1-2), Diabetes was present in 12 (71%) cases, all from the time of diagnosis.The majority of patients with pancreatic cancer are already exocrine insufficient when pancreatic cancer is diagnosed and within a few months almost all have developed an exocrine insufficiency. Clinical signs of steatorrhea, however, are less frequently observed, which is probably due to a reduced fat intake of these patients. To improve quality of life and to prevent additional weight loss and malnutrition, attention should be given to diagnosing and treating EPI, even in the absence of steatorrhea-related symptoms. This is of particular importance in patients who receive (neo) adjuvant cancer treatment. Given the very high prevalence of EPI, routine enzyme treatment should be considered at diagnosis.

Tumor progression after preoperative portal vein embolization

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The aim of the study is to evaluate tumor growth in a series of patients undergoing liver resection after portal vein embolization (PVE). PVE is used to increase volume of the future remnant liver (FRL) in patients considered for liver resection. PVE induces atrophy of the embolized liver segments, and compensatory hypertrophy of the contralateral liver, resulting in increased volume of FRL. Although there are no solid data, literature suggests that PVE enhances tumor growth after PVE because of the induction of liver regeneration. PVE was performed in 47 patients with liver tumors between 2004 and 2011 in our center. Among these, 28 PVE-patients diagnosed with colorectal metastases (CRM) were compared with a non-PVE/CRM control group of whom 30 had two CT-scans preoperatively. Tumor volume (TV) and tumor growth rate (TGR, mL/day) were measured by CT volumetry. Also, patients with newly diagnosed tumors in the FRL after PVE were analyzed. Mean TV increased significantly after PVE. The median TGR of PVE patients was 0.53 mL/day (range -4.24–8.00) vs 0.09mL/day (range -5.01–8.74; p=0.03) in non-PVE patients. TGR was 0.15 (range -3.79–1.00)mL/day before PVE, and 0.85 (range -1.46–4.67)mL/day after PVE in the same patients (p=0.08). Seven (25.0%) patients showed new tumor lesions in the FRL after PVE. Three of these patients (10.7%) were deemed unresectable after PVE for this reason. Survival was significantly better for non-PVE/CRM patients with a 3-year survival rate of 77% versus 26% in patients with CRM undergoing PVE (p<0.001). TV and TGR were increased after PVE in the majority of our patients. Our study also showed that PVE potentially induces new tumor in the FRL. Short intervals as well as interval chemotherapy between PVE and resection are therefore advised.

PET/CT using ^{18}F-fluoromethylcho to detect hepatocellular carcinoma and assess extent of the disease

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Background: Diagnosis of HCC primarily entails imaging, including MR, multiphase-CT and ultrasound. Positron emission tomography (PET) with the glucose (FDG) tracer has shown additional value in the detection of metastatic disease in several tumors, but is not sensitive for HCC. The aim of this study was to assess the usefulness of PET using the ^{18}F-fluoromethylcho tracer (^{18}F-FCH) for detection of HCC and evaluation of extent of the disease. Methods As of December 2010, 21 patients with HCC >1 cm were included (mean age 62y; range 47-79y). Fifteen minutes after iv injection of ^{18}F-FCH a whole-body PET/CT was performed. All patients underwent a baseline-PET prior to treatment, 3 patients underwent a control-PET after treatment, and 2 underwent a follow-up-PET after 3-6 months. Standard of reference for diagnosis was two imaging studies (MR, CT, or ultrasound) if histopathological diagnosis was not obtained. The standardized uptake value (SUV) of the lesion and surrounding tissue were assessed, and SUV-ratios calculated. ^{18}F-FCH PET scan was considered positive if the SUV-ratio exceeded 1.15. Results Standard diagnostic work-up revealed 38 hepatic lesions in 21 patients. In 35/38 lesion (92%, CI 79-97%) the ^{18}F-FCH PET scan was positive (SUV-ratio 2.06 (±0.67)). Standard diagnostic imaging to assess metastatic disease showed 6 suspicious lesions in lung or abdomen (all PET positive). Additionally, 1 abdominal lesion, 4 lung and 2 skeletal lesions were found PET positive and in retrospect also recognized on standard diagnostic imaging. Finally, 1 lymph node and 2 skeletal lesions were found positive on PET and remained undetected on standard imaging, but were proven to be HCC during follow-up. Three patients underwent follow-up PET. Progressive/metastatic disease was detected by ^{18}F-FCH PET in lung and abdomen of 2 patients, confirmed by histo-pathology or additional imaging. Overall, if based on the ^{18}F-FCH PET scan, staging was changed in 7/21 patients (33%), possibly changing treatment.
Conclusions: These results show promising results in detection of HCC using ^{18}F-FCH PET/CT, with possible implications for staging and treatment. ^{18}F-FCH PET/CT may therefore be of value as additional non-invasive imaging tool for evaluation of HCC, including metastatic disease, treatment response, and follow-up.

The diagnostic value of the double duct sign in patients with a periampullary lesion

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This study aimed to evaluate the diagnostic means of a double duct sign in patients with a periampullary lesion. A search was performed to indentify all patients diagnosed with a periampullary lesion from January 1987 through July 2011. A total of 228 patients were eligible for inclusion in this study. Factors analyzed by two independent observers included patients' characteristics, histological diagnosis of the tumor biopsy, width of the common bile duct and the main pancreatic duct, the level of bilirubin and the final clinico-pathological diagnosis. Of the 228 included patients, 134 patients were given the diagnosis carcinoma on biopsy and 94 patients were given the diagnosis dysplasia. The imaging of both ducts (i.e. the common bile duct and the main pancreatic duct) could be assessed in 182 patients, among them the imaging of 105 patients could be matched with the histological diagnosis. On final clinico-pathological diagnosis, 103 of the 105 patients were diagnosed with a malignancy, of which 74 had a double duct sign (71.8%). In patients with a dysplasia on biopsy, imaging was accessible in 77 of the 94 patients. On final clinical diagnosis 39 of the 77 turned out to have a carcinoma, of which 28 patients had a double duct sign (71.8%). In patients with high- or low-graded dysplasia (38 patients), 10 patients had a double duct sign (26.3%). This study demonstrates that a double duct sign can be used as an additional predictive marker for malignancy of a periampullary lesion.

Factors determining long-term survival after HIPEC

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Cytoreductive surgery combined with heated intraperitoneal chemotherapy (CRS-HIPEC) is the only potentially curative treatment option for various peritoneal-surface malignancies. Since 1995, CRS-HIPEC has been offered as a treatment for peritoneal surface malignancies of colorectal and appendiceal origin in the Netherlands. No series have been presented with a minimum of ten-year follow-up. Factors determining the prognosis of patients who survived the first five years after CRS-HIPEC have not yet been studied. Purpose of this study was to determine prognosis in patients five years after CRS-HIPEC and identify predictors of survival once five-year follow-up as been completed. Until May 2001, 126 patients underwent CRS-HIPEC for peritoneal-surface malignancies of colorectal and appendiceal origin. Their clinico- pathological and follow-up data were prospectively collected and analyzed. The following data were collected; gender, T-stage, N-stage, synchronous presentation of the peritoneal surface malignancy, differentiation grade and location of the primary tumor. Ronnett's classification was used to classify mucinous peritoneal surface malignancies into dissiminated peritoneal adenomucosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA). Non-mucinous (<50%) peritoneal surface malignancies were scored as peritoneal carcinomatosis (PCA). Residual tumor at the end of CRS-HIPEC was scored according to thickness; no residual tumor as R1, if less then 2.5mm as R2a or R2b if over 2.5mm. Survival rates were calculated using the Kaplan-Meier method. The relationships between various variables and survival were calculated using uni-variable Cox proportional-hazard models. If complete cytoreduction was accomplished, five- and ten-year overall survival rates for DPAM were respectively 62 and 54%. For PMCA they were 41 and 24%. For PCA they were 21 and 14%. For the whole group gender, histological classification of the peritoneal surface malignancy, extent of disease and result of cytoreduction were identified as significant predictors of survival. After surviving the first five years after treatment only histological classification of the peritoneal surface malignancy and extent of disease remained significant prognostic factors for survival. After CRS-HIPEC most important predictive factors are histological classification of the peritoneal surface malignancy and extent of disease, even in the long run. Patients treated for PMCA and PCA alive five years after CRS-HIPEC, still have a 40% chance of cancer-related death within the next five years. Patients treated for DPAM have a much lower risk of cancer related death (13%). Solely based on survival rates, one could argue whether to continue follow-up five years after CRS-HIPEC for DPAM.

Contrast Enhanced abdominal Ultrasound in IBD. Comparison with Ileocolonoscopy and MR Enterography

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Contrast-Enhanced Ultrasound (CE-US) as a diagnostic tool in IBD may be a patient-friendly, easy applicable and less costly alternative for endoscopy and MR Enterography. CE-US measures tissue perfusion density which reflects the intensity of inflammation. We compared quantitative parameters of contrast-enhanced ultrasound (CE-US) examination of the small bowel with endoscopic inflammatory activity and findings at Magnetic (MRE) in patients with small bowel Crohn's disease. We prospectively evaluated 46 patients with Crohn's disease in the distal ileum, performing ileocolonoscopy followed within 14 days by CE-US and MRE. The radiologists were blinded for the endoscopic disease activity. Standardized ultrasound examination, colour-coded duplex sonography and CE-US of the small bowel was performed using Sonovue ® . Contrast-enhanced sonographic perfusion maps were generated to derive the peak intensity (PI) and the time to peak (TTP), by using the quantification software Qontrast®. We scored the endoscopic disease activity in the ileum as: none, moderate (aphtous ulcers with normal mucosa between lesions, or diffuse aphthae) and severe (large ulcers with diffuse inflamed mucosa, nodule and/or stenosis). The maximum enhancement at MRE was similarly scored as none, moderate and severe. The endoscopic disease activity was scored in 46 patients as no lesions: 4 patients; mild:14 patients; severe: 20 patients and stricturizing disease: 8 patients. A peak intensity value of 10% at CE-US had an overall sensitivity and specificity of 100% in predicting any inflammation at endoscopy. For the MRE the overall sensitivity and specificity were, 80% and 100%, respectively. A peak intensity value of 30% had a sensitivity of 85,7 % and 80% in the prediction of moderate or severe grade of inflammation at endoscopy, respectively. The enhancement grade at the MRE showed a sensitivity of 50% and 65% in predicting moderate and severe inflammation at endoscopy, respectively.
Conclusions: Quantitative bowel enhancement of the terminal ileum obtained by using CE-US highly correlates with severity grade of inflammation determined at endoscopy. CE-US is more sensitive than MRE in detecting moderate and severe inflammation of the small bowel in Crohn's disease.

Myosin Vb controls the apical localization and activation of ezrin in human enterocytes, which is inhibited in Microvillus Inclusion Disease

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Background: Microvillus inclusion disease (MVID) is a rare enteropathy in neonates that is characterized by congenital diarrhea and the inability to absorb nutrients. Villus atrophy and, at the cellular level, loss of brush border proteins and microvillus atrophy are typically observed. Recently, mutations in the MYO5B gene have been identified in MVID patients. However, the pathogenesis of the disease remains unknown. Here we have investigated in MVID enterocytes the localization and activation of ezrin, a protein that is essential for microvillus formation in enterocytes by linking the actin cytoskeleton to apical plasma membrane proteins. Methods: Small intestinal biopsies of MVID patients and age-matched control patients were subjected to immunofluorescent labeling, laser scanning confocal microscopy and Western blot analyses to determine the localization and activation of ezrin and the organization of actin in MVID enterocytes. Knockdown of myosin Vb using shRNA technology was performed in Caco-2 cells to address a causal relationship between MYO5B and phenotypes observed in MVID enterocytes.
Results: In control enterocytes, ezrin and its Thr567-phosphorylated (activated) form localize exclusively at the apical brush border where they colocalize with apical actin filaments. By contrast, in MVID enterocytes, ezrin and Thr567-phosphorylated ezrin are mislocalized to the cytoplasm, while the fraction of Thr567-phosophorylated ezrin is significantly reduced. In agreement, apical actin organization is severely perturbed in MVID enterocytes, and this correlates with the severity of microvillus atrophy observed between MVID patients. Knockdown of myosin Vb by RNA interference in human intestinal epithelial Caco-2 cells mimics the ezrin phenotype observed in MVID enterocytes. In retrospective analyses of MVID biopsies we identify villus fusions, a characteristic of ezrin-KO mice, in the MVID intestine.
Conclusions: Our data demonstrate that MYO5B loss-of-function in MVID enterocytes and an intestinal epithelial cell inhibits the apical localization and activation of ezrin, a key protein in microvillus formation as well as villus development. These effects are likely to contribute to the greatly reduced absorptive surface area in the MVID small intestine. This is the first demonstration of (a part of) the cellular mechanism(s) via which MYO5B mutations cause MVID.

Transanal endoscopic microsurgery: a retrospective multicenter analysis of patients with a pT2/pT3 cN0M0 rectal carcinoma

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Transanal endoscopic microsurgery (TEM) is a technique used as a treatment for large rectal adenomas. In cT1 rectal carcinoma total mesorectal excision (TME) is the standard surgical treatment. However, TEM has also been implemented in the treatment of selected malignant rectal tumors. Its current use is mainly restricted to well or moderately differentiated T1 tumors. The transanal endoscopic approach has proved to have a lower morbidity rate compared to the TME in pT1 rectal tumors. Due to staging errors an assumed T1G1/2 cN0M0 tumor treated with TEM sometimes is actually a pT2 or more invasive tumor at pathology. Standard procedure then would be additional surgery (completion TME) which is associated with higher morbidity, a mortality of 4% and therefore has an assumed negative impact on patients' quality of life. Because of this, some patients with a pT2 or more invasive rectal tumor choose a watchful waiting policy instead of additional TME, despite adverse histopathological features. The assumption is that these patients have worse oncologic and non-oncologic outcomes compared to patients who underwent TEM with completion TME (TEM+TME). This study was designed as a retrospective multicenter, observational cohort study in five tertiary referral centers comparing TEM to TEM with completion TME. Patients with a primary pT2/pT3cN0M0 rectal adenocarcinoma treated with TEM were included. The TEM alone group consisted of 40 patients and the group TEM with completion TME consisted of 33 patients. Possible confounding was corrected performing Cox regression analysis. At base significant difference was found in mean age between both groups (respectively 79 years in the TEM group and 63 in the group TEM+ TME). The median follow-up was 30 and 32 months respectively. In the TEM group the recurrence rate was 28% (11 patients) compared to 12% (4 patients) in the group TEM + TME (p = 0.106). The Hazard Ratio (HR) of 1.49 (CI 0.24-9.36) showed no significant difference between both groups regarding recurrence risk. There was also no significant difference in development of distant metastases (p = 0.74) between both groups. The overall 3-year survival was 63% in the group TEM and 92% in the group TEM+TME respectively. A Cox regression analysis was performed. After correction for confounding the HR (1.69, CI: 0.47-6.08) showed no significant difference between both groups. The disease specific 3-year survival was 91% in the TEM group versus 95% in the TEM+TME group (p = 0.25). From an oncologic perspective TEM in pT2/3cN0M0 rectal tumors is clearly inferior to TEM+TME. However, it could be considered with palliative intent in old and comorbid patients.

Radiofrequency ablation combined with endoscopic resection for Barrett's esophagus with early neoplasia in 132 patients: results of a prospective European multicenter study (EURO-II)

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Radiofrequency ablation (RFA) with prior endoscopic resection (ER) for removal of focal lesions has proven highly effective for Barrett's esophagus (BE) with high-grade dysplasia (HGD) or early cancer (EC) in a number of small-sized single center studies. We prospectively evaluated this approach for BE with HGD/EC in a multicenter setting. Investigators from 13 European centers with expertise in BE-neoplasia management were uniformly trained at the coordinating site. At each site the first 4 RFA cases were supervised by the principal investigator, a study monitor attended all treatments and first follow-up (FU). Central pathology review of all ER/biopsies was performed at the coordinating site. Pts with BE≤12 cm and HGD/EC were included. Visible lesions were removed with ER, followed by biopsy to exclude residual EC. Subsequent RFA was scheduled every 2-3 mo until clearance of BE achieved with max. 5 RFA sessions allowed. Escape treatment was permitted for residual BE after RFA (APC for islands <5mm, ER for islands >5mm or suspicious lesions). FU endoscopy was scheduled at 3-9 mo after the last treatment, with biopsies (4Q/2cm) from neosquamous epithelium (NSE) and <5mm distal to the neo-Z- (gastric cardia). Endpoints were eradication of neoplasia (CR-neo) and intestinal metaplasia (CR-IM); and durability of CR-neo/CR-IM at 9-mo FU.132 pts (107M, mean 65yrs, median BE C3M6) underwent ER (en-bloc n=63,piecemeal n=56) with worst pathology: EC (n=78), HGD (n=31), LGD (n=7), no dysplasia (n=3); or no-ER (n=13). Worst grade post-ER/pre-RFA: HGD (n=36), LGD (n=45), no dysplasia (n=51). By Dec-11 5 pts were still under treatment, 7 discontinued due to unrelated causes. After a median of 3 (3-4) treatments, including ER (n=12) or APC (n=14), per intention-to-treat analysis (counting drop-outs as failures) CR-neo was reached in 115/127 (91%), CR-IM in 112/127 (88%) pts. In a per-protocol analysis (censoring all drop-outs) CR-neo/CR-IM were achieved in 96% and 93% respectively. Of 5 CR-neo failures 1 was referred for surgery (T1sm1G2 cancer), 4 pts are being treated endoscopically (out-of-protocol). CR-neo was maintained in 99/100 pts reaching the 9-mo endpoint; in 1 pt a small island with focal HGD was treated with APC. IM upon single biopsy recurred in 1 pt without visible BE (1,974 NSE biopsies analyzed); focal non-dysplastic IM of the cardia was detected in 11 pts at single FU; none of which required re-treatment. This is the largest prospective multicenter trial on RFA combined with ER for treatment of HGD/EC in BE. Our outcomes suggest that this combined approach is highly effective and durable for eradication of neoplasia in the majority of patients.

The relation between stress, microscopic inflammation and visceral sensitivity in patients with irritable bowel syndrome

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Repeated exposure to stress leads to mast cell degranulation, microscopic inflammation and subsequent visceral hypersensitivity in animal models. To what extent this pathophysiological pathway plays a role in patients with the irritable bowel syndrome (IBS) has not been properly investigated. The aim of this study was to assess the relationship between visceral hypersensitivity, microscopic inflammation and the stress response in IBS.Microscopic inflammation of the descending colonic mucosa was evaluated by immunohistochemistry in IBS patients and healthy volunteers (HV). Rectal sensitivity was assessed by a barostat study using an intermittent pressure-controlled distension protocol. Salivary cortisol to a series of 3 psychological stress tests (i.e. stroop test (color-word conflicting test), mirror tracing test and public speech test) was measured to assess the stress response in a subgroup of patients. Dpeak cortisol levels, expressed as the maximal increase from baseline, was calculated (median (range), ug/ml). 66 IBS patients (74% female (F), age 38 ± 2 yr) and 20 HV (65% F, 31 ± 3 yr) were included in this study. Of all IBS patients, 52% (n=33) were considered visceral hypersensitive to rectal distension (i.e. threshold of discomfort <24 mm Hg above MDP). In IBS, mast cells (IBS: 186 ± 10 vs. HV: 370 ± 39 / mm^2, p<0.001) CD8 T-cells (IBS: 388 ± 28 vs. HV: 526 ± 50/ mm^2, p=0.02) and macrophages (IBS: 729 ± 64 vs. HV: 1261 ± 146/ mm^2, p<0.003) were decreased . Similarly, l free light chain (FLC) positive mast cells were decreased (IBS: 1 (0-34) vs. HV: 7 (0-33) /mm^2, p=0.004), but not IgE- and IgG positive mast cells. There were no differences between hypersensitive and normosensitive IBS patients. No relation was found between any of the immune cells studied and the thresholds of discomfort, urge or IBS symptoms. 22 IBS and 18 HV underwent the stress test. Base and Dpeak cortisol were comparable between IBS and HV (IBS: base 5.3 (22.1), Dpeak 1.3 (18.3); HV: base 6.8 (19.7), Dpeak 1.3 (29.6); NS). The HPA-axis response to stress was not correlated with the number of mast cells (IBS: r=0.41, p=0.1; HV: r=-0.26, p=0.3) or the presence of visceral hypersensitivity.
Conclusions: Our data show a reduction of the number of mast cells, macrophages, T-cells and lFLC positive mast cells in IBS compared to HV. There is no association between the number of these immune cells and the presence of visceral hypersensitivity or abnormal stress response. Our data question the role of microscopic inflammation as underlying mechanism of visceral hypersensitivity, but rather suggest dysregulation of the mucosal immune system in IBS.

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Cholinergic anti-inflammatory pathway in Post-Operative Ileus: role of the spleen and intestinal innervation

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In the last decade, many studies have enlightened the regulatory role of the vagus nerve in diverse immune diseases. The concept of a cholinergic anti-inflammatory pathway emerged and proved to be involved in the modulation of the intestinal inflammatory process taking place in Postoperative Ileus (POI). We recently demonstrated that under endogenous conditions during POI, vagal neurons innervating the inflamed area but also the spleen are activated. In the present study, therefore, we evaluated the modulatory effect of this vagal input to the intestine and the spleen in a model of POI. Selective vagal denervation of the intestine or denervation of the spleen (splenic and direct vagal innervation) was performed in mice 2 weeks prior to Intestinal Manipulation (IM). 24hrs after IM, the spleen and the intestine were collected for cytokine measurement (mRNA, proteins) and analysis of immune cell populations using FACS. For statistical analysis, ANOVA tests were performed. Results are expressed as mean ± SEM.Vagal denervation of the intestine led to an enhanced inflammation in the muscularis externa of mice that underwent IM, as shown by an increased mRNA expression of the pro-inflammatory cytokines IL-6 (10.2 ± 1.9 vs 36.5 ± 1.5; pË,0.05), IL-1b (16.1 ± 3.5 vs 38.2 ± 1.8; pË*ƒ*0.05), TNFa (12.7 ± 2.4 vs 33.6 ± 1.8; pË*ƒ*0.05). Denervation of the spleen did not significantly affect the level of pro-inflammatory cytokines in the inflamed intestinal tissue. IM led to a decrease in the intestinal protein level of IL-10 (1 ± 0.04 vs 0.78 ± 0.09; pË,0.05) which was abolished by spleen denervation. Interestingly, IM also triggered a decrease in the number of splenocytes (by 26%) associated with a 25% decrease in spleen weight. This reduction in splenocytes was abolished in spleen denervated animals. IM led to a decrease in the mRNA expression of the homeostatic chemokine CCL19 (20.4 ± 2.7 vs 11.1 ± 3.3; pË,0.05). This decrease was abolished in spleen denervated animals indicating that splenic innervation may influence lymphocyte trafficking in the spleen during POI. In the present study, we demonstrated that the endogenous vagal activation specifically targeting the inflamed zone (i.e. the small intestine) provides an anti-inflammatory input to the inflamed intestine. This study also shows for the first time that the spleen responds to a local/confined intestinal inflammation, an effect mediated by the splenic innervation. The exact contribution of the spleen in the modulation of the intestinal inflammation however remains unclear and needs to be further investigated.

Esophageal electrical tissue impedance spectroscopy can detect esophageal permeability changes in gastroesophageal reflux disease during upper endoscopy

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Introduction: Esophageal barrier function might be impaired in gastroesophageal reflux disease(GERD). Permeability can be assessed by measuring transepithelial electrical resistance (TEER) and fluorescein flux over esophageal mucosa mounted in Ussing chambers. However, these are time-consuming procedures, not suitable for clinical practice. Electrical tissue impedance spectroscopy (EIS) measures extra- and intracellular resistance of tissue and is performed in vivo using a probe advanced through the working channel of an endoscope. We hypothesized that esophageal permeability changes are present in the mucosa of GERD patients, and that these changes are accompanied by a change in extracellular resistance levels in vivo. Methods: Twelve patients with reflux esophagitis grade A-B and 7 healthy volunteers were included. During upper endoscopy EIS measurements were performed in 4 quadrants at 5 cm proximal to the gastroesophageal junction at macroscopically uninflamed mucosa. At the same locations, 4 biopsies of esophageal mucosa were obtained and transferred to Ussing chambers. TEER was calculated at baseline, and transmucosal fluorescein flux was measured at periodic intervals during a 2-hour period. Transmucosal fluorescein flux occurs through passive paracellular diffusion, area under the curve of the total 2-hour period was calculated Results: Extracellular mucosal resistance from GERD patients, measured in vivo by EIS, was significantly lower (5354 Ωm, IQR 2450-8567) than extracellular mucosal resistance from controls (10256 Ωm, IQR 7216-12416, $p<0.05$). Transmucosal fluorescein flux in Ussing chambers was significantly higher in biopsies from GERD patients compared to biopsies from controls (area under the curve 290 umol/cm^2/2h versus 105 umol/cm^2/2h, $p<0.05$). In with this, base TEER measurements tended to be lower in biopsies from GERD patients than those in biopsies from controls, 79 Ωcm^2 (IQR 74-100) versus 113 Ωcm^2 (IQR 71-124) however this did not reach significance. There was an excellent negative correlation between TEER and fluorescein flux (Spearman r -0.80, $p<0.001$). Extracellular resistance measured by EIS also correlated negatively to transmucosal fluorescein flux (Spearman $r=-0.64$, $p<0.005$).
Conclusions: Macroscopically non-inflamed esophageal mucosa from patients with GERD is characterized by a decreased transepithelial electrical resistance and an increased esophageal paracellular permeability compared to mucosa from healthy volunteers. Electrical tissue impedance spectroscopy can be used to detect permeability changes in a clinical setting and may be helpful to promptly characterize potential GERD patients during endoscopy.

Sensation of stasis is poorly correlated to impaired esophageal bolus transport

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Background: It is unclear what causes the sensation of dysphagia in patients with non-obstructive dysphagia. Furthermore, it is unknown how many of these patients have impaired bolus clearance and/or abnormal esophageal motility as assessed with fluorography and high-resolution manometry (HRM). Methods: Twenty healthy volunteers and 20 patients with dysphagia underwent HRM and concurrent videofluoroscopy. Each subject swallowed 5 liquid barium and 5 solid barium boluses, and esophageal contraction parameters and bolus transport were evaluated. After each swallow, subjects reported if they perceived incomplete bolus passage. A stasis score was used to quantify the degree of stasis on videofluoroscopy. Results: Stasis of liquid barium boluses occurred in patients in 3.5 [2-5] of 5 swallows, while in the controls 2 [0-4] of 5 swallows were incompletely cleared (p=0.07). Both in patients and controls most of the swallowed solid boluses were incompletely cleared (patients 4.5 [3-5] of 5 vs controls 4 [4-5] of 5, p=0.9). During liquid bolus swallows, dysphagia was much more frequently reported by patients (1 [0-3] of 5) than by controls (median 0 [0-0]), p=0.003). Likewise, dysphagia during solid bolus swallows was more frequently reported by patients than by controls (3 [2-4] of 5 swallows vs. 0.5 [0-2], p=0.001). Using the stasis score's cut-off value of ≥3 as the definition of unsuccessful bolus transit, the sensitivity of dysphagia for incomplete liquid bolus swallow was 42.2% in patients and 4.9% in controls (p=0.002), whereas the specificity of dysphagia was 77.8% in patients and 96.6% in controls (p=0.002). For solid bolus swallows, the sensitivity for stasis was 67.5% in patients and 23.5% in controls (p=0.002), whereas the specificity was 65.0% in patients and 89.5% in controls (p=0.002). The sensitivity of dysphagia was higher for solid bolus stasis than for liquid bolus stasis, both in patients and controls (both p=0.028), whereas the specificity of dysphagia was higher for liquid bolus stasis than for solid bolus stasis, in both groups (both p=0.028). Significant associations between stasis score of solids and esophageal manometry parameters were found for transition zone length, contraction amplitude, IRP, DCI and IBP, whereas no correlation was found between the stasis score for liquids and manometric parameters.
Conclusions: Both in patients and controls, the symptom dysphagia does not correlate well with stasis of liquids or solids, or with HRM parameters. These findings indicate that esophageal hypersensitivity rather than incomplete bolus clearance is the most important pathophysiological mechanism in patients with non-obstructive dysphagia.

Effect of Transoral Incisionless Fundoplication on the occurrence of transient lower esophageal sphincter relaxations (TLESRs) in GERD patients

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Transient lower esophageal sphincter relaxations (TLESRs) are considered the major mechanism causing gastroesophageal reflux. A reduction in rate of TLESRs and percentage of TLESRs associated with reflux has been shown after conventional fundoplication, and it is thought to contribute to the antireflux effect of the procedure. In this study we aimed to evaluate the effect of Transoral Incisionless Fundoplication (TIF), a new endoluminal treatment of GERD, on the mechanisms of reflux, especially on the role of TLESRs. In 14 GERD patients with abnormal acid exposure and hiatal hernia ≤2 cm (10 males; mean age 42, range 23-66 yrs) mechanisms of reflux were studied using stationary high-resolution manometry (HRM) and impedance-pH monitoring, before and 6 months after TIF. Patients were given a standardised high caloric liquid meal (480 ml, 960 kCal) directly prior to a 120 min measurement. After 90 min, 500 ml of air was inflated intragastrically, and measurements were continued for an additional 30 min period. This was followed by 24 hr ambulatory impedance-pH monitoring. Six months after TIF, the total number of TLESRs decreased significantly during the postprandial period (pre vs post: 21.4 ± 1.6 vs 12.1 ± 1.2, $p<0.01$). This effect was also present during the 30 min period after air-inflation ($p=0.02$). The number of TLESRs associated with reflux episodes on impedance-pH monitoring also decreased significantly (14.9 ± 1.7 vs 7.6 ± 0.8, $p<0.01$), showing a significant decrease in TLESR-associated liquid reflux episodes ($p< 0.01$). The effect on TLESR-associated gas reflux episodes was not distinct ($p=0.14$). The total number of postprandial reflux episodes decreased as well (24.3 ± 2.6 vs 12.4 ± 1.4, $p<0.01$), showing significant reductions in liquid ($p<0.01$), but not in gas reflux episodes ($p=0.26$). Acid exposure time (pH< 4.0) during 24 hr pH-metry was reduced by TIF (10.8 ± 2.1% vs 7.7 ± 1.6%, $p=0.11$) and significantly reduced in upright position (11.9 ± 2.5% vs 6.8 ± 1.1%, $p=0.02$). Furthermore, the percentage of acid reflux episodes with a duration longer than 5 min decreased significantly ($p= 0.03$). Acid exposure time improved in 71.4% (10/14) patients and normalised (<5.0%) in 42.9% (6/14) patients. Symptom scores (HRQL) improved significantly after 6 months ($p<0.01$).
Conclusion: Transoral Incisionless Fundoplication leads to a significant reduction in the total number of postprandial TLESRs and in TLESRs associated with reflux episodes. This resulted in a reduction of the total number of postprandial reflux episodes and improvement in esophageal acid exposure. Therefore, TIF improves gastroesophageal reflux by affecting TLESRs.

Esophagogastric junction (EGJ) distensibility in GERD patients as measured with an endoscopic functional luminal imaging probe: correlation with endoscopic and pH-impedance reflux parameters

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Increased esophagogastric junction (EGJ) distensibility is considered a key factor in GERD permitting increased volumes of reflux across the EGJ. Using an endoscopic functional luminal imaging probe (EndoFLIP), it was shown that EGJ distensibility was greater in GERD patients than in controls. We aimed to assess the correlation between EGJ distensibility and endoscopic and pH-impedance reflux parameters in a homogeneous group of GERD patients. Thirty-one GERD patients with abnormal acid exposure time and hiatal hernia ≤2cm (19 males; mean age 44, range: 21-67 yrs) underwent upper GI endoscopy, EndoFLIP measurement and ambulatory 24hr pH-impedance monitoring. During endoscopy, length of hiatal hernia and qualitative grading of EGJ patency (gastroesophageal flap valve grade according to Hill classification: I-IV) were assessed. Using an EndoFLIP probe with an inflatable bag, EGJ distensibility (cross- sectional area of the diaphragmatic hiatus (CSA)/pressure within bag during distensions; mm^2/mmHg) was measured with 20-, 30-, and 40-mL distensions. Analysis of 24hr pH-impedance measurements included acid exposure time, number of liquid and acid reflux episodes. Correlations between EGJ distensibility, endoscopic and pH-impedance parameters were assessed.EGJ distensibility increased progressively with distending volumes (20 mL: 2.0±0.3; 30 mL: 2.5±0.4; 40 mL: 4.0±0.8; $p<0.001$). Also CSA (mm^2) and pressure within the EndoFLIP bag during distensions (mmHg) increased progressively with distending volumes ($p<0.001$). A significant correlation was found between EGJ distensibility and gastroesophageal flap valve grade at the different distending volumes (20 mL: $r=0.41$, $p=0.02$; 30 mL: $r=0.57$, $p=0.001$; 40 mL: $r=0.60$, $p=0.004$) but not between EGJ distensibility and presence of small hiatal hernia. Mean EJG distensibility was significantly higher in patients with abnormal flap valve (Hill grade III and IV) than in patients with normal flap valve (Hill grade I and II) during 20- and 30-mL distentions ($p=0.02$). Furthermore, a positive correlation was found between EGJ distensibility and number of liquid reflux episodes (20 mL: $r=0.41$, $p=0.03$; 30 mL: $r=0.40$, $p=0.03$; 40 mL: $r=0.41$, $p=0.08$). Acid exposure time and number of acid reflux episodes did not correlate with EGJ distensibility.

Conclusion: In a homogeneous group of GERD patients, esophagogastric junction (EGJ) distensibility as measured by EndoFLIP correlates significantly with endoscopic gastroesophageal flap valve grade and with the number of liquid reflux episodes. Quantifying EGJ distensibility may help to discern subsets of GERD patients with respect to medical, endoluminal and surgical therapies.

Gastric belching and supragastric belching are two distinct pathophysiological entities: A study using combined high-resolution manometry and impedance monitoring

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Background: Supragastric belches, but not gastric belches, are associated with severe belching complaints. However, the exact mechanism of supragastric belching is not known. We aimed to compare the esophageal pressure characteristics during supragastric belches and gastric belches using combined high-resolution manometry and impedance monitoring. Methods: We included 10 patients with complaints of severe and frequent belching. Combined high-resolution manometry and impedance monitoring was performed during 90 minutes after a standardized meal. Results: Nine patients exhibited supragastric belches during the measurement. Eight out of nine patients exhibited a specific pattern of supragastric belches which was characterized by concurrent (i) movement of the diaphragm in aboral direction (median (IQR) displacement: 2 (1-2) cm) and increase in median (IQR) EGJ pressure (20 (10-51) mmHg), (ii) pressure decrease in the esophagus (5 cm: -10.7 (-13.2- -4.3), 10 cm: -9.3 (-12.4- -3.6), 15 cm: -7.7 (-8.3- -5.4) mmHg), (iii) upper esophageal sphincter (UES) relaxation preceding the airflow, (iv) antegrade airflow and (v) increase in esophageal pressure (5 cm: 17.7 (8.5-23.3), 10 cm: 13.2 (5.5-27.3), 15 cm: 20.6 (4.7-36.4) mmHg) and air being forced out of the esophagus in retrograde direction. In contrast, gastric belches were characterized by (i) decreased or unchanged EGJ pressure which was significantly lower than during supragastric belches (0 (-2.5-0) mmHg, $p<0.05$), (ii) significantly higher esophageal pressure or unchanged esophageal pressures, compared to supragastric belches, preceding the esophageal airflow (5 cm: 2.5 (-0.6-5.7) ($p<0.05$), 10 cm: -2.3 (-12-2) (NS), 15 cm: 0 (-4-2.3) ($p<0.05$) mmHg), (ii) retrograde airflow into the esophagus, (iii) common cavity phenomenon characterized by an increase in esophageal pressure (5 cm: 16.3 (5.4-18.3), 10 cm: 14.0 (1.3-18.1), 15 cm: 18.0 (9.3-27.5) mmHg) which was not different from supragastric belches and (iv) UES relaxation after the onset of the retrograde airflow. A specific phenomenon of repetitive supragastric belches but not of repetitive gastric belches was observed in the majority of patients. Notably, one out of nine patients exhibited a different pattern of supragastric belches in which the antegrade airflow was preceded by an increase in pharyngeal pressure up to 250 mmHg and not by a decrease in esophageal pressure.
Conclusions: Supragastric belches and gastric belches are characterized by two clearly distinct esophageal pressure patterns. Movement of the diaphragm in aboral direction, negative esophageal pressure and UES relaxation are essential events in the generation of a supragastric belch.

Clinical examination remains more important than anorectal function tests in patients with constipation to identify treatable conditions

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Introduction: Many patients with chronic constipation are referred for anorectal function tests (AFT) when they fail initial conservative treatment with lifestyle advice and laxatives. Aim: To prospectively investigate the diagnostic potential of AFT in patients with constipation in order to identify treatable conditions. Methods: Between May 2003 and June 2011, all patients with constipation referred to our tertiary referral centre were evaluated by a questionnaire regarding their perianal complaints, physical examination and evaluated according to our AFT protocol including anorectal manometry (ARM) and anal endosonography. Results: In total 136 patients were referred and classified as idiopathic constipation (n=117), neurological disorder (n=14) and others (n=5). Of the 100 women with idiopathic constipation, clinical examination identified 25 (25%) with hypertonia of the pelvic floor (dyssynergic pelvic floor) and 15 (15%) with a rectocele. In 37/100 women, also complaining of impaired evacuation, the yield of rectocele was 15 (41%) and of hypertonia 5 (14%). Of the 17 men with idiopathic constipation, 6 (35%) were identified with hypertonia. Patients with hypertonia were younger (43 vs. 54 years; P=0.003) and could relax less during straining on ARM (61% vs. 91%; P=0.001) compared to patients without pelvic hypertonia. Other ARM measurements showed no differences between patients with evacuation disorders, rectoceles or hypertonia. Anal endosonography showed no internal sphincter hypertrophia.
Conclusion: A potentially treatable condition is found on clinical examination in 40% of women with idiopathic constipation. Impaired evacuation has a high yield for a rectocele. ARM contributes little and should be reserved for selected cases.

Long term course of perianal and anorectal complications in IBD-patients: a single centre inceptive cohort analysis

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Aim: To prospectively evaluate the course of anorectal complains and anorectal function in patients with inflammatory bowel disease (IBD) and perianal lesions.Patients and methods: In the period 1993-2000, 43 Crohn's disease (CD) and 13 ulcerative colitis (UC) patients with perianal complaints underwent extensive anorectal function tests in our tertiary referral centre. Of these, 21 (38%) patients (19 CD patients) were evaluated at base measurement due to fistulous disease. One patient had a temporary ileocolostomy to permit healing of ileorectal anastomosis after total colectomy. They were approached in 2009-2010 to complete questionnaires including Inflammatory Bowel Disease Questionnaire (IBDQ), Perianal Disease Activity Index (PDAI), fecal incontinences grading scales (Vaizey and Wexner) and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF). In case that the patient declined participation, the reason for refusal was documented, and additionally, if consented, complaints were noted.Results: Nine patients (16%) were lost to follow-up, 1 patient (2%) had died, 16 patients (29%) were interviewed by phone and 30 patients (54%) returned the questionnaires of whom 16 underwent anorectal function tests. Median follow-up was 14 years (IQR 25-75: 13-15 years). In 25 of these 46 remaining patients (54%) perianal complaints including faecal incontinence (7), soiling (17) and fistula pain (1) persisted. There were no statistically significant differences between complaints in patients with CD and UC. At follow-up 19 patients (41%) (13 CD; 6 UC) had an ileocolostomy, of whom 11 (58%) still had perianal complaints. Mean IBDQ was as low as 178 (SD 29), consistent with mildly active disease, mean Vaizey was 7 (SD 5), and Wexner was 5 (SD 3). Additionally, 7 patients had complaints of urine incontinence. Of the 16 patients who underwent follow-up anorectal function tests, 2 patients had active fistula, 2 patients anal stenosis and 1 patient Bowen's disease. The PDAI of these patients was 4.4 (SD 2.9). Nine of these 16 had previous fistulous disease.Anal rest and squeeze pressures as well as rectal compliance remained unaltered.
Conclusion: Quality of life of patients with IBD remained low over a very long period and 54% of the patients have persistent mild perianal complaints. Furthermore, 41% had a ileocolostomy of whom 58% still had persisting perianal complaints.

Fecal immunochemical test results in different stages of colorectal cancer: A colonoscopy controlled study

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Background: Most fecal immunochemical test (FIT) screening studies are not colonoscopy controlled and therefore FIT sensitivity and specificity for colorectal cancer (CRC) can not be determined directly. Moreover, FIT screening studies often have a low yield of CRC cases, which makes it difficult to stratify the FIT results per cancer stage. Therefore, accurate data on FIT performance particularly in early stage tumors are lacking.
Aim: To determine the performance of a frequently used FIT at different cut-off levels stratified for stage. Patients and methodsSubjects scheduled for colonoscopy between 2006 and 2010 in five hospitals were asked to perform a FIT (OC sensor®) before elective colonscopy. FIT results were compared to colonoscopy outcomes. Cut-off levels of ≥50, ≥75 and ≥100 ng haemoglobin/ml were used to call a test positive. Primary outcome variables were sensitivity and specificity for all stages of CRC. Results: In 5,836 subjects who underwent complete colonoscopy, 159 (2.7%) were diagnosed with CRC. Fifty-four (34%) were diagnosed with stage I, 45 (28%) with stage II, 44 (28%) with stage III, 16 (10%) with stage IV cancer. Sensitivity of FIT using a cut-off level of ≥50 ng/ml for stage I, II, III and IV CRC was 85.2%, 88.9%, 97.7%, 93.8%, respectively. Sensitivity of FIT using a cut-off level of ≥75 ng/ml for stage I, II, III and IV CRC was 83.3%, 88.9%, 97.7%, 93.8%, respectively. Sensitivity of FIT using a cut-off level of ≥100 ng/ml for stage I, II, II and IV CRC was 81.5%, 88.9%, 93.2%, 93.8%, respectively. Specificities ranged from 82.8% to 87.9% with increasing cut-off levels.
Conclusion: In this large mixed referral population with a high yield of early stage CRC, FIT sensitivity for stage I and II CRC was very good, even at higher cut-off levels.

Gender disparity in colonic tumorigenesis depends on male hormone tumor promotion, not female hormone protection

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Background and Aims: Several large colonoscopy colon cancer screening studies have found a significant sex and age-specific prevalence of advanced adenomas and colorectal cancer in males, with females showing a delayed onset and decreased incidence of advanced lesions. It is thus believed that gender disparity depends on a protective effect of female hormones, since postmenopausal hormonal replacement therapy has been found to protect from colorectal cancer development. Similar to humans, it was previously shown that polyposis in the rat colon (ApcPirc/+) rats show a gender bias, with females having a later onset and reduced tumor burden compared to males. We therefore set out to investigate the contribution of both female and male hormones in the development of colorectal tumorigenesis using two independent models in rats. Methods: We induced tumor precursor lesions that are known as aberrant crypt foci (ACFs) by injection of azoxymethane (AOM) in rats. Additionally, we studied formation of tumors in ApcPirc/+ rats that harbor a genetic mutation predisposing to colorectal tumor formation. Rats were submitted to ovariectomy (OVX) or castration (ORX) and sham operations were performed as control. OVX and ORX operation efficiency was monitored by measuring body weight or hormone levels in serum. For hormone substitution, pellets with estradiol (E2) or the progestin medroxyprogesterone acetate (MPA) or placebo were placed subcutaneously. Results: In female rats, abrogation of endogenous hormone production by OVX did not affect ACF formation in the AOM model ($P = 0.864$) or tumor burden in ApcPirc/+ rats ($P = 0.406$). Additionally, hormonal replacement with E2, MPA or a combination of both did not prove protective in either the ACF model or in ApcPirc rats ($P = 0.455$ and $P = 0.902$ respectively). On the other hand, subjecting male mice to castrations dramatically decreased tumorigenesis in both the ACF model (85.6 vs. 47 $P < 0.01$) and in ApcPirc/+ rats (25.6 vs. 11.2 $P < 0.02$). Conclusions: We show in two independent models for colonic tumorigenesis in rats, that gender disparity in development of colorectal tumors depends on tumor promoting properties that we contribute to male hormones rather than protective anti-tumor effects of female hormones. Since male hormones affect early lesions (ACFs), we conclude that tumor initiation is affected. Our data thus suggest that androgens promote colorectal tumorigenesis.

Lumican and Versican predict good outcome in stage II and III colon cancer

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Background and Purpose: Tumor stroma plays an important role in the progression and metastasis of colon cancer. The glycoproteins versican and lumican are overexpressed in colon carcinomas and are associated with the formation of tumor stroma. The aim of the present study was to investigate the potential prognostic value of versican and lumican expression in the epithelial and stromal compartment of stage II and III colon cancer. Methods: Clinicopathological data and tissue samples were collected from stage II (n=226) and stage III (n=160) colon cancer patients. Tissue microarrays (TMAs) were constructed with cores taken both from the center and the periphery of the tumor. These were immunohistochemically stained for lumican and versican. Expression levels were scored on digitized slides. Statistical evaluation was performed using SPSS.
Results: Versican expression by epithelial cells in the periphery of the tumor, i.e., near the invasive front, was correlated to a longer disease free survival (DFS) for the whole cohort (P=0.01), stage III patients only (P=0.01), stage III patients with microsatellite instable (MSI) tumors (P=0.04) and stage III patients with microsatellite stable (MSS) tumors who did not receive adjuvant chemotherapy (P=0.006). Lumican expression in epithelial cells overall in the tumor was correlated to a longer disease specific survival (DSS) in stage II patients (P=0.05) and to a longer DFS and DSS in MSS stage II patients (P=0.02 and P=0.004).
Conclusion: In the present series, protein expression of versican and lumican predicted good clinical outcome for stage III and stage II colon cancer patients, respectively.

Incidence and potential causes for metachronous colorectal cancer: a 10-year retrospective survey

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Although a number of studies estimated the incidence rates of colorectal cancer (CRC) occurring during post-CRC surveillance, data pertaining to main explanations of these cancers are presently scarce. We therefore examined the incidence and potential explanations of metachronous colorectal cancers (mCRCs) in our everyday practice.
Methods: We reviewed clinicopathologic data of all patients diagnosed with CRC at our university hospital from January 2001 to December 2010. Digital colonoscopy and histopathology records were collected and verified using data from the national pathology database (PALGA) and the Dutch Cancer Registry. Patients with hereditary forms of CRC or inflammatory bowel disease were excluded. Metachronous CRCs were defined as second primary colorectal adenocarcinomas diagnosed at least 6 months after the index CRC. We classified CRCs according to their macroscopic aspect into flat or protruded and according to location into proximal or distal to the splenic flexure. Potential explanations for the occurrence of mCRC were divided into i) potentially missed lesions during surveillance, ii) incompletely resected precursor lesions (i.e. mCRCs developed in the same anatomic segment as a previous polypectomy) or iii) non-compliance with surveillance guidelines. Results: We analyzed 1.232 patients with 1.300 CRCs (mean age 70.2 yrs and 55.2% males). In total, 29 (2.4%) patients were diagnosed with 33 mCRCs (mean age at time of index CRC: 69.2 yrs, range 47-88). The median time between index CRC and diagnosis of mCRC was 49 months (interquartile range: 21-82). Logistic regression analyses, adjusting for age and gender showed that mCRCs were significantly more often <1 cm in size (OR 7.2, 95%CI 2.0-26.4, p<0.01) and had more often a flat macroscopic appearance (OR 2.2, 95%CI 1.1-4.6, p=0.03) than sporadic CRCs. No significant differences were found between mCRCs and sporadic CRCs with regard to location and stage at time of diagnosis. Potential explanations for the occurrence of mCRCs were missed lesions in 17 (59%) cases, incomplete polypectomy in 4 (14%) cases or inadequate surveillance in 8 (27%) cases. In 5 out of the 17 cases in whom mCRCs were related to potentially missed lesions, cancers were diagnosed during the first post-operative colonoscopy, and therefore synchronous lesions could not be ruled out.
Conclusion: In this Dutch population, mCRCs accounted for 2.4% of all CRCs detected and the majority of them could be explained by procedural failure or suboptimal surveillance. Careful colonic examination and adherence to post-CRC surveillance guidelines are mandatory should the quality of colonoscopic cancer surveillance be optimized.

Potential Benefits of Proton Pump Inhibitor Use on Acute Coronary Syndromes: Results of a Decision Analysis

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Gastroprotection by proton pump inhibitors (PPIs) is recommended for patients with an increased gastrointestinal risk profile using low-dose aspirin for cardiovascular (CV) prevention. Co-prescription of PPIs decreases patients' susceptibility for aspirin-induced upper gastrointestinal (UGI) complications, including dyspepsia. This positive effect of PPI co-therapy on UGI complications may result in an increased compliance to low-dose aspirin, resulting in a reduced risk of CV events. We aimed to study the association between PPI use and PPI compliance and the risk of acute coronary syndromes. We used decision-analysis with Markov modeling to calculate the incidence of acute coronary syndromes (ACSs) in 3 treatment strategies for a base-case 60-year-old male receiving low-dose aspirin for primary (assuming 10-year ACS risk of 10%) or secondary CV prophylaxis: (1) aspirin monotherapy; (2) aspirin+PPI co-therapy; and (3) single tablet formulation of aspirin and PPI. We derived 13 probability estimates for the model with a systematic review of the literature and varied each estimate over a wide range in sensitivity analysis. We evaluated a range of relationships between ACS risk, UGI bleeding risk, and aspirin-induced dyspepsia as a function of PPI's impact on aspirin compliance (evaluating the hypothesis that PPI use could potentially improve aspirin compliance). In primary prevention, the model projected that patients on the single tablet formulation had a marginally lower lifetime incidence of ACS (27.9%) vs. aspirin monotherapy (28.8%) and aspirin+PPI (28.5%) ($p<0.01$ in simulation). The number needed to treat (NNT) with aspirin+PPI vs. aspirin alone in order to prevent one additional ACS was 435. The NNT for the single table formulation vs. aspirin was 124. In secondary prevention, patients treated on the single tablet formulation also had a lower lifetime incidence of ACS (67.4%) vs. aspirin alone (68.8%) and aspirin+PPI (68.5%) ($p<0.01$). The NNT with aspirin+PPI vs. aspirin and single tablet vs. aspirin were 385 and 74, respectively. UGI bleeding risk did not influence the relative risk of an ACS among groups. In secondary prevention patients on aspirin+PPI there was a projected 0.12% increase in ACS risk for every 20% decrease in PPI compliance.
Conclusions: Adding PPI therapy to low-dose aspirin resulted in a lower risk of ACS. This association is sensitive to PPI compliance, with the highest effect for the single tablet formulation in patients using low-dose aspirin for secondary prevention. Future research should evaluate whether aspirin compliance varies with PPI use and whether PPIs could indirectly reduce CV outcomes.

Potentially reversible risk factors for peptic ulcer bleeding in average-risk users of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin (ASA)

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Background & Aim: We previously reported that a substantial proportion of NSAID- (60%) and low-dose aspirin (25%)-associated ulcer bleeding occurred in average-risk users. Prevention of ulcer bleeding in these patients is difficult because gastroprotective cotherapy is not routinely required according to current guidelines. We aimed to identify potentially reversible factors for peptic ulcer bleeding in average-risk NSAID and ASA users. Methods: In this single center, case-control study, patients with endoscopically proven peptic ulcer bleeding who used NSAIDs or ASA before hospitalizations were screened for risk factors of ulcer bleeding. Average-risk patients, who were defined as having none or 1 clinical risk factor and no history of ulcer/ulcer bleeding, were recruited. Controls were NSAID and ASA users who did not have ulcer bleeding. Assuming a prevalence of H. pylori infection of 25% among controls, a sample size of 537 cases and 268 controls would be required to detect an odds ratio of 1.7 with 90% power at 5% level of significance. Univariate logistic regression was performed to examine factors potentially associated with ulcer bleeding among NSAID and ASA users separately. Those factors showing a p value of <0.2 were analyzed in the multivariate stepwise (backward) logistic regression model. Results: Between January 2000 and July 2011, we identified 1163 cases (627 NSAID and 536 ASA users) and 659 controls (372 NSAID and 287 ASA users). Average-risk patients with NSAID- and ASA-associated ulcer bleeding were less likely to receive gastroprotective agents before the onset of bleeding (O.R. 0.32, 95% CI 0.23-0.44, P<0.001 and O.R. 0.30, 95% CI 0.22-0.42, P<0.001, respectively). On multivariable analysis, H. pylori infection was a significant risk factor both in the NSAID group (O.R. 2.09, 95% CI 1.52-2.87, P<0.001) and the ASA group (O.R. 2.68, 95% CI 1.91-3.76, P<0.001). Other risk factors in the NSAID group included age >70 (O.R. 3.56, 95% CI 2.55-4.98, P<0.001), male gender (2.83, 2.09-3.84, P<0.001), comorbidity (2.79, 1.29-6.05, P=0.009), and duration of NSAID use ≤4 weeks (2.09, 1.51-2.91, P<0.001). In the ASA group, smoking was the additional risk factor identified other than H. pylori (previous smoking O.R. 1.82, 95% CI 1.28-2.58, P<0.001; current smoking 1.71, 1.04-2.83, P=0.036).
Conclusion: Among average-risk NSAID and ASA users who had none or only 1 clinical risk factor and no history of ulcer/ulcer bleeding, the presence of H. pylori infection significantly increased the risk of ulcer bleeding. Screening for H. pylori in these patients may reduce the burden of NSAID- and ASA-associated ulcer disease.

Use of prophylactic gastroprotective therapy in patients with nonsteroidal anti-inflammatory drug- and aspirin- associated ulcer bleeding

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Backgroumd & Aim: Poor adherence to gastroprotective agents (GPAs) among users of nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin (ASA) is common. To date, there is no data on the utilization of GPAs among NSAID and ASA users complicated by peptic ulcer bleeding. We aimed to study the utilization of GPAs among NSAID and ASA users before ulcer bleeding. Methods: This was a prospective, single-center study. Consecutive patients presenting with ulcer bleeding confirmed by endoscopy between January 2000 and December 2009 were systematically evaluated for exposure to NSAIDs, ASA, and GPAs. NSAID- or ASA-associated ulcer bleeding was defined as exposure to these drugs within 4 weeks before the event. GPAs included proton-pump inhibitors (PPIs), histamine-2-receptor antagonists (H2RAs), and misoprostol. Patients were classified as having high ulcer risk if they had a history of ulcer/ulcer bleeding or ≥2 other risk factors. Results: Between 2000 and 2009, 1093 and 2277 patients had NSAID- and ASA-associated ulcer bleeding, respectively. Overall, 36% of patients in the NSAID group and 29% on the ASA group were prescribed GPAs before ulcer bleeding. 39% of patients in the NSAID group and 75% in the ASA group had high ulcer risk. Among these high risk patients, only 42% in the NSAID group and 31% in the ASA group had received GPAs before ulcer bleeding.
Conclusion: A substantial proportion of high-risk NSAID and ASA users had not received prophylaxis with GPAs before ulcer bleeding. These bleeding episodes were avoidable.

Upper gastrointestinal hemorrhage: Missed opportunities for prevention?

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Introduction: Upper GI hemorrhage is a risky event for patients and also a costly in any healthcare system. Worldwide guidelines have been implemented to prevent upper gastrointestinal hemorrhage in high-risk patients. Our impression is that a low adherence to these guidelines, resulting in many preventable admissions and endoscopic procedures. Aim of the study: 1) Asses prevalence and causes of upper GI bleeding Assess non-compliance due to non-adherence to guidelines. Patients and methods: Consecutive patients with a suspected upper GI hemorrhage were identified via the endoscopy database of our department. Known risk-factors (RFs) (age, history of (bleeding) ulcer, helicobacter pylori (HP) infection, co-morbidity, NSAIDs, anti-platelet- and anti-coagulant therapy) and compliance with proposed guidelines were assessed.
Results: 100 consecutive patients (61 males; mean age 66 (SD 14] yrs) were identified between January 2010 and October 2010 with a suspected upper GI hemorrhage. Endoscopic diagnoses were: Bleeding ulcer (48), varicealbleeding (10), angiodysplasia (6), Mallory-Weiss tear (6), gastritis/duodenitis (15), acid reflux disease (3), other (2), and no focus (10).The distribution of risk factors for upper gastrointestinal bleeding was : 9 no RFs, 20 pts had 1, 25 pts had 2 RFs, and 46 pts had 3 or more RFs. Of all comers with ≥3 RFs, 52% (24/46) did not receive gastroprotection. Moreover, 64% (16/25) of patients with an established ulcer bleeding and ≥3 RFs did not receive gastroprotection.
Conclusion: More that half of pts admitted with a suspected GI hemorrhage did not receive adequate preventive measures representing missed opportunities. This observation suggests that in the last 10 years no improvement in adherence to guidelines for prevention of stomach damage have been made[1].

Hyoscine N-butylbromide does not improve polyp detection during colonoscopy: A double-blind randomized placebo-controlled clinical trial

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Aim: colonoscopy is used for the detection of neoplastic polyps, although a significant miss rate has been reported. Limited data suggest that the administration of the antispasmodic hyoscine N-butylbromide (Buscopan®) during colonoscopy improves polyp detection. We investigated whether the use of 20 mg Buscopan® intravenously during colonoscopy improves polyp detection or removal. Methods: a prospective, double-blind, placebo-controlled randomized clinical trial in a non-academic teaching hospital. Analysis was done on intention-to-treat basis. Patients who were routinely referred and accepted for either diagnostic or screening colonoscopy were invited to participate. Patients were randomized to receive intravenous injection of either 1 ml Buscopan® (n=340) or 0.9% NaCl solution (n=334) when withdrawal from the cecum was started. Endpoints were polyp detection rate (PDR), adenoma detection rate (ADR) and the advanced lesion detection rate (ALDR), 5% trimmed mean number of polyps, mean withdrawal time. Results: 674 Patients were randomized. Cecal intubation rate was 96%. The PDR, ADR and ALDR were 56 versus 60, 30 versus 31 and 14 versus 14 % in the Buscopan® and placebo group respectively (all p-values > 0.25). The means of the total number of detected, removed and harvested polyps per patient were 1.13 versus 1.21, 1.03 versus 1.06 and 0.89 versus 0.89 in the Buscopan® and placebo group respectively (all p-values > 0.37). Mean withdrawal time was 561 versus 584 seconds in the Buscopan® and placebo group respectively (p=0.34). Multivariate analysis demonstrated no effect of Buscopan® on the investigated parameters.
Conclusion: we found no evidence to support the use of Buscopan® during withdrawal of the colonosope to improve polyp detection or removal.

Remotely controlled, small intestinal release of 99mTc-pertechnetate using an ingestible electronic device: the IntelliCap

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We developed an ingestible electronic drug delivery and monitoring device: the IntelliCap, which comprises a 300 µl drug reservoir, a pH- and temperature sensor, a stepper motor, and a transceiver for 2-way real time wireless communication. Data are relayed via a data recorder to a computer. The stepper motor can be remotely actuated to expel the contents from the drug reservoir. We recently showed that the device is safe and well tolerated in healthy subjects. In the current study, we assessed functionality of various components of the IntelliCap and correlated anatomical localization of the IntelliCap based on pH data and nuclear imaging using 99mTc-pertechnetate (^{99}Tc).Ten healthy volunteers were included in the study who ingested an IntelliCap in the morning, stayed in the unit during the day, went home at night and returned to the unit next morning. The drug reservoir of the IntelliCap was filled with ^{99}Tc. After ingestion of the IntelliCap, luminal temperature, pH and status of the drug reservoir were monitored. Static and dynamic nuclear images were obtained at predetermined time intervals and when –based on pH changes- the IntelliCap passed the pylorus and the ileocecal valve. When pyloric passage was confirmed the IntelliCap was remotely actuated to expel 75% of the total volume of the drug reservoir.Temperature and pH profiles of all 10 subjects were recorded from ingestion to excretion or 45 hours – whichever came first. Average data reception fidelity was >95%. Remotely controlled expulsion of ^{99}Tc was successful in 9 of 10 subjects. Pyloric passage based on pH correlated well with passage based on nuclear imaging. Ileocecal passage based on pH could be correlated with nuclear imaging in 9 of 10 subjects. A good correlation was found between pH and nuclear imaging based localization in the ileocecal area. After expulsion of ^{99}Tc from the IntelliCap, both the capsule and the luminally released ^{99}Tc were clearly visualized during nuclear scanning, particularly in the first few hours. In general the capsule seemed to lag behind the released ^{99}Tc. All subjects tolerated the procedure well. No serious adverse events were noted.

Conclusions: During passage through the gastrointestinal tract, the IntelliCap reliably records pH and temperature. As a good correlation is found between anatomical localization based on pH and on nuclear imaging, it is feasible to remotely expel contents from the drug reservoir triggered by pH readings. The IntelliCap may therefore be used to deliver drugs to well defined regions of the gastrointestinal tract.

Correction of hepatosteatosis by hydrophobic iminosugars modulating glycosphingolipid metabolism

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Glycosphingolipids (GSLs)are important constituents of the cell membrane, forming semi-ordered structures called lipid rafts in which specific proteins preferentially reside. Abnormalities in GSLs lead to abnormal cell-cell interactions and cell behavior. Excess of gangliosides, a subset of GSL, has been implicated in the metabolic syndrome. We designed small compound inhibitors that can modulate GSL levels. Oral administration of these so-called iminosugars in obese mice and rats results in corrections of excessive GSLs. This biochemical correction is associated with phenotypic improvements. Imino-sugar treatments leads to remarkable improvement of insulin sensitivity and correction of glucose homeostasis. Moreover, prevention of hepatosteatosis in various mouse models has been observed. The validity of the target for intervention of iminosugars, i.e. the enzyme glucosylceramide synthase (GCS) catalyzing the first step of GSL synthesis, has been meanwhile substantiated. A chemically different class of inhibitors of GCS equally prevents hepatosteatosis in obese mice. Finally, we have noted that iminosugar treatment can even efficiently revert existing hepatosteatosis in various models. The past and ongoing work is described and discussed in the presentation. Part of the work, supported by MLD WO 07-66 is published: Aerts JM et al. Diabetes (2007), 56, 1341-9; Bijl N et al. Hepatology (2009) 50, 1431-4; Bijl N et al. Hepatology (2009), 49, 637-45; Wennekes T et al. Angew. Chem. Int. Ed Engl.(2009), 48, 8848-69; Zhao Y et al. Hepatology (2009), 50, 85-93.

A randomized sham-controlled trial of left lateral body positioning and acid suppression for infantile gastroesophageal reflux: A concept test for efficacy of reflux inhibition in infants

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Introduction: The number of gastroesophageal reflux (GER) episodes is reduced in left lateral position (LLP) compared to right lateral position (RLP) in infants. LLP reduces all types of reflux over the entire post-prandial period but does not alter the proportion of reflux episodes that are acidic (pH<4). The current study evaluated the effect of left lateral positioning in combination with acid suppressive therapy on GER related symptoms in infants 0-6 months of age. Methods: Infants 0-6 months with symptoms suggestive of GERD were investigated using 8 hour pH-impedance, gastric emptying breath test and the I-GERQ-R parental questionnaire. Using a parallel group design, infants demonstrating a positive relationship between GER and symptom episodes such as crying, coughing or regurgitation (symptom association probability>95%) were randomized to one of four therapeutic arms; 1. LLP+PPI (1mg/kg esomeprazole o.d.) 2. HE+PPI 3. LLP+AA (antacid o.d.) 4. HE+AA. For the purposes of this trial HE and AA were considered 'sham' therapies. PPI/AA was administered double blind. LLP/HE were performed for 2 hours following feeding during for 14 days. Then the 8 hr studies were repeated on therapy. Results: Fifty-one patients were included in the study (27 males, mean age 13.6 (range2-26) weeks). Combination of PPI+LLP is most effective in reducing the number of GER and esophageal acid exposure (Table 1). Vomiting was reduced in LLP+AA from 7 (2) to 2 (0), p=0.042. Despite the reduction in GER episodes and acid exposure none of the treatment groups showed a symptomatic improvement in crying or irritability. Comparing the influence of posture regardless of medical intervention, LLP produced a greater reduction in total number of GER episodes compared to HE (-21 (4) vs -10 (4), p=0.056). PPI therapy regardless of position produced a greater reduction in reflux index compared to AA (-6.8(2.1) vs -0.9(1.4) p=0.043. We observed an inverse relationship between symptom improvement and a slowing of the gastric emptying rate. In contrast, the change in number of symptoms did not correlate with improvement in any of the GER parameters.
Conclusion: In this study of SAP positive infants with 'symptomatic GERD', a reduction vomiting and reflux episodes was achieved, although crying and irritability were not reduced. The SAP did not appear to identify irritable infants responsive to anti-reflux therapies.

Surgery for Anterior Cutaneous Nerve Entrapment Syndrome: a double blind randomised placebo controlled trial

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Anterior Cutaneous Nerve Entrapment Syndrome (ACNES) is hardly considered in the differential diagnosis of chronic abdominal pain. However, for many of these patients a permanent solution can be achieved by simple measures. Purpose of the present trial was to clarify the role of a neurectomy on refractory patients following conservatively treated ACNES. We hypothesized that pain attenuation following neurectomy is the result of resection of the entrapped nerve at the level of the ventral Rectus fascia. Patients >18 years meeting the inclusion criteria were randomised to receive a neurectomy or sham procedure. Both patient and principal investigator were blinded to the nature of the procedure. Pain was recorded using a Visual Analogue Scale (VAS: 1-100 mm) and a Verbal Rating Scale (VRS: 0 = no pain, 5 = severe pain) during physical examination prior to and 6 weeks after surgery. A reduction of at least 50% on VAS and/or 2 points on VRS was considered a 'successful response'. Between August 2008 and December 2010 some 44 patients were randomised (5 males and 39 females, median age 42, both arms n=22). In the sham group 3 patients reported a successful response compared to 15 in the neurectomy group (p = 0·001).
Conclusions: Pain reduction following neurectomy in these ACNES patients is based on resection of the entrapped nerve at the ventral Rectus fascia. This simple procedure is successful in a substantial number of refractory patients following conservative measures.

Sexual abuse history in GI-Illness, how do gastroenterologists deal with it?Results of a Dutch survey

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Data support an increased prevalence of sexual abuse (SA) among patients with gastrointestinal complaints. Sexual abuse causes multiple symptoms related to pelvic floor and stress mediated brain-gut dysfunctions. There is a growing awareness of the adverse health outcomes associated with SA among patients with GI symptoms, especially in IBS, which is a huge healthcare problem. Treating these patients asks for a holistic approach, using centrally targeted interventions. However, gastroenterologists have never been surveyed regarding their practice patterns and constraints about inquiring into SA.We aimed to evaluate whether gastroenterologists address SA in their daily practice and to evaluate their knowledge regarding the implications of SA in GI-illness.A 42-itemed anonymous questionnaire was mailed to the members of the Dutch Society of Gastroenterology (gastroenterologists and residents). The questionnaire addressed SA and pelvic-floor-related complaints. In result of this mailing, 183 of the 402 (45.2 %) questionnaires were returned. Over all 4.7% of the respondents asked their female patients regularly about SA, in males this percentage was 0.6%. Before performing a colonoscopy, these percentages were even smaller (2.4% resp. 0.6%). When patients presented with specific complaints, such as chronic abdominal pain or fecal incontinence, 68% of the gastroenterologists asked females about SA and 29% of the males ($p<0.01$). Female doctors stated significantly less often that 'it is not important to ask male patients about sexual abuse' (19.6%) versus 36% of the male doctors ($p=0.03$).The majority of respondents stated it as quit important to receive more training on how to inquire about SA and its implications for treatment.
In conclusion: gastroenterologists do not routinely inquire about a history of SA, and they rarely ask about it before performing colonoscopy. Because SA is common in the gastroenterology practice, there is a need for training to acquire the skills and knowledge to deal with SA.

Lymfocytic and collagenous colitis have a different clinical course; experience from a single-center 10 year cohort of 125 patients

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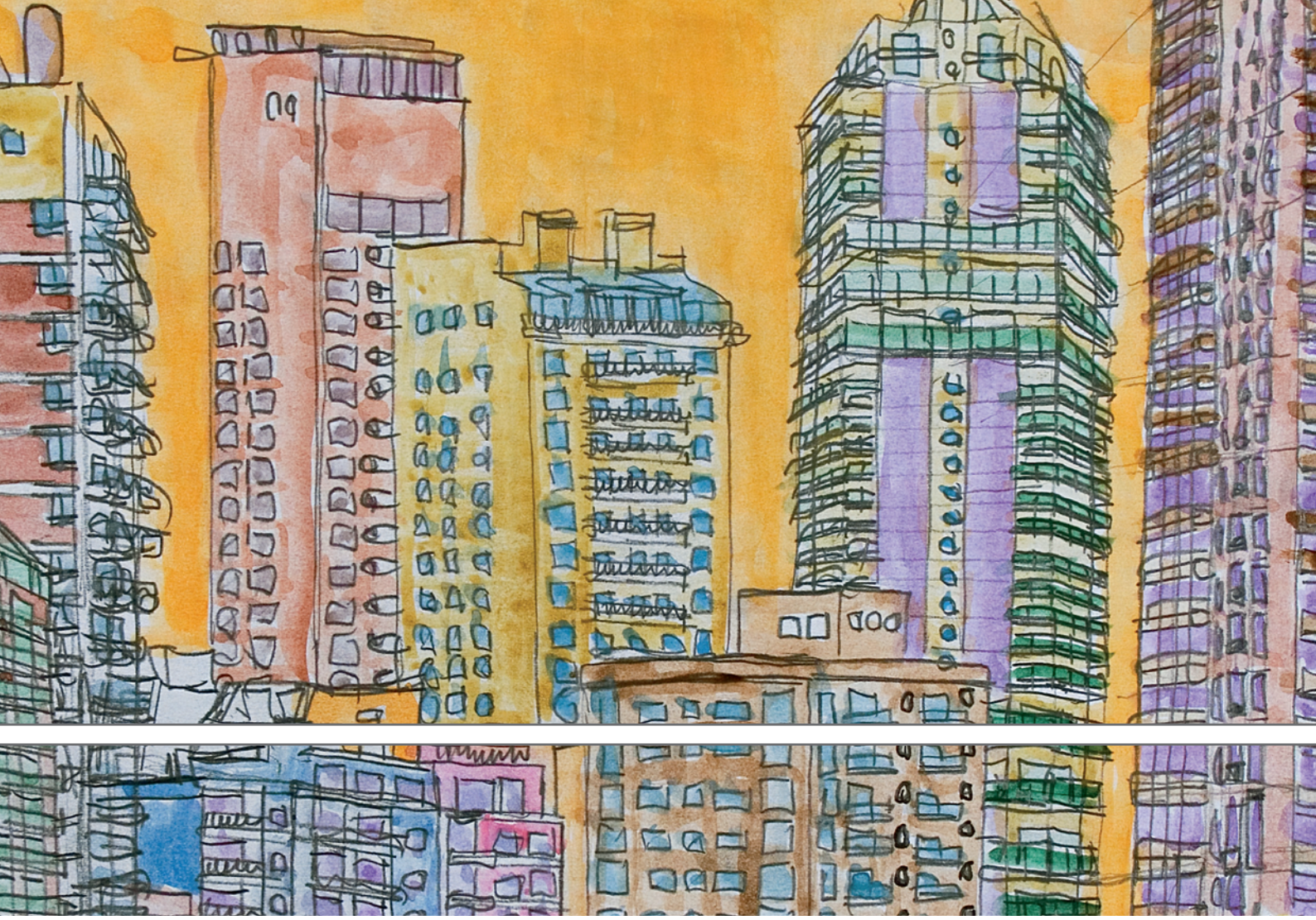
Introduction: Microscopic colitis (MC) is an infrequent cause of diarrhea, characterized by typical histopathology and normal endoscopic findings. Two types can be distinguished: lymphocytic colitis (LC) and collagenous colitis (CC). After we adapted a colonoscopy biopsy protocol demanding colon biopsies from at least six segments in all patients with diarrhea and normal endoscopic findings > 10 years ago, we increasingly encountered MC. In this study we report on the differences in diagnostic findings, comorbidity, medication use and clinical course in LC and CC in a large, regional hospital. Methods: We retrospectively studied patients with MC between 1998 and 2009. Patients were identified from the pathology database using the search terms: MC, LC or CC. All charts were reviewed and all biopsies re-evaluated. The location of biopsies for making the diagnosis was established during the pathology revision. Comorbidities and medications were recorded, and the clinical course was categorized using three types: a single episode, a chronic remittent course , and a chronic continuous course. To complete follow-up an enquiry was sent to all patients with a last outpatient visit > 12 months ago. Results: We identified 181 patients in whom biopsies were available for revision. In 8, an infectious agent was lateridentified, in 48 histopathology was not conclusive for the diagnosis (mainly because only epithelial lymphocytosis was seen without submucosal inflammation, always LC, never CC). In the remaining 125patients LC was diagnosed in 77, and CC in 48. The follow-up was median 42 (1-154) months. Biopsies from the right colon were diagnostic in 100% vs. 86% from the left colon (P<0.001). The mean age did not differ between LC and CC (57 and 59 yrs), the F/M ratio was 2.1 in LC and 3.5 in CC. The calculated incidence rate for LC and CC was 3.9 and 2.4 per 100.000 inhabitants. A single MC period was seen more often in LC (49% vs 22%, p=0.02), while chronic continuous and relapsing pattern was seen more often in CC (33% vs 21% and 42% vs 32%, respectively). The cumulative rate of relapse was significantly lower in LC (41% vs 63% p = 0.04). Medication use included NSAID and SSRI in LC in 9% and 12%, and in CC in 17% and 4 %, respectively. In 64 patients duodenal biopsies were taken during work-up. In 52% they showed varying levels of celiactype abnormalities were found (M-I in 67%, M-II in 12% and M-III in 21%).
Conclusion: A full colonoscopy with strict histological criteria is mandatory to diagnose LC. Almost halve of LC patientsexperience only one colitis period, CC is chronic in the vast majority. Left-sided biopsies would havemissed 14%; right-sided biopsies were diagnostic in all. Duodenal histopathology suggested celiac-type abnormalities in 51% of those who were studied.



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Should screening for latent tuberculosis infection be repeated after travel to tuberculosis endemic areas in patients treated with TNF-alpha inhibitor therapy?

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Rationale: Treatment with prophylactic therapy in case of latent tuberculosis infection (LTBI) is necessary before TNF-alpha-inhibitor treatment. Data concerning the development of active tuberculosis infection during TNF-alpha-inhibitor treatment are rare. The aim of this study is to evaluate the safety of TNF-alpha-inhibitor treatment after screening for and treatment of LTBI. Methods: A prospective, single-center study was conducted. Adult patients with immune mediated disorders from gastro-enterology, dermatology and rheumatology outpatients department, planned for TNF-alpha-inhibitor treatment, were included from 2007 until 2011. Screening for LTBI included Tuberculin Skin Test (TST), defined positive above five millimeters skin reaction, and an Interferon Gamma Release Assay (IGRA): ELISpot. Prophylactic therapy according to the Dutch guidelines was given to BCG-vaccinated persons with positive IGRA. on-BCG-vaccinated persons received prophylactic therapy when at least one test was positive. All patients were observed during and after TNF-alpha-inhibitor treatment for development of active tuberculosis infection. Results: A total of 195 subjects were included; 109 subjects were female. The majority (164 persons) was not BCG-vaccinated. Twenty-eight persons were born in a tuberculosis-endemic country, 77 others were at risk for LTBI, because of traveling to those countries, history of tuberculosis infection, or exposure to someone with tuberculosis. Fourteen persons, all diagnosed with LTBI, received prophylactic therapy before TNF-alpha-inhibitor treatment. During the TNF-alpha-inhibitor treatment, two persons developed active tuberculosis infection. To one of them, a 48-years old woman, no prophylactic therapy was prescribed, because of a negative TST and an indeterminate IGRA. Few months after TNF-alpha-inhibitor treatment, she traveled to a tuberculosis-endemic country. In the weeks after return, she developed tuberculosis meningitis and died. Second, a 41-years old male person developed active extra-pulmonal tuberculosis during TNF-alpha-inhibitor treatment. Again, no prophylactic therapy was given, because of a negative TST and IGRA. He also recently traveled to a tuberculosis-endemic country. A primary tuberculosis infection is likely in these two cases.
Conclusion: TNF-alpha-inhibitor treatment is safe after screening for and treatment of LTBI. However, traveling to tuberculosis-endemic countries during TNF-alpha-inhibitor treatment should be strongly discouraged. We recommend screening for LTBI after travelling to tuberculosis-endemic areas.

Over a quarter of the general adult population experiences gastrointestinal symptoms influencing health-related quality of life: results of 50,000 questionnaires

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Gastrointestinal symptoms in the community are highly prevalent and associated with enormous healthcare costs. The last extended dyspepsia prevalence population studies in the west are dated over two decades ago. Since then, the importance and prevalence of risk factors have shifted within the community and ask for an update. The aim of this study is to investigate 1) the current population prevalence of gastrointestinal symptoms; 2) their impact on health-related quality of life; and 3) to assess factors associated with presence of gastrointestinal symptoms. A total of 51,869 questionnaires were sent to a representative sample of the Dutch adult general population in December 2008. Questions about demographics, gastrointestinal symptoms, medication use, co-morbidity and health-related quality of life were stated. Presence of gastrointestinal symptoms, and type of individual symptoms were assessed. Health-related quality of life was measured with the EQ-5D and multivariable logistic regression analysis assessed factors associated with gastrointestinal symptoms. A total of 18,317 questionnaires were returned (response rate 35%), of which 16,758 surveys were eligible for analysis. Prevalence of gastrointestinal symptoms was 26% with a median symptom duration of 8 years (IQR 3-18). Most reported symptoms were bloating (63%), borborygmi (60%) and flatulence (71%). A total of 1,771 respondents reported proton pump inhibitor (PPI) use, of which 610 (34%) reported no gastrointestinal symptoms. Health-related quality of life in persons with gastrointestinal symptoms was impaired, with a mean Dutch utility score of 0.81 (SD=0.21), compared to 0.92 (SD=0.14) for persons without symptoms. Female gender (adjusted odds ratio (aOR) 1.59, 95% CI 1.4 - 1.77), presence of asthma/COPD (aOR 1.47, 95% CI 1.21 - 1.79), use of paracetamol (aOR 1.33, 95% CI 1.20 - 1.47), antidepressants (aOR 1.56, 95% CI 1.22 - 2.00) and use of acid-suppressive medication (antacids aOR 4.22, 95% CI 3.53 - 5.05, histamine-2 receptor antagonists aOR 9.93, 95% CI 6.72 - 14.7, PPIs aOR 9.29, 95% CI 7.91 - 10.9) were independently associated with an increased frequency of gastrointestinal symptoms. Age over 65 years (aOR 0.75, 95% CI 0.65 - 0.87), and use of statins (aOR 0.75, 95% CI 0.61 - 0.93) were associated with a decreased frequency of gastrointestinal symptoms.
In conclusion, a quarter of this large sample of the general adult population reported gastrointestinal symptoms, which was associated with a decreased health-related quality of life. We speculate that the actual presence of symptoms is even higher, if we include PPI users who reported symptom relief while on therapy.

New insight into dynamics of plasma Intestinal Fatty Acid Binding Protein as a marker for epithelial damage in human small intestinal ischemia-reperfusion

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Intestinal ischemia-reperfusion (IR) is a serious clinical problem with high morbidity and mortality. Early detection of intestinal ischemia could theoretically improve patient outcome. A potential marker for early diagnosis of intestinal ischemia is Intestinal Fatty Acid Binding Protein (I-FABP), a small cytosolic protein present in mature enterocytes at the tip of the villus. To integrate I-FABP in daily clinical practice, more insight in the characteristics of I-FABP is needed. The aim of this study was to investigate dynamics of I-FABP as a potential marker for intestinal damage during IR, and to investigate the relation between circulating I-FABP and extent of epithelial damage. Using a newly developed human experimental model, the effects of intestinal IR was studied. In 10 patients a part of jejunum, to be removed for surgical reasons, was selectively exposed to 15 (15I) or 60 minutes (60I) of ischemia followed by 30 and 120 minutes of reperfusion (R). Arterial en venous blood was sampled at all time points and arteriovenous (V-A) concentration differences of I-FABP were measured using enzyme-linked immune-sorbent assay (ELISA). Tissue sections were collected at all time points and stained for I-FABP and haematoxylin/eosin (HE). Histological results showed minor damage of epithelial cells on villus tips in jejunum that was exposed to 15 minutes of ischemia. I-FABP V-A differences were significantly increased at this time point, indicating enterocyte membrane integrity loss. These data emphasize the high sensitivity of I-FABP to detect minor epithelial damage early. During reperfusion, the epithelial lining remained intact while I-FABP levels gradually decreased. To study whether I-FABP could discriminate between minor tissue damage and severe epithelial damage, we next investigated consequences of 60IR on histology and plasma I-FABP levels. In contrast to the histologic appearance of tissue exposed to 15I, severe epithelial damage was observed in jejunum exposed to 60I. This was accompanied by massive loss of I-FABP positive villus tips into the intestinal lumen. In line, I-FABP V-A differences were significantly higher at 60I compared to 15I ($P<0.001$). In addition, I-FABP levels correlated strongly with length of ischemia.
In conclusion, this study shows the direct relation between plasma I-FABP levels and severity of epithelial damage of jejunum exposed to IR. I-FABP increased significantly upon minor ischemic periods, demonstrating its high sensitivity. In addition, I-FABP levels could predict the severity of intestinal epithelial damage.

Moderate dosage of ethanol increases small and large intestinal permeability in healthy volunteers

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Introduction: Ethanol-induced endotoxemia resulting from gut barrier disruption plays a major role in the pathogenesis of alcoholic liver disease. Both a single high dose and chronic ethanol consumption have been shown to induce small intestinal barrier dysfunction. However, little is known about effects of moderate dosages on small as well as large intestinal barrier function. Aims: To investigate the effect of intraduodenal administration of 20 g ethanol (2 standard drinks) on intestinal permeability in healthy volunteers. Methods: Intestinal permeability of 12 male subjects (Age 31.23±11 yr, BMI 23±2 kg/m^2) was assessed after intraduodenal administration of either 20 g ethanol or placebo, in a randomized cross-over trial, by means of a multi-sugar test and 24 hour urine collection. Blood samples were collected to determine plasma ethanol levels and liver function. Urinary sugar recovery reflecting gastroduodenal (0-2 hours fraction), small intestinal (0-5 hours fraction) and colon permeability (5-24 hour fraction) was assessed by high pressure liquid chromatography-mass spectrometry (HPLC-MS). Results: Intraduodenal administration of ethanol resulted in an increased blood ethanol levels reaching a peak (58.5 mg/dL) after 15 min, decreased gradually thereafter and reached the basal values (11.1 mg/dL) after 3 h without changes in liver function.There was no significant difference in the gastroduodenal permeability, indicated by urinary sucrose excretion, after ethanol versus placebo administration (0.357±0.547 vs. 0.710±1.250, respectively; P>0.05). In contrast, the small intestinal permeability, defined by the lactulose/rhamnose ratio, was significantly increased after ethanol vs. placebo (0.085±0.041 vs. 0.056±0.040, respectively; P<0.05). Colon permeability, indicated by the sucralose/erythritol ratio, was also significantly increased after ethanol administration compared to placebo (0.317±0.180 vs. 0.026±0.027, respectively; P < 0.01). Conclusions: The present data show that intraduodenal administration of 20 g ethanol increases small intestinal permeability. In addition, for the first time, an increase was found in colon permeability. This study indicates that even a moderate dosage of ethanol decreases small intestinal barrier function thereby potentially increasing the risk of enhanced endotoxin translocation and consequently, liver inflammation. Furthermore, impairment of colon permeability may contribute to alcohol-related colorectal carcinogenesis.

HLA-DQ genotype distribution in Type 1 Diabetes Mellitus patients with concomitant Celiac Disease

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Background & Aims: The estimated prevalence of celiac disease (CD) in patients with Type 1 Diabetes Mellitus (T1DM) is 5%. Both multifactorial diseases CD and T1DM are strongly clustered in families and in both diseases human leukocyte antigen (HLA) class II molecules HLA-DQ2.5 (DQB1*02-DQA1-05) and DQ8 (DQB1*0302-DQA1*0301) are key genetic risk factors. Therefore, the aim of the present study is to investigate HLA-DQ distributions in patients diagnosed with both T1DM and CD. Associations will be examined between HLA-DQ genotypes and age of clinical onset of both diseases and autoimmune comorbidity. Material & Methods: Patients with T1DM and concomitant CD were recruited from 33 hospitals in the Netherlands. We retrospectively collected data of the moment of T1DM diagnosis, CD diagnosis and comorbidity of autoimmune diseases. The diagnosis of T1DM was defined as an absolute requirement of insulin and the diagnosis of CD was based on international criteria (ESPGHAN-criteria). Genomic DNA was obtained from peripheral blood for typing of HLA-DQA1* and DQB1* alleles, performed with a combined single stranded conformation polymorphism. Patients were divided in childhood onset of T1DM (onset before 20 years) and adult onset of T1DM due to the fact that childhood onset of T1DM is strongly associated with HLA haplotypes. Results: The total group consisted of sixty-one patients diagnosed with T1DM and CD (67.2% female) with a mean age of 41.5 ± 20.1 years with a duration of T1DM and CD of 22.6 ± 16.8 years and 8.3 ± 10.4 years ($P<0.01$), respectively. All patients were unrelated and self-reported Dutch Caucasians. Patients carried HLA-DQ2.5 in 80.3% (heterozygous in 50.8% and homozygous in 29.5%) of the cases. 19.7% of the T1DM + CD patients were HLA-DQ2.5/DQ8. HLA-DQ8 heterozygous (without HLA-DQ2.5) was present in 16.4% of the cases and HLA-DQ8 homozygous in 3.3%. Only 9.8% (6 of 61 patients) of the patients were diagnosed with CD before T1DM, 3 out of 6 of them were HLA-DQ2.5 homozygous. In the childhood onset of T1DM group (n= 38) the age of T1DM onset was significantly lower in those who were HLA-DQ8 heterozygotes versus other genotypes (mean of 4.9 years versus 8.0 years ($P<0.05$). No associations between HLA-DQ type and the prevalence of autoimmune comorbidity or onset of CD were found.
Conclusions: In patients with T1DM and CD a prevalence of carriers of HLA-DQ2.5 of 80.3% is found. Interestingly, in the childhood onset group a younger age of onset of T1DM is associated with heterozygous HLA-DQ8. No associations were found between HLA-DQ type and the prevalence of autoimmune comorbidity or the onset of CD.

Can the systemic compartment contribute to barrier disruption in diarrhea predominant IBS patients?

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Introduction Irritable bowel syndrome (IBS) is a functional gut disorder and comprises different subtypes, based on predominant symptoms or underlying pathophysiological mechanisms. Increased intestinal permeability has been observed, especially in diarrhoea-predominant IBS. Apart from intestinal factors, systemic mediators may contribute to the increased intestinal permeability and differences among subtypes. We employed a 3D cell model of Caco-2 cells that form fully polarised spheroids with the lumen inside, providing a useful in vitro integrity model to study basolateral exposure of the intestinal epithelium. Our aim was to investigate whether the systemic compartment can induce an increased permeability in diarrhoea- (IBS-D) compared to consti-pation-predominant IBS (IBS-C) and healthy controls (HC). Materials & Methods Sodium-heparin plasma was collected from 7 IBS-D and 7 IBS-C patients (Rome III criteria) and 7 HC. Caco-2 cells were grown in an extracellular matrix (Matrigel) for 5 days to form fully polarised spheroids. The spheroids were exposed to two-fold diluted plasma of IBS patients and HC for 24h. EGTA (2mM) was used as positive control. Barrier function was assessed by the flux of FITC dextran 4KD (FD4) from the basal to the luminal compartment using live cell imaging. Results were expressed as the mean luminal/basal FD4 ratio of 8 spheroids from 3 independent experiments using 7 different plasma samples per group. Plasma protease activity was assessed fluorometrically by conversion of Boc-Gln-Ala-Arg-AMC. Endotoxin concentrations were measured using the enzyme-based Limulus Amoebocyte Lysate assay. Data are expressed as mean ± SEM or median [range] depending on normality of distributions.Results The FD4 ratio, indicating paracellular permeability, was significantly increased in IBS-D vs. IBS-C vs. HC (0.14450 ± 0.00472 vs. 0.00089 ± 0.00001 vs. 0.00021 ± 0.00003, resp.; $P < 0.01$). Plasma protease activity of IBS-C (67.66 ± 34 U/mL), IBS-D (59.64 ± 1.83 U/mL) and HC (61.09 ± 1.52 U/mL) did not differ significantly ($P = 0.23$). Plasma endotoxin concentrations were 36.5 [30.0 – 61.0]; 31.0 [26.0 – 38.0] and 26.5 [24.0 – 34.0] EU/mL in IBS-D, IBS-C and HC, respectively ($P < 0.05$ in IBS-D vs. HC).
Conclusion: These findings indicate that plasma of IBS-D patients has a stronger potency than that of IBS-C patients to decrease barrier function in vitro. Plasma analyses did not reveal differences in protease activity but pointed to elevated endotoxin levels between IBS subtypes. Additional analyses need to be performed to elucidate whether the increased endotoxin concentrations are cause or consequence of the increased intestinal permeability.

Clinical impact of autofluorescence imaging on the endoscopic treatment for early Barrett's neoplasia: a prospective assessment of 371 patients

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Five recently conducted studies have shown that autofluorescence imaging (AFI) increases the targeted detection of high-grade intraepithelial neoplasia (HGIN) and early cancer (EC) in Barrett's esophagus (BE). Information lacks on the clinical relevance of AFI detected lesions. Do lesions found by AFI influence management or do they merely add up to neoplasia already detected by white light endoscopy (WLE) and random biopsies (RBx) without changing the initial treatment plan? The aim was to investigate the clinical impact of AFI on the management of patients with early neoplasia in BE. Data on patients, endoscopy and histology was extracted from databases of the aforementioned 5 prospective studies and related to treatment outcome. The additional diagnostic value of AFI was defined as the proportion of patients with HGIN/EC detected by AFI-targeted biopsies only. The additional therapeutic value of AFI was defined as the proportion of patients with any HGIN/EC lesion that was primarily detected with AFI and changed the therapeutic plan based on WLE/RBx. 371 BE-patients (65 yrs, 305 males) were enrolled. Patients were referred for surveillance (183), work-up for early neoplasia (161) or follow-up after treatment (27). HGIN/EC was diagnosed in 133 patients: 85 were diagnosed based on lesions detected with WLE; 24 patients were diagnosed based on RBx only. In 24 patients, HGIN/EC was only diagnosed in AFI-targeted biopsies. However, 22 of these 24 "AFI-only" patients had been diagnosed with HGIN/EC in RBx at the previous referring endoscopy. In 13 "AFI-only" patients an endoscopic resection (ER) was performed; 11 had flat type lesions that were ablated. No ER specimen showed undifferentiated (sub)mucosal carcinoma or lymph-angioinvasion that would have made the original treatment plan unjustified. The additional diagnostic value of AFI in this cohort of 371 patients was therefore limited to 2 patients (1.5%), both referred for BE surveillance, in whom AFI led to the detection of HGIN that was missed by WLE/RBx. The additional therapeutic value of AFI: 56 patients had one or more HGIN/EC lesions detected by AFI, not detected by WLE (24 "AFI-only" patients and 32 patients who had other AFI-detected HGIN/EC lesions besides the primary WLE- or RBx-detected lesion). ER was performed in 30 patients; 26 patients had flat lesions that were ablated. No ER specimen showed findings that changed the initial management plan based on WLE/RBx. Although AFI may increase the targeted detection of early neoplasia in BE, the additional diagnostic value on top of WLE plus RBx is small and the impact of AFI-detected lesions on therapeutic decision-making is virtually absent.

Prospective long-term follow-up after radiofrequency ablation for Barrett's esophagus with high-grade dysplasia and/or early cancer

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Radiofrequency ablation (RFA) results in high rates of complete eradication of Barrett's esophagus (BE) with high-grade dysplasia (HGD) and/or early cancer (EC), and may be safely preceded by endoscopic resection (ER) in case of focal lesions. Less is known about the long-term durability of this approach. Under an IRB approved protocol we prospectively evaluated the 5-year durability of treatment response after RFA+/-ER for HGD/EC in a cohort of 55 BE pts, included in 4 earlier IRB approved studies. Initial treatment was performed in pts with biopsy proven HGD/EC on 2 endoscopies, confirmed by an expert pathologist. Visible lesions were removed with ER, residual EC was excluded by post-ER biopsy. At least 6 weeks after ER primary circumferential ablation was scheduled. Subsequent RFA was performed every 2-mo until clearance of BE achieved. Follow-up (FU) was performed at 3/6/12 mo and annually thereafter with high-resolution endoscopy with NBI and biopsies (4Q/2cm) from neosquamous epithelium (NSE) above the top of the gastric folds, and <5mm distal to the neo-Z- (gastric cardia). At 5-yr FU an EUS and endoscopic resection of NSE were performed. Endpoints: 1) complete histological remission of HGD/EC (CR-neo) and intestinal metaplasia (CR-IM), 2) presence of buried glands in NSE biopsies/ER specimens, 3) IM in gastric cardia biopsies. 55 pts were included (45M, mean age 65yrs, median BE C4M5). In 40/55 pts entry ER was performed (worst pathology: EC (n=23), HGD (n=14), LGD (n=3)). Worst grade post-ER/pre-RFA: HGD (n=39), LGD (n=11), IM (n=5). After treatment 54 pts reached CR-neo/ CR-IM, 1 pt underwent surgery for persistent HGD. Median follow-up for 54 pts since study entry was 60 (IQR 50-65) mo, with a median of 6 (5-6) FU endoscopies and 73 biopsies per pt. In 7 pts FU was discontinued because of unrelated comorbidity or emigration (median FU 30 months); all were CR-neo/CR-IM at last visit. Sustained CR-neo and CR-IM was observed in 52/54 (96%) of pts; at 5 years FU a mucosal cancer was radically removed by ER in 1 pt, and in 1 pt a small Barrett's island with LGD was treated with APC. Analysis of 3,351 NSE biopsies showed buried glands in 3 biopsies (0.09%), and 51/1,070 gastric cardia (4.8%) biopsies demonstrated focal non-dysplastic IM, not treated. The latter finding appeared randomly during FU with no increase in incidence over time. All 5-year EUS investigations were normal and none of the ER specimens of NSE showed signs of buried Barrett's. Outcomes of this prospective 5-year follow-up study suggest that after RFA+/-ER for BE with HGD/EC, complete eradication of neoplasia and IM is maintained in the vast majority of patients at 5-years.

A prospective multicenter study to identify predictive markers for initial treatment response after circumferential radiofrequency ablation for Barrett's esophagus with early neoplasia.

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Background: Endoscopic radiofrequency ablation (RFA) is safe and effective for eradication of neoplastic Barrett's esophagus (BE). However, some patients demonstrate minimal regression of the BE epithelium at 3 months after initial circumferential balloon-based RFA (c-RFA). Predicting which patients may have poor response at 3 months may be important for clinical decision-making, therefore, base predictive factors for poor response at 3 months should be identified. AIMS: To identify predictive factors for poor response at 3 months to c-RFA; to relate 3 month BE regression to c-RFA to final treatment outcome. Methods: We included consecutive patients who underwent c-RFA for eradication of flat high-grade intraepithelial neoplasia (HGIN) or for removal of residual BE after endoscopic resection (ER) of HGIN/cancer. 72 factors relating to patient characteristics and treatment were registered prospectively. The % BE surface regression at 3 mo was scored independently by 2 expert endoscopists (blinded to clinical information) using endoscopic images prior to c-RFA and at 3 mo after c-RFA. Logistic regression analysis was performed using a cut-off value of BE regression <50% at 3 mo ('poor initial response'). Results: A total of 284 patients were included (227 male, age 63 (±13) years, median BE C4M6), of whom 180 underwent ER prior to RFA. Complete response for neoplasia (CR-N) and intestinal metaplasia (CR-IM) was achieved in 251 (96%) and 235 (90%) of 262 patients, respectively (24 remain under treatment). There were 38 (13%) patients with <50% BE regression at 3 mo. In these poor initial responders, CR-N was ultimately achieved in 83% (vs 98% in good responders; p<0.01), CR-IM in 60% (vs 93%, p<0.01). Poor responders required a median time for RFA treatment of 11 mo (vs 6 mo; p<0.01) and a median 4 RFA-sessions (vs 3; p=0.03). Multivariate analysis identified the following base predictors of poor response at 3 mo: regeneration of ER scar with BE tissue (OR 4.7; p=0.01); base esophageal narrowing (asymptomatic) pre-RFA (OR 4.6; p=0.02); years of neoplasia before RFA (OR 1.2; p=0.03). BE length was not associated with poor response at 3 mo. Conclusions: Patients with a poor initial response to c-RFA showed a higher rate of ultimate failure for CR-N/CR-IM, required more treatment sessions, and had a longer treatment period than those with a good initial response to c-RFA. A poor initial response to c-RFA does not depend on the Barrett's segment length, but is more likely to occur in patients who regenerate their ER wound with BE, have neoplasia in BE for a longer time period prior to RFA or have a narrowing of their esophagus prior to RFA.

Simplifying radiofrequency ablation of Barrett's esophagus: a randomized multicenter trial comparing three different treatment regimens for circumferential ablation using the HALO^{360} System

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Background: The current regimen of circumferential balloon-based radiofrequency ablation (c-RFA) for removal of Barrett's esophagus (BE) consists of two ablation passes with an intervening cleaning step to remove debris from the ablation zone and electrode. A simplified regimen may be of clinical utility, if it were easier and faster, yet equally safe and efficacious. AIMS: To compare the safety and efficacy of three c-RFA ablation regimens. Methods: In 3 centers, consecutive BE patients scheduled for c-RFA for flat-type low-grade or high-grade intraepithelial neoplasia (LGIN/HGIN) or for residual BE after prior endoscopic resection for HGIN/cancer were enrolled. Ablation (c-RFA) was delivered by the HALO^{360} device (12J/cm^2) in all randomized cohorts. Standard: c-RFA, remove device, clean, c-RFA. Simple+clean; c-RFA, clean without removing device, c-RFA. Simple-no-clean: 2 applications of c-RFA, no removal of device or cleaning. After c-RFA, patients underwent focal RFA every 2-3 months until achieving complete response for neoplasia and intestinal metaplasia (CR-N; CR-IM). BE regression (%) at 3 months was graded by 2 expert endoscopists, blinded to the allocated regimen, using endoscopic images of every 1-2 cm of BE, obtained immediately prior to c-RFA and at 3 months. Primary outcome: BE surface regression at 3 months (mean of 2 expert endoscopists) (calculated sample size 57 patients, non-inferiority defined as <20% difference in BE regression). Secondary outcomes: procedure time, introductions, complications. Results: 57 patients (45M, 64±15yrs, median BE C3M5) were randomized, 28 had prior ER. Base BE length, prior ER, and base histology were similar among groups. Overall median BE regression at 3 months for all 3 groups was 83% (IQR61-93): 83% with standard; 78% with simple+clean; and 88% with simple-no-clean (p=0.14). RFA procedure time was 20 min (IQR18-25) using standard vs 13 min (IQR11-15) using simple+clean vs 5 min (IQR5-9) using simple-no-clean (p<0.01). Median number of introductions (RFA devices/endoscope) using standard was 7 vs 4 in both simplified regimens (p<0.01). Four minor complications occurred: 2 lacerations during sizing, 1 hospitalization for pain, 1 stenosis resolving upon 1 dilation (pre-existing esophageal narrowing) (NS). CR-N and CR-IM were achieved in 42/43 (98%) and 37/43 (86%) of patients that finished treatment by Nov '11. There were no differences in CR-N and CR-IM among groups.
Conclusions: This randomized study suggests that the current regimen used for c-RFA could be made to be easier and faster, without sacrificing safety or efficacy, by omitting or simplifying the cleaning phase in between ablations.

A multicenter randomized trial comparing two ablation regimens for focal radiofrequency ablation of Barrett's mucosa using the HALO^{90} system

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Background: The currently recommended regimen for endoscopic focal radiofrequency ablation (RFA) of Barrett's esophagus (BE) comprises two applications of energy, cleaning of the device and ablation zone, and two additional applications of energy. A simplified regimen may be of clinical utility, if it were faster, easier and equally safe and effective. Aim: To compare the efficacy of two focal RFA regimens. Methods: In 3 centers, consecutive patients scheduled for endoscopic focal RFA of BE were enrolled having flat type BE with at least 2 BE islands or mosaic groups of islands (each less than the surface area of two HALO^{90} ablation catheters). Targeted BE areas were paired according to similar size: one of each area was randomized to the 'standard' regimen (2x15J/cm^2-clean-2x15J/cm^2) or 'simplified' regimen (3x15J/cm^2-no clean), allocating the second area automatically to the other regimen. The % surface area of each target was scored at 2 months by the endoscopist, who was blinded to patient and regimen type. Patients underwent RFA every 2 months until complete histological response of each targeted BE area was achieved for neoplasia and intestinal metaplasia (CR-N; CR-IM). Primary outcome: CR-IM for each target at 2 months (non-inferiority defined as <20% difference in the paired proportions, sample size calculated at 46 pairs). Secondary outcome: surface regression (%) for each target at 2 months. Results: Forty-five equivalent pairs of target BE areas were randomized by Dec '11, in 40 patients (29 male, age 64±12 years, BE C4M7). The proportion of targets showing CR-IM at 2 months after focal-RFA was 30/45 (66.7%) for standard and 33/45 (73.3%) for simplified: a difference of 6.7% (95%CI -12.2 to +25.6). The median surface regression for each target at 2 months was 100% in both groups, whereas for not completely eradicated areas this was 77.5% (IQR50-90)% for standard and 75% (IQR50-90) for simplified (p=1.0). No complications occurred. By Dec '11, CR-IM and CR-N was achieved in 91.1% (31/34) and 100% of patients, whereas 7 patients are under treatment.
Conclusions: The results of this multicenter randomized trial suggest that a simplified 3x15J/cm^2 focal ablation regimen is not inferior to the standard regimen. Therefore, the simplified regimen may be recommended for residual BE islands.

Safety of simultaneous use of endoscopic resection and radiofrequency ablation: evaluation of two variants of "single step" treatment in an esophageal porcine model

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Radiofrequency ablation (RFA) is safe and effective for eradication of Barrett's esophagus (BE) after endoscopic resection (ER) of neoplasia. Widespread ER prior to RFA (>2cm or >50% circumference) however, is likely to induce stenosis which hampers subsequent circumferential RFA (cRFA). Patients with widespread neoplasia might therefore benefit from a "single step" procedure in which ER and cRFA are performed in the same session. Two variants are possible: ER of the neoplastic lesion directly followed by cRFA of the remaining BE including the resection wound (ER-RFA); and cRFA of the whole BE including the neoplastic lesion followed by ER of the ablated neoplastic lesion (RFA-ER). RFA-ER has been reported in clinical care, but is technically demanding. ER-RFA would be easier to perform and could improve histological assessment of the resection specimen, but ablating onto the resection wound might carry a risk for perforation, and has therefore not been tested before. Aim: first, to evaluate the perforation risk of ER-RFA using increasing RFA energy doses. Second, to compare the stenosis rate after ER-RFA vs. RFA-ER. In the first experiment (exp) 6 female pigs were treated with ER-RFA. A total of 24 treatment areas (TAs) were treated with widespread ER (3cm, 50% circumference) directly followed by cRFA with increasing energy setting: 2x10, 2x12, 3x12, 4x12, 5x12, and 6x12J/cm^2. Two pigs were immediately euthanized, 2 were aimed to be euthanized after 1 day, and 2 after 3 days. In the second exp, 8 pigs each had 4 TAs in randomized order: ER-RFA, RFA alone, ER alone, and RFA-ER. RFA energy was set at 2x10J/cm^2. All animals were handled in accordance with European Union guidelines. Endpoints were number of acute and delayed perforations after ER-RFA (exp 1), and number and severity of stenosis after ER-RFA, RFA-ER, RFA and ER (exp 2). No acute perforations occurred when ablating the ER wounds. In exp 1, one delayed perforation occurred at the 5x12J/cm^2 TA after 1 day. In exp 2 another delayed perforation occurred in 1 pig at the ER-RFA (2x10J/cm^2) at day 8. The remaining 7 pigs developed severe stenosis and were therefore prematurely euthanized after a mean of 23 days (range 16-30 days). In these 7 pigs, all ER-RFA and RFA-ER areas had a severe stenosis versus 5/7 areas with RFA alone, and 0/7 areas with ER alone. Conclusion: The "single step" variant ER-RFA is not safe in a porcine model and seems therefore not ethical to evaluate further in humans at this stage. Given the high rate of stenosis after RFA-ER and after RFA alone, however, one might question the validity of the pig esophagus as a model for this type of experiments.

Does Lugol's staining prevent stenosis formation induced by radiofrequency ablation of oesophageal squamous epithelium? A study in a porcine model

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Background: Radiofrequency ablation (RFA) is safe and effective for eradication of Barrett's oesophagus (BO). RFA has been less well studied for oesophageal squamous cell neoplasia (OSCN). Preliminary data suggest that squamous epithelium is more sensitive to RFA induced damage and stenosis. Potential contributing factors may be RFA energy settings, number of ablation passes, use of cleaning in between passes, or use of Lugol's staining (LS) directly prior to RFA. LS may exaggerate stenosis formation by direct mucosal or submucosal injury. On the other hand, LS may be protective against deeper thermal injury by inducing submucosal oedema, or by inducing oesophageal spasm which may lead to the use of a smaller caliber ablation catheter after oesophageal sizing.Aim: To study the effect of LS on the rate of RFA induced stenosis in oesophageal squamous epithelium, and to investigate possible underlying mechanisms.Methods: 16 pigs (63 kg [50-69 kg]) were included in this survival experiment. In each pig the distal oesophagus was sprayed with LS, followed by circumferential RFA (12 J/cm^2) in the stained (distal) and unstained (proximal) oesophagus. A control area (non-RFA) was maintained in both unstained and stained parts. In all, an RFA sizing balloon was inflated under endoscopic view directly prior to and immediately after LS (before RFA).Pigs were euthanised at day 0 (n=4), 3 (n=4) and 28 (n=8). On histology the amount of oedema was determined in the LS and non-LS areas at day 0 and depth and severity of inflammation and necrosis at day 3. At 28 days the mucosal circumference of each treatment area was measured at the center of the treatment area and at the control area. To compare the severity of the stenosis in the LS and unstained part, the ratio of the circumference of the RFA area to the control area was calculated. Results: Oesophageal diameter was 22.7 mm [IQR 22.0–24.0] before LS and 22.4 mm [IQR 21.1–24.1] after LS (NS). Histology at day 0 showed submucosal oedema in 2/4 LS+RFA and in 1/4 control LS area; no oedema was seen in the unstained areas. Depth of inflammation and necrosis was similar in the stained and unstained areas at day 3. At day 28, stenosis was seen in 5/8 LS+RFA areas compared to 0/8 RFA areas without LS. The ratio of the circumference of the RFA area to the control area was 0.40 [IQR 0.29–0.45] after LS and 0.72 [IQR 0.66–0.77] without LS (p=0.012).
Conclusions: In this porcine survival model, Lugol's staining immediately prior to RFA increased the stenosis rate after RFA of squamous epithelium. Lugol's staining thus may be a contributing factor in the altered response of squamous epithelium to RFA as compared to BO.

Predictors of mortality in patients with esophageal adenocarcinoma in a large Dutch population-based cohort

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Despite an improvement in the therapeutic options for esophageal adenocarcinoma (EAC), the prognosis remains poor due to the fact that it is frequently detected at an advanced stage. Knowledge of predictors of mortality in EAC may aid in improving its prognosis. The aim of this study was to identify predictors of 2-year mortality in a large nationwide population-based cohort of patients with EAC. All patients diagnosed with EAC between 1999 and 2009 were identified in the Dutch cancer registry. These data were linked to PALGA, a nationwide registry of histopathology diagnoses. Multivariate Cox proportional hazards regression analysis was performed to identify predictors of 2-year mortality. Surveillance participation was defined as ≥ 1 additional biopsy sampling episode between the first BE diagnosis and EAC detection.In total, 9,243 patients diagnosed with EAC were identified. Two-year mortality rate was 72% (6,627) during a median follow-up of 0.8 (IQR 0.3-1.6) person-years. Two-year mortality was increased in EAC patients aged between 60 and 80 years (hazard ratio (HR) 1.13, 95%CI1.07-1.21) and over 80 years (HR1.27, 95%CI1.17-1.39) compared to patients under 60 years, and for EACs located in the upper third of the esophagus (HR1.24, 95%CI1.01-1.53) compared to the lower third. Mortality was reduced when patients were participating in a surveillance program prior to EAC diagnosis (HR0.73, 95%CI0.64-0.82) compared to when patients were not participating, in well-differentiated (HR0.62, 95%CI0.52-0.74) and moderately differentiated EACs (HR0.76, 95%CI0.71-0.81) compared to poorly differentiated EACs, in tumor stage 0 (HR0.16, 95%CI0.09-0.27), stage I (HR0.20, 95%CI0.17-0.25), stage II (HR0.42, 95%CI0.38-0.46) and stage III (HR0.70, 95%CI0.65-0.75) compared to stage IV tumors, when treatment was fully or partially performed in a university hospital (HR0.84, 95%CI0.78-0.90) compared to a general hospital only. In addition, mortality was reduced when surgery was combined with neoadjuvant chemo/radiotherapy (HR0.62, 95%CI0.53-0.72) and increased when treated with definite chemoradiation therapy (HR1.52, 95%CI1.33-1.75) and chemo- or radiotherapy (HR2.38, 95%CI2.17-2.60) compared to surgical resection only. Volume of EACs per center did not predict mortality.
Conclusion: In this large nationwide EAC cohort, mortality was decreased when patients were known with prior surveillance, when treatment was fully or partially performed in a university hospital, with a lower tumor stage at diagnosis and when surgery was combined with neoadjuvant chemo/-radiotherapy. These factors can be used in a prediction model for survival in patients diagnosed with EAC.

Botulin and steroid injection directly after widespread endoscopic resection do not prevent severe stenosis in an esophageal porcine model

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Endoscopic resection (ER) of early neoplasia in the esophagus is the first step in endoscopic treatment as it allows for histological evaluation and adequate staging. When performing large ER (≥3cm in length and ≥75% circumference) the risk of stenosis increases considerably. Steroids are used for the treatment of benign stenosis, while botulin may prevent stenosis formation by relaxing the muscularis propria. Aim: to determine the efficacy of botulin and steroid injections immediately after extensive endoscopic resection to prevent severe stenosis A total of 8 female pigs of 46-53 kg were included. In each pig, three treatment areas were marked in the esophagus, and piecemeal ER was performed 3cm in length and 75% circumference with the cap technique. Each resection wound was then injected in randomized order, with one of the following substrates: botulin 100 E (Botox) dissolved in 4 ml of sa 0.9% and injected as 0.5 ml aliquots (12.5 E) in 4 quadrants at two levels; triamcinolonacetonide 40 mg (Kenacort-A '40' 1 ml ampoule) dissolved in 3 ml of sa 0.9% and injected as 1 ml aliquots (10 mg) in 4 quadrants at one level; or 1 ml aliquots of sa 0.9% injected in 4 quadrants at one level as control. At the end of the procedure, all treatment areas were marked just proximal with two tattoos. All pigs were euthanized after 42 days at which the esophagi were harvested. After stretching on paraffin and before fixation in formalin the mucosal circumference of each treatment area was measured with a ruler at the center of the treatment area and at the upper edge of the treatment area. Endpoints were number and severity of stenosis after botulin, steroid and sa injection, depth of fibrosis in the esophageal wall on histology and number of delayed perforations. No acute or delayed perforations occurred. Stenosis occurred in all ER areas injected with botulin, steroids or saline. The ratio of the circumference at the center and the upper edge of the ER area was not significantly different between the area injected with botulin 0.18 (±0.07), steroids 0.19 (±0.07) or sa 0.22 (±0.03). Fibrosis reached always the muscularis propria in areas injected with botulin or steroids and in 6/8 areas injected with saline. Fibrosis was seen transmurally in 1/8 ER areas injected with botulin, 2/8 injected with steroids and 0/8 injected with saline.
Conclusion: Extensive ER results in deep fibrosis reaching the muscularis propria, which is probably the cause of severe stenosis. Botulin and steroids do not prevent the stenosis formation after extensive ER in a porcine model. Other therapies preventing stenosis after extensive ER still need to be explored.

Safety of Endoscopic Removal of Self-expandable Stents after Treatment of Benign Esophageal Diseases

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Temporary placement of self-expandable stents has been increasingly used for management of benign esophageal diseases. Still little data exist regarding the safety of removing these devices and the effect of dwell time on adverse events during removal. We sought to evaluate the safety of endoscopic removal of esophageal self-expandable stents placed for the treatment of benign esophageal diseases. A multicenter retrospective chart review was performed from May 2002 to August 2011 which included 6 tertiary care centers from the U.S. and Europe. Univariate and multivariate analyses using the Mann-Whitney test and logistic regression were performed to identify risk factors.A total of 329 stents were removed, including 265 (80.5%) self-expandable metal stents (SEMS) and 64 (19.5%) self-expandable plastic stents (SEPS). The primary indications for stent placement were benign strictures (n = 158; 48.0%) and fistulae (n = 164; 49.8%). SEMS were fully covered (n = 171; 64.5%) or partially covered (n = 94; 35.5%). The mean stent dwell time was 60 days (interquartile range 20 – 77, range 0 – 659 days). Partially covered SEMS (PCSEMS) had a mean dwell time of 45 days (median 25) and were removed sooner than fully covered SEMS (FCSEMS) and SEPS, which had a mean dwell time of respectively 61 days (median 45; $p < 0.001$) and 80 days (median 48.5; $p = 0.003$). At the time of removal, 91 (27.7%) stents had migrated and 15 (4.6%) stents were found to be severely imbedded. A total of 35 (10.6%) stent-related complications during removal were reported, including 7 (2.1%) major complications, i.e. perforation 3 (0.9%), esophageal avulsion 1 (0.3%), stridor requiring intubation 1 (0.3%), stent imbedded requiring surgical removal 1 (0.3%), and fistula formation 1 (0.3%). Univariate analysis showed increased odds of stent removal-related complications for PCSEMS ($p \leq 0.020$), large (≥ 23 mm) diameter stents ($p = 0.005$) and if the stent was imbedded in granulation tissue ($p = 0.051$). Stent migration was a favorable factor for safe stent removal ($p = 0.008$). No association was found between stent dwell time and the occurrence of removal-related complications ($p = 0.145$). Multivariate analysis revealed PCSEMS ($p < 0.001$) as a predictive factor for the occurrence of removal-related complications. Favorable factors were FCSEMS ($p < 0.012$) and stent migration ($p = 0.010$).

Conclusions: Endoscopic stent removal of FCSEMS, PCSEMS and SEPS in benign diseases appears to be safe and feasible, with an acceptable major complication rate of 2.1%. The occurrence of removal-related complications was not time dependent. FCSEMS were more successfully removed than PCSEMS and SEPS.

Peroral Endoscopic Myotomy (POEM) for the treatment of achalasia: preliminary feasibility and safety results

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The majority of patients with symptomatic achalasia are treated with either endoscopic pneumodilation or Heller myotomy. A pure endoscopic myotomy could be an effective alternative with less procedure related morbidity. Aim of this ongoing study is to evaluate the safety and feasibility of Peroral Endoscopic Myotomy (POEM) for the treatment of achalasia in a tertiary referral center. Primary endpoints are safety and feasibility. Secondary endpoints include technical success and procedural time. Patients with symptomatic achalasia based on manometry, barium swallow and gastroscopy are included in the study. Patients with previous surgery of the esophagus or stomach are excluded. POEM procedures are performed under general anesthesia with endotracheal intubation and using endoscopic CO2 insufflation (Erbe). A forward-viewing gastroscope with a distal cap is used to create a submucosal tunnel by repeated injection and dissection of the submucosa using a triangle-tip knife (Olympus) with spray coagulation (Erbe), starting 12-14 cm above the LES and extending 2 cm into the cardia. After creation of the tunnel, a myotomy of the circular muscle fibres is performed from proximal to distal starting 2-3 cm below the distal margin of the mucosal incision. After completion of the myotomy the mucosal incision is closed with 7-10 EZ-clips (Olympus). A water soluble contrast X-ray is performed day 1 postoperatively after which patients can resume oral intake. Per protocol all patients are admitted to the hospital for 4 days. From 08/11 till 12/11, 8 patients (5 males) were included in the study. Median age was 47.5 (range 20-73) years. Three patients had undergone prior treatment for their achalasia and symptom recurrence. Median preoperative Eckardt score was 6 (range 3-8). Median preoperative LES pressure was 21.1 (range 13-45) mmHg. All procedures were technically successful performed with complete section of all circular muscle fibres and a median procedure time of 117 (range 85-237) minutes. Median length of the myotomy was 11 (range 8-18) cm. No serious adverse events occurred. In two patients a pneumoperitoneum occurred peroperatively that was successfully desufflated using a 14 G needle. Due to a minor peroperative bleeding, one patient was briefly monitored postoperatively on the medium care. In none of the patients, leakage of water soluble contrast was seen the next day. Median postoperative C-reactive protein was 71.7 (range 14.8-108.5).
Conclusions: The preliminary results of this study show that POEM is feasible and safe and technically successful performed in all patients. Long-term studies will determine whether POEM will earn a place in the standard treatment of achalasia.

Treatment of GERD patients with Transoral Incisionless Fundoplication leads to a significant reduction in reflux symptoms and objective reflux parameters at six and 12 months follow up

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Transoral Incisionless Fundoplication (TIF) is an endoluminal surgical approach for the treatment of gastro-esophageal reflux disease (GERD). In the evaluation of TIF, a discrepancy in the degree of symptom improvement versus improvement of objective reflux parameters has been reported. Aim of the present study was to assess the effect of the TIF procedure on reflux symptoms and objective reflux parameters in GERD patients. Thirty-six patients with GERD and symptoms refractory to medication (25 males; mean age 45, range: 23-68 yrs) underwent a TIF procedure. Base evaluation included upper gastrointestinal endoscopy, 24 hr pH-impedance monitoring, manometry and GERD-HRQL questionnaires off antisecretory medication. Six and 12 months after TIF, tests were repeated (in 36 and 17 patients, respectively; follow up is ongoing). Analysis of 24hr ph-impedance measurements included total reflux time (pH<4) as well as number of liquid, proximal and acid reflux episodes. Six months after TIF, GERD-HRQL scores off antisecretory medication were significantly improved ($p<0.001$). Daily use of antisecretory medication was discontinued by 58.3% and reduced in dose by 30.6% of the patients. Total and upright acid reflux time was not significantly reduced (total from 10.0±1.0% to 8.3±1.2%, $p=0.22$; upright from 12.2±1.3% to 9.4±1.2%, $p=0.12$). However, total acid exposure time was improved in 63.9% and even normalized in 41.7% of the patients. Mean number of liquid, proximal and acid reflux episodes decreased significantly after TIF (liquid from 96±6 to 78±6, $p=0.03$; proximal from 45±3 to 31±3, $p=0.001$; acid from 62±5 to 45±4, $p=0.005$). Furthermore, mean resting pressure (mmHg) of the lower esophageal sphincter increased significantly (from 14.4±0.9 to 17.1±0.9, $p=0.03$). Twelve months after TIF, GERD-HRQL scores off PPI remained significantly improved ($p<0.001$). Total and upright acid reflux time were not significantly reduced (total from 11.3±1.7% to 7.9±1.3%, $p=0.06$; upright from 13.2±2.1% to 10.0±2.1%, $p=0.24$), but total acid exposure time improved in 76.5% and normalized in 35.3% of the patients. Furthermore, the mean numbers of acid and proximal reflux episodes remained significantly reduced ($p=0.01$ and $p=0.007$, respectively).
Conclusion: Transoral Incisionless Fundoplication leads to a significant reduction in reflux symptoms at six and 12 months follow up and this improvement is associated with a significant reduction in the number of proximal and acid reflux episodes. As normalization of acid exposure time was not achieved in the majority of patients, further studies are needed to identify which subgroup of GERD patients may benefit most from this treatment.

A cost study of covered transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic treatment for secondary prevention of gastro-oesophageal variceal bleeding

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Endoscopic variceal band ligation, usually combined with administration of B-blockers, is the accepted first therapy for the secondary prevention of variceal bleeding. Recent data suggest that transjugular intrahepatic portosystemic shunt (TIPS) is more effective and may become the preferred treatment. However, the comparative costs of these treatment strategies have not been well defined.We aimed to compare the initial and total medical costs of TIPS versus endoscopic treatment for the secondary prevention of gastro-oesophageal variceal bleeding in the first year following the index bleed. Cost comparisons included comprehensive data of TIPS placement and endoscopic band ligation, hospital admission costs and diagnostics. The initial costs for both interventions consisted of detailed measurement of investments in manpower, equipment, materials, housing and overhead. Health care consumption data were based on observed data in 52 consecutive patients (26 TIPS/26 endoscopy) surviving an acute first or second variceal bleeding due to liver cirrhosis-related portal hypertension. TIPS-treated patients received a mean of 1.2 interventions (range 1-3) in the first year, with a mean of 1.1 stents placed per intervention. Coil embolization of the collaterals was necessary in 16% of interventions. Patients treated by endoscopy needed a mean of 2.9 interventions (range 0-9) in the first year for varices obliteration. In 59% of endoscopic procedures rubber band ligation was performed, in 4% N-butyl cyanoacrylate mixed with lipiodol was used and in 37% no intervention was needed. Initial costs were higher for TIPS compared to endoscopic treatment (€11,525 vs. €545; P<0.001), mainly based on personnel (€865 vs. €82; P<0.001), material costs (€4114 vs. €78; p<0.001) and hospital admission (€3908 vs. €251; p<0.001). Despite a lower number of interventions in the TIPS-treated patients compared to the patients treated endoscopically (1.2 vs. 2.9 intervention; P=0.007), the total medical costs became barely more convergent (€13,830 vs. € 1580; P<0.001). Despite a larger number of interventions needed in endo-scopy-treated patients, total costs of TIPS in the first year of treatment for portal hypertension are more than eight times as high as endoscopic therapy. This is mainly due to much higher initial costs of TIPS. Besides efficacy and risk, costs may have an important impact on determining the preferred modality in management of patients with portal hypertension.

EUS-guided drainage is an effective treatment for the majority of symptomatic peripancreatic fluid collections

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Endoscopic drainage is a well accepted treatment modality for symptomatic peripancreatic fluid collections (PFC). Although some results on conventional or EUS-assisted PFC-drainage are available, data on the efficacy and safety of EUS-guided drainage performed in large patient cohorts are scarce and techniques used for drainage heterogeneous. To evaluate clinical success and complication rate of EUS-guided drainage of PFCs and to identify prognostic factors for complications and recurrence of PFCs.Consecutive patients undergoing EUS-guided drainage of a PFC in the period 2004-2011 were included. Patient characteristics, drainage techniques and follow up data were obtained by chart review. Technical success was defined as the ability to enter and drain a PFC by placement of a transmural plastic double pigtail stent, while clinical success was defined as complete resolution of a PFC on follow-up CT. Procedure related mortality was defined as patients dying within 1 month after drainage as a consequence of the drainage procedure. Hundred-eight patients (56% males, mean age 55 (SD 14) years) underwent EUS-guided drainage of a symptomatic PFC. Indications for drainage included abdominal pain (n=29), fever/sepsis (n=52), dyspepsia/jaundice due to obstruction of the biliary/GI-tract (n=21) or other (n=3). Prophylactic antibiotics were administered in 70/108 (71%) patients. The PFCs were drained through the stomach, duodenum or distal esophagus in 102, 4 and 2 cases, respectively. The procedure was technically successful in 105/108 (97%) of patients and a median of 2 (range 1-3) 7F or 10F pigtails were placed. Drainage was not successful in 2 patients due to perforation of either the PFC or stomach wall. The PFC collapsed in 1 patient before a pigtail could be placed. Following EUS-guided drainage, 33 patients (31%) underwent 93 endoscopic transluminal necrosectomies (median 3 (range 1-9)). Clinical success was observed in 87/104 (84%) patients after a median follow up of 53 (IQR 21-130) weeks, while PFC recurrence was seen in 15/83 (18%) patients. Complications occurred in 21/105 (20%) patients, i.e. secondary infection in 11, bleeding in 5, perforation in 4 and both infection and bleeding in 1 patient. No procedure-related mortality was seen. Patients on prophylactic antibiotics had a significantly lower complication rate (16%) than those not receiving antibiotics (37%, p=0.03).Conclusions: EUS-guided drainage of PFCs is effective in the majority of patients. Although the complication rate of the procedure is fair (20%), these did not result into mortality. Prophylactic antibiotics may reduce the complication rate of EUS-guided drainage.

Growth rate of pancreatic neuroendocrine tumors in MEN1 syndrome; an EUS surveillance study

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In multiple endocrine neoplasia type 1 (MEN1) syndrome, endoscopic ultrasonography (EUS) has become the standard imaging technique for identifying and localizing pancreatic neuroendocrine tumors (PNETs). For asymptomatic and small (<2 cm) PNETs, the role of EUS-based surveillance is not clear, particularly because the natural course of these lesions is largely unknown. Our aim was to asses the annual incidence and growth rates of small, asymptomatic PNETs in MEN1 syndrome as assessed by EUS.All patients with MEN1 syndrome who underwent EUS of PNETs in the period 2005 and 2011 in our hospital, which is a national referral center for MEN1 syndrome, were reviewed. Follow-up EUS was performed every 6-12 months while a CT, MRI or Somatostatin Receptor Scan (SRS) was performed at first diagnosis. In total 36 patients (males 67%, mean age 43 ±13 years) were included, in whom 107 PNETs were found at the index EUS. PNETs were located in the pancreas caput in 27/107 (25%), confluence caput/corpus in 5 (5%), corpus in 42 (39%), confluence corpus/tail in 9 (8%) and tail in 24 (22%). Median diameter was 6.4 mm (range 2-24 mm) and 91 (85%) PNETs were ≤10 mm. Only 42 of 107 PNETs were also identified by other imaging techniques with a sensitivity of 20/38 (53%) for CT, 22/70 (31%) for MRI and 6/22 (27%) for SRS. Twenty-eight patients (100 PNETs; mean 3.6±3.3 PNETs/patient) had at least two consecutive EUS procedures (range 2-7) during a median follow-up period of 22 months (range 4-51). Incidence rate was 1.32 PNETs per person year and the median growth rate of lesions was 0.37 mm per year (range -6 mm to +10 mm). PNETs ≤10 mm (84%) had a median growth rate of 0 mm per year (range -6 mm to +4.8 mm; IQR -0.19 to 0.8), while PNETs >10 mm (16%) had a median growth rate of 1.3 mm per year (range from -2.7 mm to +10 mm; IQR 0 to 2). During follow-up, 8 patients (29%) underwent surgery because of symptoms (n=3), lesions ≥20 mm (n=4) and metastases (n=1). No correlations were found between growth rate of PNETs and age or sex.
Conclusion: EUS based pancreatic surveillance in a large, single-center cohort of MEN1 patients demonstrates that the overall growth rate of PNETs is slow, although PNETs >10 mm seem to grow faster than those ≤10 mm. Surveillance intervals for performing repeat pancreatic EUS should depend on the size of a PNET found at the most recently performed EUS with an estimated interval of 2-3 years.

Visible light spectroscopy in diagnosis of chronic gastrointestinal ischemia: results of a cohort study

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Introduction: Chronic gastrointestinal ischemia (CGI) is more common than previously thought. Present-day diagnostics including CT angiography (CTA) and functional testing by means of the recently introduced visible light spectroscopy (VLS) contribute to diagnosis and selection of patients who are eligible for treatment. The aim of this study was to evaluate treatment response in patients with consensus diagnosis of occlusive CGI. Methods: Patients referred to our tertiary center for evaluation of CGI were prospectively included. All patients had a standard work-up, consisting of evaluation of symptoms, CTA or MRA for evaluation of gastrointestinal arterial patency, and VLS. After discussion in a multidisciplinary team, a consensus on presence or absence of CGI was reached, and patients with occlusive CGI were offered endovascular or surgical revascularization. A positive response was defined as: complete or > 50% disappearance of postprandial pain and weight gain or stabilization during follow-up (FU). Results: In 3 years, 212 pts were referred for evaluation of suspected CGI. Occlusive CGI was diagnosed in 112 (53%) pts. The most reported symptoms were postprandial pain (74%), weight loss (69%), and nausea (36%). Single vessel disease was found in 72/112 (64%), and multivessel disease in 40/112 (36%). In total, 96 (86%) received treatment. FU was available in 93/96 (97%) pts (59 single and 34 multivessel disease) with a median duration (interquartile range) of 15 (9-20) months. Sixty-seven out of 93 (72%) pts had sustained response, and 26 (28%) did not respond. In the latter group, 19/26 (73%) were primary non-responders, and 7/26 (27%) had an initial response to treatment, but had symptom recurrence during FU. CT angiography revealed patent vessels in all patients in the latter group. The persistent response rate thus was 38/59 (64%) in pts with single vessel disease, and 29/34 (85%) in pts with multivessel disease, P = 0.054. VLS was repeated in 22 pts. In pts with sustained response VLS improved in 10/13 (77%) pts. In primary non- responders VLS improved in 2/4 (50%) of pts, and in pts with loss of primary response in 4/5 (80%).
Conclusion: A multi-diagnostic, including VLS as a functional test, and -disciplinary approach for suspected CGI patients, provides a high response rate on mid-long term FU. Sustained response was achieved in 64 and 85% of single and multivessel disease patients, respectively. VLS improved in almost 80% of pts with sustained response. This emphasizes the role of functional testing for assessment of CGI and selection of pts for treatment, as well as the major impact of treatment in both single and multivessel CGI.

Real-time in vivo imaging of early mucosal changes during ischemia-reperfusion in human jejunum

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Small intestinal ischemia-reperfusion (IR) is a frequent, potentially life threatening phenomenon. There is a lack of noninvasive diagnostic modalities. For many intestinal diseases, visualizing the intestinal mucosa using endoscopy is gold standard. However, limited knowledge exists on small intestinal IR-induced, early mucosal changes. In this study, we combined a newly developed human experimental small intestinal IR model with the technology of video capsule endoscopy (VCE), to obtain first insight into the early endoscopic changes in human jejunum exposed to IR. In addition, this allowed us to investigate the concordance between endoscopic appearance and histology.In 23 patients a part of jejunum that had to be removed for surgical reasons, was isolated and selectively exposed to 30 or 60 minutes of ischemia with 0, 30 or 120 minutes of reperfusion. In a subgroup of 3 patients, a videocapsule was inserted in the isolated segment before exposure to IR, to visualize the mucosa. Endoscopic view at several time points was related to histology (Heamatoxylin&Eosin), obtained from 20 patients. Early ischemic lesions were confined to loss of villous structure and mucosal whitening while at 60 minutes of ischemia, punctate lesions were observed in the mucosa. This was related to appearance of subepithelial spaces and breaches in the epithelial lining in the histological view. Within a few minutes of reperfusion, the lumen filled with debris of IR-damaged, shed cells, while the underlying mucosa exhibited signs of erosions and hemorrhage. In line, histology showed massive villus tip shedding and mucosal hemorrhage at this point. Interestingly however, the mucosa healed rapidly over the course of reperfusion, since the only remaining signs of IR at 60 minutes of reperfusion were loss of villous structure and small erosions.In conclusion, this study shows a unique, real-time in vivo endoscopic view of early mucosal changes during IR of the human small intestine. Ischemia is characterized by loss of villous structure and mucosal whitening, while early reperfusion is associated with the appearance of intraluminal debris, mucosal erosions and hemorrhage. However, at longer reperfusion the mucosa recovered and only subtle signs of IR remained, emphasizing the importance of clinical suspicion and alertness of endoscopists. Future studies should evaluate usefulness of VCE in diagnosis of patients suspected of IR.

Impact of Colonoscopy in CT-Detected Colonic Wall Thickening

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Colonic wall thickening is not infrequently identified at abdominal computed tomography (CT). However, its clinical significance is still unclear. The objective of this study is to determine whether CT-detected colonic wall thickening warrants further colonoscopic evaluation. From January 2009 to December 2010 6,844 abdominal CT scans were performed at a general hospital in the Netherlands. The reports of these CT scans were retrospectively reviewed at the presence of colonic or terminal ileal wall thickening. Additionally, the results of subsequent colonoscopic work-up were collected. Five hundred sixty-five patients (8,3%) with colonic and/or terminal ileal wall thickening were identified, comprising 56% females. Median age of patients was 63 years (range 15-93). Two hundred four patients (36%) underwent further endoscopic examination. Median time interval from CT scan to colonoscopy was 27 days (± 34days). Main reasons not to perform colonoscopy were known gastrointestinal diseases, necessity of urgent surgery, absence of clinical consequences of diagnosis and failure of pre-CT scan colonoscopy. In 52 out of 204 patients (25%) who underwent colonoscopy, significant, newly diagnosed abnormalities were found, correlating with the radiological findings. The most common diagnosis made was malignancy (21 patients; 10% of all patients), followed by inflammatory bowel disease (18 patients; 9%). Other findings were ischemia, large polyps (both 4 patients; 2%), radiation colitis and infectious causes (both 2 patients; 1%). Indications of CT scan in the 52 patients with newly diagnosed diseases were predominantly acute abdominal pain (in 22 patients; 42%), screening for malignancy (in 10 patients; 19%) and symptoms of bowel obstruction in 6 patients (12%).Colonoscopy was performed in 17 patients with isolated ileal wall thickening, although in 2 of them the terminal ileum was not reached. Among the 15 patients who underwent complete ileocolonoscopy, 11 patients (73%) had abnormal findings. One patient was diagnosed with ischemia, but all other patients had Crohn's disease. In 6 patients (41%) Crohn's disease was a new diagnosis.
Conclusions: In patients with CT-detected colonic and/or ileal wall thickening endoscopy demonstrates significant abnormalities in 1 out of 4 patients. In isolated ileal wall thickening the incidence of new abnormal findings was even higher. Because of the high rate of newly diagnosed colorectal carcinoma and inflammatory bowel disease endoscopy should be performed in patients with colonic and/or ileal wall thickening.

High adenoma detection rate in first degree relatives of patients with serrated polyposis syndrome: a prospective study

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Serrated polyposis syndrome (SPS) is characterized by the presence of multiple colorectal hyperplastic polyps (HPs) and sessile serrated adenomas (SSAs) and is associated with an increased colorectal cancer (CRC) risk. First degree relatives (FDRs) of SPS patients are also believed to have an increased risk for both CRC and SPS, but only retrospective data are available. Prospective evaluation of the magnitude of these risks in FDRs is necessary to determine whether screening colonoscopies are indicated in these persons. The aim of this study was a prospective assessment of the prevalence, distribution and type of neoplasia in FDRs of SPS patients. We identified all patients with a diagnosis of SPS in 2 academic hospitals in the Netherlands. From 12/2008 to 12/2011, we invited all FDRs ≥ 35 years of age or 5 yrs younger than the index case for a colonoscopy. FDRs who had already undergone a colonoscopy in the last 3 years and FDRs with a history of CRC were excluded. All responders underwent a standard colonoscopy, either in an academic or local hospital. All polyps were removed or biopsied. Primary outcomes measures were the incidence of CRC, adenoma detection rate (ADR) and presence of multiple (≥3) proximal serrated polyps. In addition, we compared the ADR in this cohort with previously reported ADRs in subjects of the same age fulfilling the criteria of familial CRC [1]. A colonoscopy was performed in 71 FDRs (39 siblings, 28 children and 4 parents) from 35 SPS pedigrees, of which 2 FDRs had to be excluded for further analysis because of poor bowel prep and incomplete colonoscopy. Mean age at colonoscopy was 50.1 yrs (SD ± 10), 33 subjects (48%) were male. During colonoscopy, no CRC was detected. Adenomas were detected in 25 FDRs (36%) including adenomas with advanced pathology in 6 FDRs (9%). Of all FDRs ≤ 50 years of age (n=32), ≥ 1 adenoma was detected in 10 (32%). Multiple proximal serrated polyps were detected in 4 FDRs (6%) of whom 1 sibling fulfilled the WHO criteria of SPS. In conclusion, this study showed that 6% of FDRs of SPS patients harbor multiple (≥ 3) proximal serrated polyps, of whom one sibling fulfilled the WHO criteria of SPS. This is considerable as the estimated incidence of SPS is 1:3.000. The observed ADR of 36% is substantially higher compared to that in subjects of the same age fulfilling the criteria of familial CRC (19%) [1]. As current guidelines recommend endoscopic surveillance in the latter group, a screening colonoscopy in all FDRs ≥ 35 yrs or from 5 years younger than the index case seems justified. [1]

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Colonoscopy performed by nurse endoscopists is associated with high patient satisfaction

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Colorectal cancer screening programs are widely being introduced. This results in a growing demand for nurses to perform colonoscopy. Assessment of patient satisfaction with colonoscopy performed by nurse endoscopists (NE) is therefore important. The aim of this study was to compare experiences of patients undergoing diagnostic colonoscopy performed by either a NE or a physician.Nurses and GI fellows that participated in this multi-center study (Sept 2008–today) finished a training period (part I) of at least 100 supervised colonoscopies before they started to perform colonoscopies independently (part II) with supervision available if necessary. The first 135 colonoscopies of part II of each endoscopist were used to assess patient satisfaction. Patients <18 yrs and those referred for therapeutic procedures were excluded. Patient experiences were measured by 4 different questionnaires that were filled in 1 week before, prior to, 1 week after and 1 month after colonoscopy. Patients were asked to rate their satisfaction with the endoscopic procedure and the performance of the endoscopist, and to indicate whether they had a preference for a physician or NE on a 5-point Likert scale.In total, 1118 patients of part II received questionnaires. Of these, 656 (59%) returned ≥1 questionnaires. Ninety percent of patients in the NE group experienced the procedure as excellent or good and only 2% had a poor or very poor experience. Eighty-three percent of patients who underwent colonoscopy performed by a GI fellow found the procedure itself excellent/good, while 5% experienced it as poor/very poor (p=0.02). Patients were overall very satisfied with their endoscopist; 94% of patients of the NE group and 91% of patients of the GI fellow group (p=0.03) rated the endoscopist that had performed their colonoscopy excellent or very good. For 71% of patients that had undergone a colonoscopy performed by a NE it did not matter whether a NE or a physician would perform a future colonoscopy, 26% would rather have a physician perform the next procedure while 4% would prefer a NE. In the group of patients in the GI fellow group, 61% had no specific preference for a physician or NE. However, 38% chose for the physician and only 1% would rather prefer a NE. This study shows that patients who had undergo a colonoscopy performed by a NE are generally very satisfied with the procedure and with the performance of their endoscopist. However, if able to choose, about one third of all patients would still prefer a physician to perform their future colonoscopy. Information on safety and quality of colonoscopies performed by a NE and on the background presence of a supervising physician who is available on short notice may in this case reassure these patients.

Malignant colonic polyps are not benign: Outcome and guide adherence after endoscopic or surgical treatment

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The number of cases in which malignant colonic polyps are diagnosed is increasing due to colorectal cancer screening programmes. According to guidelines, patients can be divided into high- and low-risk malignant polyps, based on histologic criteria. Endoscopic polypectomy alone should be sufficient for low-risk patients. Surgical resection is recommended for malignant polyps in the high-risk category. In this study we evaluated the quality and outcome of the treatment of malignant colonic polyps in two large general hospitals. Consecutive patients with an endoscopically removed malignant colonic polyp between 1995-2007 in two large general hospitals were retrospectively studied. Patients with complete resection (≥ 2 mm free margin), well or moderately differentiated and absence of vascular invasion, were classified as low-risk. All other patients were classified as high-risk. The treatment and outcome were evaluated. The histology was revised when they found to be incomplete. Patients were followed up until August 2011. A total of 111 patients (69 males, mean age: 69 years) were included. Mean follow-up of patients was 7,7 years. 65 patients had a high-risk polyp, of which 52 patients received subsequent surgical treatment. 46 patients had a low-risk polyp, of which 35 patients got endoscopic resection. Four patients with high-risk and only endoscopic resection and 4 patients with high-risk and surgical treatment had a recurrence during follow-up. No patients with a low-risk polyp developed recurrent cancer. In total, 7% developed a recurrence, 5% died of the effects of a malignant polyp. During endoscopy, 3% had a severe complication and in the surgical group, 15% had a severe complication. Mortality from surgery was 0% in this study.
Conclusion: Nearly one third of the patients with malignant colorectal polyps did not get the treatment according to the guidelines, for various reasons. The risk of a recurrence or metastases of a malignant polyp was 7% in this study. These were all high-risk polyps. This study shows that the risk of a malignant polyp should not be underestimated.

Risk factors for lymph node metastasis in 342 surgically treated patients with early gastric cancer confined to the upper submucosal layer (Sm1)

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Introduction: Early gastric cancer (EGC) confined to the mucosal layer can be removed by endoscopic resection (ER) given the low risk of lymph node metastasis (N+). For lesions invading into the submucosa surgery is considered the treatment of choice since this allows lymph node dissection. Some studies have suggested that lesions with submucosal invasion <500 μm (sm1) have such a low risk of N+ that ER is justified here as well. These studies have, however, mainly used the Japanese way of histological evaluation and have not been published in English literature. Aim: To evaluate the N+ risk in a large cohort of sm1-EGC patients who were treated by surgical gastrectomy and lymph node dissection using dedicated histological review of specimens following Western (i.e. Vienna) criteria. Methods: All consecutive patients with EGC treated by gastrectomy (n=5005) at a single Korean center between 2000-2008 were identified. ECG specimens were cut in 3-mm slides, and evaluated routinely by expert pathologists. Data on endoscopic appearance, surgical treatment, histology and follow-up were entered into a specially designed database. For the purpose of this study, histology slides of patients with sm1-ECG were reviewed by a single expert pathologist and only cases with a confirmed diagnosis of sm1-ECG were included. Univariate analysis was conducted using the $\chi 2$, Fisher's and student t test. Multivariate analysis was performed using logistic regression, based on the significant variables found by univariate analysis. All p-values were 2-tailed and p-values less than 0.05 were considered statistically significant.Results: 342 patients with sm1-EGC were included. At surgery, a median of 34 (IQR 19) lymph nodes were resected per patient. N+ was detected in 41 cases (12%). Univariate analysis showed a significant association with N+ for tumor size (≥ 2cm) (p= 0.009), endoscopic appearance (Paris classification 0-I, 0-IIa, 0-II-is, 0-IIb) (p= 0.049), lymphatic (p= 0.000) and vascular (p=0.014) invasion. Multivariate analysis showed a significant association for tumor size (OR 3.7; p= 0.046) and lymphatic invasion (OR 13.0; p=0.000).
Conclusion: Given the relatively high risk of N+ in sm1-EGC patients (12%), the use of ER for this indication may not be as safe as suggested by some studies. Especially the presence of a tumor ≥ 2cm or lymphatic invasion were significantly associated with N+, suggesting that these patients might better be treated by surgical gastrectomy and lymph node dissection.

Long-term survivors of esophageal cancer in the Netherlands

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Background + Aims: Long-term survival is low in esophageal cancer (EC), and mostly influenced by tumor characteristics. The aim of this study was to assess differences in prognostic factors affecting short- and long-term survival (1, 3 and 5 years) in esophageal cancer patients. Methods: The Eindhoven Cancer Registry maintained by the Comprehensive Cancer Centre South was used to select all patients diagnosed with primary EC in the period 1990-2009. The registry records data on patient and tumor characteristics of all patients that were newly diagnosed with EC in an area with 2.3 million inhabitants. Patients receiving curative intended treatment were included in the analyses. Multivariable logistic regression analysis was used to identify determinants of 1-, 3-, and 5-year survival. Results: A total of 647 patients were included for the 1-year survival analysis, 504 for the 3-year analysis and 391 patients for the 5-year analysis based on availability of follow-up data. Sixty-seven percent were still alive 1 year after the diagnosis. The variables related with poor prognosis were age older than 80 years (Odds ratio (OR) 0.27; 95% Confidence Interval (CI) 0.09 – 0.80, vs. age < 60 years), lymph node (LN) status N1 (OR 0.60; 95% CI 0.39–0.93 vs. N0) and having one or more comorbidities (1 comorbidity: OR 0.60; 95% CI 0.39–0.93; ≥ 2 comorbidities: OR 0.55; 95% CI 0.35–0.87 vs. no comorbidities), while having an adenocarcinoma was related with a better prognosis (OR 1.79; 95%CI 1.20 – 2.66, compared to squamous cell carcinoma). For the 3-year survival time point (34% survival rate), N1 (OR 0.51; 95% CI 0.31–0.84) and 2 or more comorbidities (OR 0.57; 95% CI 0.33–0.97) were negative prognostic factors, while female gender (OR 1.67; 95% CI 1.08–2.57) and having an adenocarcinoma (OR 1.91; 95% CI 1.22–3.01) were positive prognostic factors. For the 5-year survival time point (23% survival rate), female gender (OR 1.94; 95% CI 1.13–3.34) and having an adenocarcinoma (OR 1.86; 95% CI 1.05–3.29) were positive prognostic factors, N1 was a negative predictive factor (OR 0.48; 95% CI 0.24–0.96). Conclusion: Prognostic factors affecting survival after curative treatment for esophageal cancer vary between 1-, 3- and 5-year survival. Of the non-tumor-related factors, short term survival is negatively affected by older age and comorbidities, while long-term survival is associated with female gender. Tumor-related factors of survival are positive lymph nodes and having an adenocarcinoma. Further studies are needed to determine how cancer histology and gender specifically influence survival.

Familial clustering of Barrett's esophagus and esophageal adenocarcinoma in the Netherlands

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Both genetic and lifestyle factors have been recognized to play a role in the development of Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). Although familial clustering of BE and EAC have been reported, differences between familial and non-familial BE have until now not been identified.The aim of this study was to determine clustering of reflux symptoms, BE and EAC in first and second degree relatives of patients with BE and EAC and to identify differences between familial and non-familial cases.A structured questionnaire was sent to all patients (n=838) with a diagnosis of BE (≥2cm) or BE associated EAC between 2000 and May 2011 from one university and two general hospitals. Information about risk factors of BE, reflux symptoms, and a family history of reflux symptoms, upper endoscopy, BE and esophageal cancer was collected and medical records were reviewed. Diagnoses of affected first and second degree relatives with BE and esophageal cancer was confirmed in the nationwide histopathology database (PALGA). Familial BE status was defined as 'definitive' if at least one first or second degree relative was confirmed with a diagnosis of BE or EAC, 'possibly' if a reported BE or esophageal cancer diagnosis was stated but not histologically confirmed, 'unlikely' with a negative family history of BE or esophageal cancer, or 'unknown'. Differences between 'definitive' and 'unlikely' groups were analyzed using chi-square and Mann-Whitney U testing. A total of 595 index patients responded (response rate 71%), of which 19% reported affected relatives. After confirmation of the diagnosis, familial BE was 'definitive' in 6% (36/595), 'possibly' in 6% (37/595), 'unlikely' in 49% (292/595) and 'unknown' in 39% (230/595) of the index patients. Definitive familial BE cases reported reflux symptoms in 11% of first degree relatives compared to 5% in unlikely familial BE ($p<0.001$). Additionally, 5% of the definitive familial BE first degree relatives underwent upper endoscopy compared to 2% in unlikely familial BE ($p<0.01$). Definitive familial BE cases were younger at onset of heartburn compared to unlikely familial BE: 29% vs. 11% aged under 20 years ($p<0.01$). No significant differences in BMI, smoking, alcohol consumption, presence of hiatal hernia, severity of reflux symptoms, age at BE diagnosis, BE segment length, and highest dysplasia grade were found.
Conclusion: This large case series shows that familial BE is present in 6% of patients with BE and EAC. Familial cases reported more often reflux symptoms and a prior upper endoscopy in family members and were younger at onset of reflux symptoms, which may suggest a genetic basis of familial BE.

Electrical stimulation of the lower esophageal sphincter in patients with gastroesophageal reflux disease is technically feasible and results in a decrease in symptoms

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Background: Patients with gastroesophageal reflux disease frequently exhibit excessive amounts of gastroesophageal reflux episodes caused by LES dysfunction. Electrical stimulation of the LES could, in theory, restore LES function in patients with LES dysfunction. Recently, a device was developed which can provide electrical stimulation to the lower esophageal sphincter, the so called Endostim device. In this pilot study, we aimed to determine whether implantation of the Endostim device is technically feasible and safe. Furthermore, we aimed to determine whether electrical stimulation of the LES will result in a decrease in symptoms of GERD. Methods: We included 3 patients (median age: 51 (range: 45-54) years, 2 female) with typical symptoms of GERD, a pathological esophageal acid exposure time (time pH<4 >6%) and a positive correlation between symptoms and reflux episodes during ambulatory reflux monitoring (SAP>95%). During a laparoscopic implantation, the device was connected to the endoscopically identified LES with two electrical leads. Technical success of the procedure was evaluated by measuring the electrical resistance in the two leads during the first electrical stimulation session. Cardiac monitoring was performed during the first stimulation session after implantation to evaluate cardiac safety. Symptoms of GERD were evaluated on PPI at baseline, off PPI at base and 1 month after implant using the GERD-QOL questionnaire. Results: Median (range) duration of the procedure was 2:51 (2:38-3:15) hours. No per-operative or post-operative complications were observed. No cardiac rhythm abnormalities were observed during electrical LES stimulation. All patients demonstrated resistance levels of the leads within the normal range during first stimulation session, indicating correct placement. Median (range) post-operative GERD-QOL score (7 (4-13)) was significantly lower than the pre-operative GERD-QOL score off PPI (38 (28-40), $p<0.05$) and on PPI (22 (17-22), $p<0.05$). All patients had ceased using their PPIs at the 1 month follow-up visit. Furthermore, all patients were satisfied with their surgical outcomes during the 1 month follow-up visit. Notably, all patients experienced mild epigastric pain after the implantation which quickly resolved within 2-4 weeks in all patients.
Conclusions: Implantation of the Endostim device and stimulation of the lower esophageal sphincter is a safe and feasible. Furthermore, stimulation of the lower esophageal sphincter results in a decrease in symptoms of GERD, decrease in PPI usage and increased patient satisfaction. However, further results have to be awaited to determine its potential use in clinical practice.

High enzyme activity UGT1A1 or low activity UGT1A8 and UGT2B4 genotypes increase esophageal cancer risk

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Esophageal cancer has an increasing incidence worldwide with poor curative treatment options and survival rates. Different etiologies and risk factors participate in the global incidence variation of the two histological subtypes; squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). UDP-glucuronosyltransferases (UGTs) are a superfamily of phase II biotransformation enzymes essential for the detoxification of a variety of exo- and endogeneous carcinogens. Polymorphisms in the UGT genes may alter their enzyme activity and play a role in the etiology of esophageal cancer by modifying the rate of detoxification of reactive compounds. Therefore, rather than solely establishing differences in allele distribution between patients and controls, we are interested to see whether functional polymorphisms in UGT genes, with modified in vitro enzyme activities, possibly leading to altered in vivo enzyme activities, may influence esophageal cancer risk. We conducted a large case-control study with 351 Caucasian esophageal cancer patients and 592 age, race and sex matched controls to examine whether esophageal cancer susceptibility is modified by altered predicted enzyme activity UGT genotypes. Based on esophageal expression and relevance to upper aerodigestive neoplasm etiology, we determined polymorphisms in genes of four UGT1A and three UG2B isozymes by using real time polymerase chain reaction. The in vitro enzyme activity for each allele has previously been identified. On this basis genotypes were classified according to their predicted in vivo enzyme activity into three categories: high, intermediate and low. The UGT1A1 and UGT1A8 predicted high enzyme activity genotypes were significantly more (OR 1.62; 95% CI 1.02-2.56) and less frequent (OR 0.36; 95% CI 0.15-0.84) among ESCC patients than controls, respectively. Combined genotypes of UGT2B4 associated with predicted medium and high activities, were significantly less often present in ESCC patients (OR 0.35; 95% CI 0.18-0.68). This case-control study did not detect an association between polymorphisms in UGT genes and EAC risk.
Conclusions: The predicted high activity UGT1A1*1/*1 genotype, associated with low serum levels of the antioxidant bilirubin, was associated with an increased risk of ESCC. The UGT1A8*3 and UGT2B4*E458 alleles, both associated with a decreased predicted enzyme activity, were significantly associated with an increased risk of ESCC, probably due to a decreased detoxification of carcinogens. Polymorphisms in UGT genes do not seem modifiers of EAC risk.

Rapidly increasing incidence of eosinophilic esophagitis in a nationwide cohort

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Recent literature has suggested that the incidence and prevalence of eosinophilic esophagitis (EoE) are increasing. Aim of this study was to estimate the true population-based incidence rates of EoE by using a large national database.We performed a cross-sectional study of the pathology reports describing esophageal eosinophilia from 1996 through 2010, using the Dutch nationwide registry of histopathology reports (PALGA). All histopathology reports of the Netherlands (16,615,394 inhabitants in 2010) enter this database. Cases were identified and classified according to the diagnosis made by the pathologist. Annual incidence rates of EoE were estimated and adjusted for age and sex.Our search yielded 8,838 pathology reports. Diagnosis of EoE was made in 674 patients, of which 501 (74.3%) were male and 173 (25.7%) female. In another 174 cases no difference was made between eosinophilia caused by reflux disease or by EoE. The incidence of EoE increased considerably with time, being 0.01 (95% CI 0-0.02) in 1996, 0.01 (95% CI 0-0.03) in 2000, 0.14 (95% CI 0.08-0.20) in 2005, and 1.31 (95% CI 1.13-1.48) per 100,000 persons per year in 2010. EoE was diagnosed in all age groups, but the highest incidence was seen in patients in the male 20-29 year age group in 2010, in which it was estimated to be 3.23 (95% CI 2.13-4.33) per 100,000 persons. The incidence in children was 0.73 (95% CI 0.45-1.02) per 100,000 persons in 2010. No seasonal variation in diagnosis of EoE was seen.
Conclusion: We found a rapidly increasing incidence of EoE in the past 15 years that did not reach a plateau yet. This augmentation could be explained on the one hand by an increased awareness of EoE by physicians and pathologists, and on the other hand by a true increase of incidence of the disease. The latter would be in with the parallel increase in other atopic diseases.

Short- vs. long-term value of prognostic factors in colon and rectal cancer: a population based study

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Colorectal cancer (CRC) mortality strongly depends on TNM-stage, but is also affected by factors like age, gender and co-morbidity of patients. Previous results from population based studies on prognostic factors other than TNM-stage for CRC mortality vary widely due to heterogeneity and limited possibility to adjust for treatment. Moreover, the prognostic value of these factors may be dependent on analyses for short- and long-term mortality. The aim of this study to investigate the prognostic value of various clinical and tumor related factors for different endpoints of mortality in colon and rectal cancer. All patients diagnosed with CRC in the period between 1994 and 2009 in one of the Dutch Cancer Registry areas (approximately 2.4 million inhabitants) were included in this study. Demographic and clinical data were retrospectively collected. Multivariable Cox proportional hazard models were used to estimate adjusted hazard ratios (HR) for age, gender, tumor characteristics, co-morbidity, socio-economic status (SES), year of diagnosis and treatment, at 1, 3 and 5 years after diagnosis. A total of 24,448 CRC patients were included (62% colon, 37% rectum, 1% unknown localization). One-, three- and five-year overall survival rates were 76%, 52% and 37% for colon cancer, respectively, and 76%, 53% and 38% for rectal cancer, respectively. Independent factors associated with mortality in colon cancer were advanced TNM-stage, poorly differentiated tumor, older age, male gender, co-morbidity and low SES for all endpoints. In rectal cancer, factors independently associated with mortality for all endpoints were advanced TNM-stage, poorly differentiated tumor, co-morbidity, older age and male gender. For all risk factors HR decreased over time in both colon and rectal cancer, which was most pronounced for age (HR-colon 1, 3, 5 year: 2.85, 0.99, 0.96, and HR-rectum 1, 3, 5 year: 2.81, 0.96, 0.95). In colon cancer, surgery of the primary tumor was associated with an increased mortality in the first year, but with a decreased mortality at 3 and 5 years (HR 1, 3, 5 year: 2.24, 0.65, 0.63, respectively). A similar trend was observed in rectal cancer, though not significant. Chemotherapy and radiotherapy were most protective in the first year after diagnosis.
Conclusion: in both colon and rectal cancer, prognostic factors for overall mortality are most predictive in the first year after diagnosis and to a lesser degree in the third and fifth year. Adjuvant treatment is in general most protective for the first year, while surgical treatment for colon cancer but not rectal cancer is associated with an increased mortality in the first year.

Cochrane Review: Helicobacter pylori eradication for pre-malignant lesions of the gastric mucosa

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Helicobacter pylori infection is a major risk factor for gastric cancer development. However, the effect of H.pylori eradication for prevention of gastric cancer is still controversial, in particular in patients with pre-malignant gastric lesions. This systematic Cochrane review was performed to assess the effect of H.pylori eradication therapy on different stages of pre-malignant lesions of the gastric mucosa, i.e. atrophic gastritis, intestinal metaplasia and dysplasia. Randomized controlled trials comparing H.pylori eradication therapy with placebo or symptomatic treatment in patients with pre-malignant gastric lesions were included. The trials were identified through electronic searches of the Cochrane Library, MED and EMBASE databases, using appropriate subject headings and keywords. Data were collected on histological changes of the gastric mucosa and functional parameters of gastric mucosal condition.Nineteen randomized controlled trials were included, with a total of 5.087 patients (range 20 to 1.630 patients per study). These trials compared H.pylori eradication therapy (n=2.604) with placebo or no treatment (n=1.764), or acid suppressive therapy (n=719). The effect of H.pylori eradication on gastric mucosal changes was evaluated after 8 weeks to 12 years follow-up (2 studies with follow-up ≤ 3 months; 7 studies ≤ 12 months; 5 studies ≤ 2 years; 5 studies 3 to 9 years). In 17 studies details on the effect of H.pylori eradication on atrophic gastritis were reported, of these 10 studies demonstrated less progression or even regression of atrophic gastritis (total n= 2.237; follow-up 1 to 9 years), whereas 7 studies reported no beneficial effect (total n= 904; follow-up 8 weeks to 1 year). Fourteen studies reported on the effect on intestinal metaplasia, of these 4 studies showed significant less progression (total n= 1.119; follow-up 1 to 6 years), however, this finding was not confirmed by the reports of 10 studies (total n= 1.822; follow-up 1 to 9 years). The effect on the progression of dysplasia was only reported in 3 trials, 1 study showed a significant reduction of the progression of dysplasia after 9 years follow-up in a study population of 567 patients, whereas 2 studies showed no significant effect after 5 and 6 years of follow-up in a total of 824 patients.
Conclusions: Clinical evidence for the prevention of carcinogenic progression in patients with atrophic gastritis is highly suggestive, whereas the evidence in patients with intestinal metaplasia and dysplasia is conflicting. Therefore, H.pylori eradication may be insufficient to halt gastric carcinogenesis in patients with intestinal metaplasia and dysplasia.

hsTRAIL/Apo2L-Induced Apoptosis in Enteropathy-Associated T-Cell Lymphoma

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EATL is an intestinal tumor of aberrant intraepithelial T-lymphocytes (IELs) and may be preceded by refractory celiac disease type II (RCD II). Current therapies include surgery, chemotherapy and autologous and/or allogeneic stem cell transplantation. Despite these therapies, the overall outcome of EATL is very poor with 1- and 5-year survival rates in the range of 31-39% and 8-20%, respectively. Therefore, new therapeutic options are needed. Human soluble tumor necrosis factor-related apoptosis-inducing ligand, hsTRAIL/Apo2L, a member of the TNF family, has proven to selectively kill tumor cells via an alternative, death-receptor mediated apoptosis pathway. In this present study we evaluated if hsTRAIL/Apo2L induces apoptosis in both isolated lymphoma cells of EATL biopsies and isolated cells of RCD II biopsies. hsTRAIL/Apo2L induced apoptosis in isolated EATL lymphoma cells. RCD II cells were less sensitive to hsTRAIL/Apo2L compared to EATL cells. EATL cells demonstrated high expression of TRAIL receptors R1 and R2 and almost no expression of R3 and R4, whereas RCDII cells showed little expression of TRAIL receptor R1 and R2. hsTRAIL/Apo2L-induced apoptosis in EATL cells was caspase-9 dependent, but unexpectedly only low to moderate caspase-8 involvement could be detected. RT-MLPA analysis on EATL samples confirmed this observation by showing increased levels of c-Flip in EATL cells, which suggests a blockage in the extrinsic apoptosis pathway.
In conclusion, our study showed that hsTRAIL/Apo2L induces apoptosis in EATL cells, mainly through the intrinsic apoptosis pathway. Therefore, hsTRAIL/Apo2L may be a new therapeutic option for EATL patients.

Primary colorectal cancer with unresectable synchronous metastases: chemotherapy first?

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The best treatment strategy for patients with primary unresectable metastatic colorectal cancer remains controversial. Resection of the primary tumor seems to be a good option to prevent cancer-related pain, obstruction, or bleeding. However, surgery is also associated with morbidity and mortality. Due to these complications, effective palliative chemotherapy may not follow surgery. The aim of this study was to investigate whether surgery of the primary tumor followed by chemotherapy in patients with colorectal cancer with unresectable metastases offers advantages over primary chemotherapy. The study population consisted of all patients with primary incurable stage IV colorectal cancer without acute surgical indication (i.e. obstruction or bleeding) who were diagnosed in our hospital between 1997 and 2008. Patients were divided into three groups, a primary surgical group, a group of chemotherapy and a palliative group. Survival analysis was performed using Kaplan-Meier. The log-rank test was used for univariate analysis and Cox regression for multivariate analysis. 118 patients were enrolled: 47 patients (40%) had primary surgery followed by chemotherapy, 39 patients (33%) had surgery, 15 patients (13%) chemotherapy alone and 17 patients (14%) symptomatic treatment without resectional surgery and/or chemotherapy. The groups did not differ regarding age and gender distribution. At the time of analysis, 12 patients were (10%) alive, leading to a 2-year survival of 13%. The best survival was seen in patients who had surgery followed by chemotherapy and in patients receiving chemotherapy alone. Age below 70 years (2-year survival 18% vs. 7%, respectively), left-sided tumors (17% vs. 7%), LDH level below 225 (29% vs. 7%), no extra-abdominal disease (14% vs. 7%), surgery (15% vs. 8%) and chemotherapy (19% vs. 5%) were all significantly correlated with better 2-year survival. In the multivariate analysis, left-sided tumors, no extra-abdominal disease, normal LDH levels and chemotherapy were favorable predictors for survival.
In conclusion, patients with primary colorectal cancer with unresectable synchronous metastases have the best survival with chemotherapy, with or without surgery of the primary tumor.

Low yield of advanced neoplasia within six years after negative colonoscopy : a population-based study

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BackgroundOne of the colonoscopy quality indicators is the occurrence of colorectal cancer (CRC) after a negative colonoscopy. Yet little is known on the incidence of advanced neoplasia and its predictors following a negative colonoscopy in daily clinical practice. AimTo evaluate the quality of colonoscopy in daily clinical practice by investigating the incidence of colorectal cancer and advanced adenomas after negative colonoscopy in a population-based cohort study. Material and MethodThe initial cohort consisted of all patients that underwent a complete colonoscopy in a three months period in 2005 in Northern Holland. Patients with a negative colonoscopy were followed for the subsequent occurrence of advanced neoplasia. The national Pathology Data System was used to identify patients with advanced neoplasia during six years of follow-up. ResultsIn total, 2.812 eligible patients were enrolled. Advanced neoplasia was found in 37 patients (1.3%), of which 12 patients (0.4%) were diagnosed with CRC. Eight patients were diagnosed with CRC 6 to 36 months after negative colonoscopy, two patients within 6 months and two patients after 36 months. Five out of twelve colorectal carcinomas were located in the proximal colon (42%). Twenty-five patients had advanced adenomas after negative colonoscopy, 32% were found within 3 years and 44% were located in the proximal colon. In 6/12 patients with CRC and in 16/25 patients with an advanced adenoma, the procedure indication was surveillance after CRC/polypectomy. Higher age, but not bowel preparation, sedation or endoscopist's specialty, were associated with the presence of advanced neoplasia during follow-up.
Conclusion:There is a low yield of advanced neoplasia six years after negative colonoscopy in this population-based study. Most advanced neoplasia were found in high-risk patients undergoing surveillance.

The rising incidence of esophageal adenocarcinoma is not accompanied with an increase in mortality: results of a population-based cohort study

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The incidence of esophageal adenocarcinoma (EAC) is rising faster than any other malignancy, which may be the consequence of increased adherence to surveillance in patients with Barrett's esophagus (BE). As treatment strategies have improved over time, we hypothesized that mortality rates did not increase to the same extent as the rising EAC incidence.The aim of this study was to 1) confirm the rising annual EAC incidence rate, 2) identify a parallel increasing incidence in the proportion of incident EAC cases with a prior diagnosis of BE, 3) analyze the absolute 1-year mortality rate of EAC, and 4) analyze the adjusted one-year mortality risk over time.All patients diagnosed with EAC between 1999 and 2009 were identified in the Dutch cancer registry and were linked to PALGA, the nationwide histopathology registry. Incidence rates were calculated as the number of EACs diagnosed per 100,000 inhabitants aged over 19. The proportion of patients with a BE diagnosis ³1 year prior to EAC detection were compared between the EAC incidence years using chi-square testing. Multivariate Cox proportional hazards regression analysis was performed to calculate adjusted hazard ratios (HR) for 1-year mortalities for each incidence year. HRs were adjusted for age, gender, prior BE diagnosis, tumor differentiation grade and stage, hospital of EAC diagnosis and treatment and treatment strategy. In total, 9,855 patients were diagnosed with EAC between 1999 and 2009. The EAC incidence rate increased from 5.2 per 100,000 inhabitants in 1999 to 10.0 in 2009. The proportion of patients with a BE diagnosis at least one year prior to EAC detection was not different over time (p=0.23), e.g. 10.6% in 1999 and 9.3% in 2009. The absolute 1-year mortality rate did not substantially increase over time: 3.3 per 100,000 inhabitants in 1999 versus 2.8 in 2009, whereas the adjusted one-year mortality risk decreased over time (e.g. HR 0.67, 95%CI 0.58-0.78 in 2009 compared to 1999). This was likely to be explained by the applied treatment strategy, as including this factor in the analysis abolished the association between EAC incidence year and mortality (e.g. HR 0.94, 95%CI 0.81-1.01 in 2009 compared to 1999).
Conclusion: In this large population-based cohort of EAC patients we confirm the steep increase in EAC incidence, which was neither accompanied with an increase in the proportion of patients with a prior diagnosis of BE, nor with an increase in absolute one-year mortality. The adjusted one-year mortality risk however decreased parallel to the increase in EAC incidence, which may be largely explained by more effective treatment strategies and/or an overall increase in survival.

The human leukocyte antigen DQ B1*02 is more frequent in patients with tissue-transglutaminase antibody levels ≥100 U/mL

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Patients with tissue-transglutaminase antibody (tTGA) levels ≥100 U/mL virtually always have celiac disease (CD), whereas the disease can be histologically rejected in a significant number of patients with lower tTGA levels. The aim of the current study was to evaluate whether CD patients with tTGA ≥100 U/mL show a different genetic risk profile with regards to the disease associated human leukocyte antigen (HLA) types than patients with tTGA <100 U/mL. The study included all paediatric patients with biopsy confirmed CD (Marsh III) in whom HLA typing was done between 2009 and 2011. HLA typing was performed using sequence-specific oligonucleotide Primed PCR (PCR-SSO) typing. In all patients tTGA was measured by means of ELISA using human recombinant tissue-transglutaminase as antigen. The distribution of HLA-DQ 2.5 (DQA1*05:01, DQB1*02:01), DQ 2.2 (DQA1*02:01, DQB1*02:02) and DQ 8 (DQA1*03:01, DQB1*03:02) in patients with tTGA ≥100 U/mL and patients with lower levels of tTGA was compared. P-values <0.05 were considered statistically significant. Results: A total of 95 celiac children were included in the study of whom 68 patients had tTGA ≥100 U/mL. A total of 27 patients had tTGA levels <100 U/mL of whom in only 2 children the antibody levels were <10 U/mL (negative). Compared to the low tTGA group, in the tTGA ≥100 U/mL group a higher percentage of the patients were homozygous for HLA-DQ 2.5 (23.5% versus 11.1%), although this difference was not statistically significant. Similarly, more CD children in the high tTGA group (27.9%) were HLA-DQ 2.5/2.2 heterozygous as compared to the children with lower tTGA (14.8%), although again this was not statistically significant. By contrast, when looking specifically at homozygosity for HLA-DQ B1*02, the prevalence of patients carrying 2 copies of this molecule turned out to be significantly (P-value 0.044) higher in the tTGA ≥100 U/mL group (48.5%) compared to the low tTGA group (25.9%). Finally, no differences in prevalence were found for HLA-DQ 8 homozygosity or heterozygosity for HLA-DQ8 in combination with either HLA-DQ 2.5 or DQ 2.2.

In Conclusion, patients with tTGA ≥100 U/mL have a different HLA risk profile compared to CD patients with lower tTGA levels, as almost 50% of the high tTGA group carry 2 copies of the HLA-DQ B1*02 molecule while only around a quarter of the patients in the low tTGA group carries 2 copies. Pathofysiologically, increased abundance of the highly gluten affinitive HLA-DQ B1*02 molecule may be responsible for the enhanced antibody response.

Long term follow-up of gut-directed hypnotherapy versus standard care in children with functional abdominal pain or irritable bowel syndrome

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We previously showed that gut-directed hypnotherapy (HT) is highly effective in the treatment of children with functional abdominal pain (FAP) and irritable bowel syndrome (IBS). Aim of this follow-up study was to investigate the long-term effects of hypnotherapy versus standard medical treatment plus supportive therapy (SMT). All 52 participants of our previous randomized controlled trial (RCT) were invited to complete a standardized abdominal pain diary, on which pain frequency and pain intensity were scored. Furthermore, the Children's Somatization Inventory (CSI) and a general quality of life questionnaire were filled out. Clinical remission was defined as > 80% improvement in pain scores compared to baseline. All 27 HT patients and 22 out of 25 SMT patients participated in this study. Two patients of the SMT group were lost to follow-up and one refused to participate. After a mean duration of 4.8 years follow-up (3.4 – 6.7), hypnotherapy was still highly superior to conventional therapy with 68% versus 20% of the patients in remission after treatment (P=0.005). Pain intensity and pain frequency scores at follow-up were 2.8 and 2.3 resp. in the HT group compared to 7.3 and 7.1 in the SMT group ($p<0.01$). Also somatization scores were lower in the HT group (15.2 vs 22.8;p=0.04). No differences were found in quality of life, doctors' visits, and missed days of school or work between the two groups.
Conclusion: The beneficial effects of gut-directed hypnotherapy are long lasting in children with FAP or IBS with two thirds still in remission almost 5 years after treatment, making it a highly valuable therapeutic option.

Long term effects of cognitive behavior therapy for the treatment of children with functional abdominal pain: Results of a randomized controlled trial

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Functional abdominal pain (FAP) is a common complaint in children and adolescents. Four previous randomized controlled trials (RCT) showed that cognitive behavior therapy (CBT) is an effective treatment for children with FAP. However, three of these studies suffered from methodological flaws like small sample sizes and high drop-out rates. The aim of the present study was to investigate the long term effectiveness of CBT compared to medical care (MC) on pain symptoms, symptoms of anxiety, depression, disability due to FAP, other somatic complaints and quality of life in a large RCT. A total of 104 children were randomized to CBT or MC over a three year period. Both treatments consisted of 6 weekly sessions with a trained masters-level psychologist in the CBT arm and a pediatric gastroenterologist/pediatric resident in the MC arm. Data were collected pre- and post-treatment and at 6 and 12 months follow-up. Linear mixed models analysis was used to analyze differences in effectiveness between treatment conditions for all outcome measures. Additionally, it was calculated what percentage of children had improved significantly according to Jacobsen and Truax's reliable change index. Children in both treatment conditions improved significantly in their level of abdominal pain from pre- to post-treatment and at 6 and 12 months follow-up (child report: $p<.001$; parent report: $p<.001$). CBT was equally effective as MC in improving abdominal pain, according to both child and parent report. However, there was significant variance in how well children responded to each treatment ($p<.01$). The same held true for most of the other outcome measures, except for anxiety and depression, where we found an interaction effect ($p<.05$), indicating that CBT led to a decrease in anxiety and depressive symptoms, whereas MC did not. This effect was only visible until 6 months follow-up; at 12 months after treatment, children in both groups had equal amounts of symptoms of anxiety and depression. Finally, directly after treatment 31.8% of children that received CBT were improved or recovered versus 29.8% of children that received MC; this increased to 51.2% (CBT) and 41.5% (MC) at 6 months follow-up, and to 60.0% (CBT) and 56.4% (MC) at 12 months follow-up. None of these percentages significantly differed.

Conclusions: Six weekly sessions of either CBT or MC both cause a significant decrease in abdominal pain and co-morbid complaints. CBT does not seem to be superior to MC. However, as there is significant variance in how children respond to each treatment, we need to investigate which treatment works best for which child.

Completion of toilet training in children with defecation disorders and concomitant symptoms of autism spectrum disorders

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Background Twenty-nine percent of children presenting in a tertiary motility center with functional defecation disorders (FDD) show symptoms of autism spectrum disorders (ASD) (Peeters et al., unpublished). The influence of the presence of ASD symptoms on the moment of completion of toilet training in these patients is unknown. Aim To compare the time of completion of toilet training in children with FDD with and without concomitant symptoms of ASD and healthy peers. Methods Children (4 -12 yrs) presenting at a tertiary motility center with FDD according to the ROME III criteria were included. In a previously conducted study, these patients were screened for symptoms of ASD by two validated questionnaires; the Social Responsiveness Scale (SRS) and Social Communication Questionnaire (SCQ-L). Children were defined as having symptoms of ASD if one or two questionnaires scored above the indicative cut-off value (SRS≥51; SCQ≥15). Healthy children were recruited from primary schools. Toilet training characteristics were recorded. Results In total, 223 children with FDD were included, of which 65 showed symptoms of ASD. The control group consisted of 96 children. Median age at completion of toilet training for stools in children with FDD and ASD symptoms was 3.5 yrs (range 2-12, n=46), in children with FDD only 3.0 yrs (0-6, n=123) and in controls 2.5 yrs (1-4, n=95). Differences were significant between all groups. Less children with FDD and ASD symptoms were toilet trained for stools before the age of 4 yrs than children with FDD only (45% vs. 61%, p=0.026). The proportion of children being toilet trained for stools before the age of 4 was lower in both FDD groups than in controls (95%, p<0.001). Median age at completion of toilet training for urine (daytime) in children with FDD and ASD symptoms was 3.0 yrs (range 1.5-12, n=57), in children with FDD only 3.0 yrs (1.5-8, n=123) and in controls 2.0 yrs (1-4, n=95). A significant difference was only found between children with FDD and ASD symptoms and controls. Completion of toilet training for urine (daytime) was achieved before the age of 4 in a similar proportion of children with FDD and ASD symptoms and children with FDD only (65% vs. 76%, p=0.16). Controls however, were more likely to have completed toilet training for urine (daytime) at this age (98%, p<0.001).
Conclusion: Children with FDD and ASD symptoms completed toilet training for stools at a later age than children with FDD only and healthy controls. The two FDD groups completed toilet training for urine at the same age, but were later than healthy controls. Further investigations are needed to unravel the motor, sensory or behavioral factors that may be involved.

Predicting NAFLD in severely obese children and adolescents: noninvasive prediction rules and novel biomarkers lack sufficient diagnostic accuracy

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Accurate prediction rules for liver steatosis are demanded to enable clinicians to noninvasively screen for nonalcoholic fatty liver disease (NAFLD). Several prediction rules have been developed, however external validation is lacking. Novel biomarkers, that strongly correlate with the presence of NAFLD, are continuously reported, but most have not been evaluated for their diagnostic value in noninvasive prediction models. We aimed to determine the diagnostic performance of freely available prediction rules in severely obese children, to evaluate the diagnostic value of novel biomarkers and to compare these results to the performance of ultrasound.In our study, steatosis was measured using Proton Magnetic Resonance Spectroscopy in 119 severely obese children. Diagnostic accuracy of the 'NAFLD liver fat score' (NAFLD score), the 'Fatty Liver Index score' (FLI score), a paediatric formula (ped-NAFLD score) and ultrasound was determined. Subsequently, a new equation was built using anthropometry, routine biochemistry and novel biomarkers (leptin, adiponectin, tumor necrotic factor-alfa, interleukin-6, caspase-cleaved cytokeratin-18, fibroblast growth factor-21 and adiponutrin polymorphisms). Predictive parameters for this equation were identified using multivariate logistic analysis. Parameters with $p \leq 0.10$ in univariate logistic regression analysis were entered in a multivariate model in which significance level was set at $p<0.05$.Prevalence of steatosis was 47%. The NAFLD score, FLI score and ped-NAFLD score only had a moderate predictive value in detecting steatosis (positive predictive value (PPV): 70, 61, 69% and negative predictive value (NPV) 77, 69 and 75%, respectively). The new predictive model derived from this cohort included ALT, HOMA, sex and leptin. Sex appeared an effect modifier for the effect of HOMA on steatosis. Apart from leptin, none of the novel biomarkers significantly contributed to the diagnostic accuracy of the model. This new predictive model (PPV 79% and NPV 80%) did not perform substantially better than the three other equations and did not outperform ultrasound for excluding NAFLD (NPV 82%).
Conclusions: Freely available prediction rules and the tested novel biomarkers have insufficient diagnostic accuracy for diagnosing or excluding NAFLD in severely obese children. Ultrasound remains the most suitable tool to exclude NAFLD in daily routine in this group.

Gluten challenge in the diagnosis of celiac disease

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Patients suspected to have celiac disease (CD) because of symptoms or positive serology, but with apparently normal duodenal histology, may still be suffering from CD but lack classical histology due to insufficient gluten intake. Therefore it is common practice to perform a gluten challenge (GC) in such patients, although studies supporting this approach are lacking. The purpose of this study was therefore to define the diagnostic yield of a GC in paediatric patients suspected to have CD but without histological evidence of the disease on duodenal biopsy. All patients with CD-like symptoms and/or positive CD serology who had undergone a GC between 1995 and 2011 due to the absence of classical CD histology upon duodenal microscopy were included in the study. The GC comprised of >200 mg/kg/day of gluten-powder added to the diet of the patients for a period of 6-12 weeks. All initial biopsies were revised by a single experienced pathologist, who was blinded to the clinical and serological data, using the Marsh classification. The biopsies were further classified into 4 groups: no CD (Marsh 0) but positive CD serology, border enteropathy (Marsh I-II), CD (Marsh III), and inconclusive histology (CD cannot be confirmed nor rejected). Finally, biopsy results before and after GC were compared. A total of 34 patients met the inclusion criteria of the study. Of those, 16 patients (47.1%) were diagnosed with CD at revision of the histology, including 1 patient with negative serology. The diagnosis was rejected in 2 patients who both had negative serology, making a GC unnecessary in retrospect. Of the 16 remaining patients, 8 had inconclusive biopsies initially (all with positive serology), 3 a Marsh I lesion (2 with negative serology) and 5 patients a Marsh 0 lesion but positive serology. After GC, no histological abnormalities were found in all patients with initially Marsh I lesions and in 3 of the 5 patients with a Marsh 0 lesion after revision. In the remaining 2 patients with Marsh 0 lesions the GC resulted in inconclusive biopsies. Finally, of the patients with initially inconclusive biopsies the diagnosis CD was confirmed in half of the patients, rejected in 3 patients and remained inconclusive in 1 patient.
In conclusion, in children suspected to have CD, but lacking histological confirmation, the first step is to revise the biopsies as this leads to confirmation of CD in almost half of the patients. In patients who have an inconclusive biopsy, a GC reveals CD in half of the cases. By contrast, in patients with a Marsh 0 or Marsh I lesion on initial biopsies, the yield of a GC is low.

Increased IL-21, but not IL-17A production in the small intestine is characteristic for pediatric Celiac Disease

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Celiac disease (CD) is an inflammatory response to gluten which results in a small intestinal villous atrophy and massive infiltration of gluten-reactive CD4+ T cells. Genome wide association studies have revealed that the interleukin (IL)-21 gene region is a risk variant for CD. T helper 17 cells can produce IL-21 and IL-17A. Currently, the contribution of the T helper 17-derived cytokines IL-21 and IL-17A to the onset of disease is unclear. Therefore, we studied the role of IL-21 and IL-17A in a cohort of pediatric CD patients and determined whether particular microbial stimuli are involved in IL-21 secretion.Immunohistochemistry was used to detect IL-21 and IL-17A-producing cells in intestinal biopsies obtained from children who underwent gastroduodenoscopy with suspicion of CD. Children with a normal intestinal histology served as controls (Marsh 0). For comparison, biopsies from children with active inflammatory bowel disease were obtained. In vitro T-cell stimulation assays were used to determine modulation of IL-21 secretion by microbial ligands.High numbers of IL-21 producing cells were detected in the small intestine of pediatric CD patients compared to controls. IL-21 was produced by CD4+ T cells but no significant increase in the number of IL-17A-producing cells was observed. In agreement, flow cytometric analyses of isolated lamina propria cells revealed a large population of IL-21-secreting T cells that did not secrete IL-17A. This selective IL-21 positivity was characteristic for the inflammation in CD, as biopsies from pediatric IBD patients showed increased numbers of both IL-21 and IL-17A-secrecting cells. Furthermore, in CD IL-21-producing cells were randomly distributed along the lamina propria, whereas in IBD the IL-21 producing cells were restricted to infiltrates. IL-21 plays an important role in anti-viral host defense. Antiviral responses can be mimicked by Toll like receptor (TLR) ligands. Purified peripheral blood CD4+ T cells from healthy individuals expressed mRNA for TLR2, TLR3, TLR4 and TLR7. During CD4+ T-cell activation, stimulation with the TLR3 ligand polyinosinic-polycytidylic acid resulted in a significant increase in IL-21, but not IL-17A secretion. In contrast, stimulation with theTLR2 ligand Pam3Cys enhanced IL-17A, but not IL-21 release by activated T cells.These results demonstrate that an IL-17A independent increase of IL-21 production by CD4+ T cells is characteristic for pediatric CD. We are currently investigating whether peripheral blood T cells from pediatric CD patients are more prone to release IL-21 after TLR ligation when compared to T cells from healthy children.

Rectal examination in children: digital versus transabdominal ultrasound

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To investigate two different diagnostic tests to assess the rectal filling state. Rectal filling state was assessed by transabdominal ultrasound (US) or by digital rectal examination (RE), by two independent investigators, in children with urological problems, prior to a scheduled diagnostic or surgical urological procedure. A dilated rectum filled with stool or large amounts of (usually) hard stool were both considered as a rectal fecal mass. All investigations were performed under general anesthesia. The kappa test was used to evaluate agreement between US and RE. A total of 84 children (54 boys) with a median (p25-p75) age of 9.0 years (6.4- 11) were eligible candidates. A rectal mass was found upon US and RE, in 32% and 41% of all children, respectively, with agreement between the two tests in 82.5%. Cohen's kappa showed good agreement of 0.62 (95% CI 0.45-0.79) between US and RE. The median (interquartile) diameter of the rectum was 3.3 cm (2.8-3.9) in children with a full rectum and respectively, 2.5 cm (1.8-2.8) and 2.0 cm (1.5-2.2) in patients with a half-filled and empty rectum.
Conclusion:Transabdominal ultrasound is a non-invasive and reliable alternative to assess the rectal filling state and might replace digital RE in the work-up of children with constipation.

The value of defecography in the diagnostic and therapeutic management in defecation disorders in children

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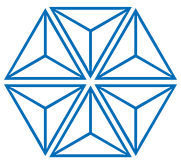
Normal anorectal function depends upon coordination among muscles of the pelvic floor, autonomic and somatic nervous system and anal sphincters muscles. Abnormalities in the function of pelvic floor activity may lead to obstructed defecation. Defecography is a dynamic radiologic study to assess the anorectal function during evacuation of the rectum. It visualizes the anal canal and rectum at rest and during defecation. Although defecography may increase our understanding of pelvic floor pathophysiology, it has not yet proven its value in the management of children with defection disorders. Aims: 1. To investigate the role of defecography in understanding the pathophysiology of defecation disorders in children and 2. To describe the value of defecography in directing the diagnostic and therapeutic management. We reviewed all defecography studies performed on children with normal anorectal motility who still required better understanding of the pathophysiology of their defecation disorders. All studies were performed and interpreted by one specialized radiologist between 2003-2009. Defecography results were classified in 3 groups; 1) Pelvic floor dyssynergia: incomplete relaxation of the pelvic musculature, inconsistent change in the anorectal angle and incomplete voluntary evacuation of the rectum; 2) Anatomical abnormality: excessive pelvic floor descent in combination with an intrarectal intussusception, rectocele, or rectal prolapse; 3) Normal pelvic floor function. Medical history, symptoms, defecography parameters, final interpretation, and recommended management after the test were reviewed. We included 18 patients (13 boys), mean age of 9.1 years (range 3-16 year) at time of the defecography. Coexistent diagnoses included spinal abnormality, imperforated anus, and behavioral problems. Indication for defecography was chronic constipation in 56%, fecal incontinence in 22% and rectal prolapse in 22%. Defecography was consistent with pelvic floor dyssynergia in 9 patients, found an anatomical abnormality in 4 and was consistent with a normal pelvic floor function in 5. After defecography 8 children (45%), all with pelvic floor dyssynergia, were referred for anorectal biofeedback treatment. Four subjects (22%) were referred to surgery; 2 for a cecostomy, 1 for peri-anal Thiersch suture and 1 for Altemeier procedure. Two patients (11%) were referred for an additional MR defecography. In 4 patients (22%) the result of the defecography did not change the management.
In conclusion; defecography can be a useful tool in understanding the pathophysiology of defecation disorders in children. In 78% of our population the test directed a change in treatment.



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Disease phenotype at diagnosis in paediatric Crohn's disease: 5-year analyses of the EUROKIDS registry

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The recent paediatric modification of the Montreal classification, the Paris classification, enables a better phenotypic classification of disease location in inflammatory bowel disease (IBD). We aimed to use this new classification to accurately phenotype newly diagnosed paediatric Crohn's disease (CD). Information was collected from the EUROKIDS registry, a prospective, web-based registry of newly diagnosed paediatric IBD patients (aged 0-18 years) in 17 European countries and Israel. When the appropriate diagnostic tests were performed (i.e. ileocolonoscopy, upper gastrointestinal (GI) endoscopy, small bowel imaging), patients with new-onset CD were evaluated for ileocolonic disease extent, oesophagogastroduodenal involvement, and jejunal/proximal ileum involvement. Disease behaviour and the occurrence of granulomas were also analysed. 1221 CD patients (mean age 12.5 ± 3.3 years; 59% male) met eligibility criteria. Isolated terminal ileal disease (± limited caecal disease, L1) was seen at presentation in 16%, isolated colonic disease (L2) in 27%, ileocolonic disease (L3) in 53%, and isolated upper GI disease (L4) in 4% of patients. In total, 26% of patients had oesophagogastroduodenal involvement (+L4A), and 26% jejunal/proximal ileal disease (+L4B). Patients with L2 disease were less likely to have oesophagogastroduodenal involvement (20%) than patients with L1 disease (31%, $p=0.049$) or L3 disease (35%, $p<0.001$). Additionally, stricturing disease behaviour was less common in patients with L2 disease (6%) than in those with L1 disease (21%, $p<0.001$) or L3 disease (15%, $p=0.005$). Terminal ileal disease, oesophagogastroduodenal involvement, and stricturing disease behaviour were more common in children diagnosed after 10 years of age than in younger patients. Granulomas were identified in 43% of patients.
Conclusions: More than half of children diagnosed with CD present with ileocolonic disease. Patients with disease involvement of the terminal ileum are more likely to present with stricturing disease complications, indicating a particular surveillance and treatment strategy. The Paris classification is a useful tool to capture the variety of phenotypic characteristics of paediatric CD.

Albumin is a neuroprotective agent for bilirubin-induced auditory brainstem dysfunction in Gunn rat pups

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Background: Free bilirubin (Bf), the fraction of unconjugated bilirubin (UCB) not bound to albumin, can induce neurotoxicity after translocation across the blood-brain barrier. Neurotoxicity can be assessed by brainstem auditory evoked potentials (BAEPs), based on the vulnerability of the auditory nerve to hyperbilirubinemia. Theoretically, albumin could reduce the risk on bilirubin neurotoxicity by decreasing Bf, and thus preventing its translocation to the brain. Aim: To determine the effects of albumin treatment on brainstem auditory evoked potentials in a rat pup models of acute hyperbilirubinemia due to hemolysis or due to bilirubin displacement from albumin. Methods: We used hyperbilirubinemic Gunn rat pups, which have a genetic deficiency of the bilirubin conjugating enzyme UDPGT1A. As a hemolysis-model, we induced hemolysis with phenylhydrazine (Phz) to mimic neonatal hyperbilirubinemia. We injected Phz in 14-days old Gunn rat pups, which were subsequently treated for 2 days with either i.p. human serum albumin (HSA; 2.5 g/kg; n=8) or sa (control, n=8). As a displacement-model, we induced acute neurotoxicity by injecting 16-days old Gunn rat pups with sulfadimethoxine (sulfa) and treated them with either human serum albumin (HSA; 2.5 g/kg, n=9) or sa (control, n=10). We recorded BAEPs, and stimulus to peak latency values were substracted to obtain interwave-interval (iwi) between peak I and peak II. An increased iwi I-II is a reflection of acute neurotoxicity. Results: Phz and sulfa significantly increased the interwave interval (iwi) I-II in the hemolysis and displacement model, respectively. Treatment with albumin completely prevented the increase of iwi I-II in either model of acute hyperbilirubinemia.
Conclusions: Albumin treatment is neuroprotective in acute hyperbilirubinemia in Gunn rat pups, irrespective of its induction by hemolysis or by bilirubin displacement from albumin. Present results favour the clinical potency of albumin treatment to mitigate neurotoxicity by acute hyperbilirubinemia.

Inhibition of MRP1 attenuates liver fibrosis in vitro and in vivo

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Introduction: Liver fibrosis invariably develops during chronic liver disease and may progress to cirrhosis and liver cancer. Two main cell types are involved: hepatic stellate cells (HSCs) and portal myofibroblasts (PMFs). These cells become proliferative, contractile and produce excessive amounts of extracellular matrix proteins (EM), including collagens, the typical feature of fibrosis. Thus, HSCs and MFBs are prime targets to treat fibrosis. Previously, we showed that activated HSCs and PMFs express increased levels of the multidrug resistance-associated Protein 1 (MRP1). Moreover, pharmacological inhibition of MRP function by MK571 lead to repression of fibrosis markers (α-SMA and Col1a1). MRP1 is an ATP-binding cassette (ABC) transporter that transports glutathione (GSH) and GSH-conjugates, including leukotriene C_4. Here, we extended our studies to identify the MRP1 substrate causing reversal of HSC/PMF activation and to establish the role of Mrp1 in a mouse model of fibrosis. Materials and Methods: The human hepatic stellate cell LX-2 was used as in vitro model of fibrosis. MRP1 activity was inhibited by MK571, Reversan or RNA-interference and quantified by CMFDA. GSH-MEE (GSH supplementation), BSO (GSH synthesis inhibition), 5-lipoxygenase inhibitor AA861 (inhibition of leukotriene synthesis) were used to identify the potential MRP1 substrate. Cell necrosis (LDH leakage), metabolic activity (WST assays), mRNA (Q-PCR) and protein (western blotting) levels were measured by standard protocols. Mrp1-/- and appropriate wild type FVB-control mice were injected with CCL_4 for 12 weeks. Control animals were treated with vehicle (corn oil). Animals were terminated after 12 weeks and livers were excised for qPCR, western blot and histological (Sirius red for collagens) analysis. Results: MK571 and Reversan dose-dependently inhibited CMFDA export from LX-2 cells, reduced α-SMA and Col1a1 mRNA levels and reduced their metabolic activity, without inducing necrosis. Partial inhibition of MRP1 by RNA interference lead to reduced expression of a-SMA. Manipulation of glutathione levels did not affect the Reversan-induced reduction of α SMA and Col1a1 expression in LX-2 cells. AA861 treatment, like MK571, suppressed a-Sma and Col1a1 expression. CCl_4 treatment lead to significant induction of a-Sma protein levels and Sirius red-positive fibrotic septa in wt control mice. Both a-Sma protein and collagen deposition was strongly reduced in CCl_4-treated Mrp1-/- mice.
Conclusion: Inhibition of MRP1 leads to suppression of liver fibrosis by preventing leukotriene export from HSCs. MRP1 is therefore a highly relevant target for the treatment of liver fibrosis.

How computer simulations of fatty-acid beta-oxidation help to elucidate metabolic disease mechanisms

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Fat metabolism plays a key role in acquired and inborn metabolic diseases, such as type-2 diabetes and deficiencies in enzymes involved in fatty-acid oxidation. For instance, the first steps of fatty-acid beta-oxidation are necessary to acquire insulin resistance, which is the first step towards type-2 diabetes. Research is hampered, however, because the intermediate metabolites are difficult to measure. Computer simulations that mimic the dynamics of the involved metabolic pathways is an important tool in revealing underlying disease mechanisms. Here, we present a dynamic computer model of fatty-acid beta-oxidation and apply it to understand the consequences of i) fat overload and ii) the deficiency of medium-chain acyl-CoA dehydrogenase (MCAD). The model is built on known kinetic equations and measured kinetic parameters, which were entirely based on literature data for rat-liver enzymes. The kinetic model predicts the fluxes through the individual enzymes of the fatty-acid beta-oxidation and the concentrations of the intermediate metabolites and their dynamic response to perturbations.To validate the model predictions, we have measured the oxygen consumption flux and the concentrations of acylcarnitines (C4 to C16) in isolated rat-liver mitochondria upon addition of palmitoyl-CoA as substrate. The oxygen flux reaches a constant value when the acylcarnitines still vary in time. The steady-state oxygen flux as well as the dynamics of the acylcarnitine concentrations, showed quantitative correspondence between model and experiment.Subsequently, we first studied the effects of an overload of fatty acids such as seen in obesity. In the model this was done by increasing the concentration of palmitoyl-CoA. The model simulations showed a flux optimum: above a certain substrate concentration the pathway was overloaded, the flux dropped and intermediate metabolites accumulated. This could be prevented by changing the ratio of NAD^+/NADH, showing a tight interplay between beta-oxidation and respiration. Secondly, an inborn enzyme deficiency of medium-chain acyl-CoA dehydrogenase (MCAD) was studied. In a mouse model of MCAD deficiency the flux through the fatty-acid beta-oxidation was equal to that of control mice; however increased concentrations of C6 and C8-acylcarnitines were observed. The computer model reproduced these results provided that the expression levels of the remaining acyl-CoA dehydrogenases were adapted. Current work aims at experimental validation of these predictions.

In conclusion, computer simulations of fatty-acid beta-oxidation have yielded new insights and hypotheses about the functioning of fat metabolism in metabolic diseases.

Role of NLRP3 in obesity-induced liver steatosis and inflammation

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The NLRP3 inflammasome is a cytosolic protein complex consisting of the regulatory subunit NLRP3, the adaptor ASC and the effector subunit Caspase-1. Activation of this inflammasome leads to production of proinflammatory cytokines. Obesity is characterized by low grade metabolic inflammation in the absence of infection. Recent studies showed NLRP3 involvement in this obesity-induced inflammation and related metabolic pathologies such as insulin resistance and liver steatosis: Nlrp3 knockout (KO) mice showed less liver steatosis and inflammation. The main focus of this project is to address the effect of Nlrp3 knockout on liver pathology and metabolism under different dietary conditions. For this, groups of C57Bl/6J wildtype and Nlrp3 KO mice were fed for 16 weeks: (1) a control diet (C), (2) a control diet plus fructose-rich drinking water (F), (3) a western (45 kcal% fat) diet (W) or (4) a Western diet plus fructose-rich drinking water (WF). During this period, food and water intake and bodyweight were documented. Multiple organs, urine and plasma were collected at sacrifice. Liver morphology (HE), steatosis (ORO), fibrosis (PSR) and glycogen content (PAS) were analysed histologically. Liver triglycerides were also measured in liver homogenates by a quantitative colorimetric assay. Liver gene expression analyses for important inflammatory cytokines and metabolic regulators were performed by quantitative RT-PCR.All Western diet subgroups (i.e. W and WF groups) showed a tendency to higher bodyweight gain than the control diet subgroups (C groups), regardless of the genotype. Histology showed more liver steatosis in the Nlrp3 KO mice W and WF groups compared to wildtype mice; mild steatosis was also present in the Nlrp3 KO mice F group whereas no steatosis was observed in the wildtype mice F group. In contrast, inflammation was more prominent in wildtype mice than in Nlrp3 KO mice and more fibrosis was seen in wildtype mice exposed to fructose water [i.e. F and WF groups]. Analysis of liver gene expression of important inflammatory cytokines and metabolic regulators are ongoing.
In conclusion: Nlrp3 KO mice subjected to a Western diet do not show reduced bodyweight gain and liver steatosis compared to wildtype mice. They do however show reduced liver inflammation and fibrosis, which implies that in this model steatosis and inflammation are not correlated.

Immunochip-based analysis of 72.000 individuals identifies 50 novel IBD loci, refining definitions of disease pathways

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Introduction: A seminal finding of the genome-wide association study (GWAS) era is the identification of a marked overlap of loci between immune-mediated diseases. The Immunochip Consortium designed a customized chip with ≈200.000 single nucleotide polymorphisms focused on: 1) fine-mapping 190 known loci for 9 different immune-mediated diseases and; 2) follow up of top 2000 UC and CD GWAS signals not previously studied. Methods: A meta-analysis was performed combining HapMap3 imputed CD and UC GWAS data with a larger case-control cohort genotyped on the Immunochip. Altogether, 19,416 CD, 17,016 UC and 36,602 controls, all of European ancestry were analyzed. Results: We identified 50 novel genomic regions with genome-wide significant association (P-value < 5 x 10-8), bringing the total number of IBD loci to 149. These new associations further implicate Th17 cells (RORC, the Th17 master transcription factor), the Th1 pathway (STAT4, involved in IL-12 signaling; IFNGR2, interferon-gamma receptor 2), co-stimulation (ITGAL, integrin alpha-L/LFA-1), the TNFi¡ pathway (LITAF, lipopolysaccharide induced TNF factor), NF-kB signaling (NFKB1/p50; TRAF3IP2), the KIR-family (KIR3DL3, killer cell immunoglobulin-like receptor), and the NOD2 pathway (CD-specific association to RIPK2, the NOD2 signaling partner). Previously identified UC loci are now also confirmed CD loci (IL2/IL21, IFNg/IL22/IL26, FCGR2A); conversely, known CD loci now demonstrate association with UC (PTPN2, LRRK2, IKZF1). The large sample size provides power to fine-map loci and define differential effect sizes. A range of CD-specific, UC-specific and IBD-general effects is observed. Among autophagy genes, while the ATG16L1 association is CD-specific, significant associations are observed for IRGM in both CD and UC, albeit with more modest effect sizes in UC compared to CD. The IFNGR2 association is CD-specific; distinct, loss-of-function mutations in IFNGR2 have been associated with increased susceptibility to mycobacterial infections. Multiple loci previously been associated with other immune-mediated diseases including rheumatoid arthritis, celiac disease, multiple sclerosis, type 1 diabetes, psoriasis and SLE are now also associated with CD (CLEC16A, SLC12A5, ANKRD55, CD40, STAT4, JAZF1) and UC (C5orf62, PSORS1C1).
Conclusions: Immune-mediated diseases are associated with numerous loci that are often shared between disease subtypes. Distinct phenotypes are distinguished by different combinations of loci, variable effect sizes and distinct allelic architectures within loci. Future genetic and genomic studies focused on these loci will facilitate therapeutic interventions across these diseases.

Genome wide analysis identifies mitotic recombination as cause of somatic loss of heterozygosity in cysts from polycystic liver disease patients

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Somatic mutations play an important role in the progression of many diseases, including inheritable cancers, and benign disorders such as polycystic liver disease (PCLD). We recently found in PCLD patients that carry a PRKCSH germ mutation, that 76% of the liver cysts had lost the wild type PRKCSH allele through loss of heterozygosity (LOH). The aim of this study was to determine the nature and the extent of the underlying somatic genomic changes. We isolated cyst epithelial cells from liver tissue which was obtained during laporoscopic cyst fenestration from a PCLD patient carrying a c.292+1G>C PRKCSH germ mutation. Cells were isolated from adjacent liver tissue using EDTA and trypsin. Identity of the cells was confirmed using CK19 staining. We performed a genome wide cytogenetic array analysis (Affymetrix CytoScan™ HD with 2.7 Million probes of which 750.000 SNP probes) for high resolution imaging of both copy number variations and LOH regions from 2 cysts. Using this approach we found that the LOH region leading to loss of the wild type PRKCSH allele was in both cysts the result of terminal copy number neutral LOH on the short arm of chromosome 19. We could identify in each cyst a single breakpoint from where the LOH continued to the end of the p arm, covering a region of 14 Mb (megabases) in the first and 18 Mb in the second cyst. The location of the breakpoint was different in each cyst, thereby indicating these cysts developed independently and resulted from a different somatic event. No other genomic abnormalities were found.
In conclusion, these data shows that a single breakpoint in the p arm of chromosome 19 is responsible for the LOH which leads to loss of the wide type PRKCSH allele in these cysts. As the LOH is not caused by a deletion, a mitotic recombination event must have occurred leading to copy number neutral LOH. These data provide important insights in the mechanisms behind somatic mutations in a benign disorder.

HSPA6 is a prominent cigarette smoke-induced gene residing in a UC susceptibility locus and protects against cytokine-induced apoptosis.

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Ulcerative colitis (UC) is a chronic inflammatory disorder of the gut resulting from a complex interplay between genetic and environmental factors. Remarkably, cigarette smoke ameliorates UC in a dose-dependent manner as it reduces colitis, drug use and hospitalizations. However, the underlying mechanisms by which cigarette smoke modulates UC remain unclear. UC is characterized by disruption of the intestinal epithelium, where intestinal epithelial cells die from apoptosis. Earlier, we showed that cigarette smoke represses inflammation-induced apoptotic cell death in both intestinal epithelial cells (DLD-1) and in T-lymphocytes (Jurkat). Here, we performed microarray analysis of cigarette smoke-induced genes in both cell types. Genes of which the expression was significantly changed by smoke and reside in known UC susceptibility loci were analyzed for their putative anti-apoptotic function in intestinal epithelial cells. DLD-1 and Jurkat cells were exposed for various periods (0-2h) and to various concentrations (0-30%) of cigarette smoke-saturated culture medium (CSM) and gene expression was determined using Illumina microarrays. After confirmation by Q-PCR, western blotting and immunofluorescence microscopy, differentially expressed genes were compared to genes in UC susceptibility loci as retrieved from recent meta-analyses. From these analyses heat shock protein A6 (HSPA6) was selected. DLD-1 cells that transiently express recombinant HSPA6 were exposed to a cytokine mixture (CM; IL-1b, INFg and TNFa) and apoptosis was quantified by caspase-3 activity.Microarray data showed smoke-induced mRNA expression of various heat shock proteins in both DLD-1 and Jurkat cells (FDR<1%). Most prominently induced genes in DLD-1 cells were HSPA6 (20.3-fold) and HSPA1B (12.0-fold), stress-induced proteins with well-known cytoprotective functions. Similar results were obtained for Jurkat cells. Importantly, cell viability and metabolic activity was not reduced in cells exposed to CSM up to 30%. HSPA6 expression was both time- and dose-dependent, with >100-fold induction after 6h exposure to 30% CSM and resulted in a strong, but transient expression of HSPA6 as analyzed by western blotting and immunofluorescence microscopy. HSPA6 is situated in close proximity of the UC-associated SNP rs1801274. DLD-1 cells transiently expressing HSPA6 showed reduced caspase-3 activity after CM treatment when compared to control-transfected/CM-treated DLD-1 cells.
We conclude that HSPA6 is a cigarette smoke-induced gene and its geneproduct HSPA6 provides protection against cytokine-induced apoptosis. HSPA6 may therefore be involved in the beneficial effect of cigarette smoking in UC.

Cigarette smoke is an environmental factor that reduces innate immune functions especially in individuals with the CD-associated risk variant ATG16L1-T300A

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Crohn's disease (CD) is a chronic inflammatory disorder of the intestine that is caused by a complex interplay between genetic and environmental factors. Genetic variants of NOD2, ATG16L1 and IRGM are associated with CD and functional studies suggest a crucial role of their gene products in innate immunity processes, including phagocytosis and autophagy. It is estimated that genetic predisposition only accounts for approximately 20% of disease development and that environmental factors largely determine the other 80%. The most prominent environmental factor is cigarette smoking, which increases ileal disease, need for immunosuppressive therapy and hospitalizations in CD. The underlying mechanisms of the detrimental effects of smoking on CD remain unclear. Here, we examined the effect of cigarette smoke on phagocytosis and autophagy in innate immune cells, including its interaction with the ATG16L1 risk allele. Mouse macrophages (RAW264.7) and human peripheral blood monocytes of healthy individuals with known ATG16L1 genotypes were isolated by $CD14^+$ magnetic beads and cultured in the presence of different concentrations of cigarette smoke-saturated medium (CSM). The phagocytotic activity was measured by quantifying incorporation of FITC-labeled E. coli bacteria using fluorescence microscopy. Autophagic activity was monitored by the conversion of LC3-I to LC3-II biomarkers using western blotting. Metabolic activity was measured by WST assays. The phagocytotic activity of RAW264.7 cells dose-dependently decreased after exposure to CSM (0-30%). In contrast, levels of LC3-II were clearly induced after CSM exposure, while no decrease in metabolic activity or increase in cell death was detected in this CSM concentration range. Remarkably, monocytes from healthy individuals homozygous for the ATG16L1-T300A risk allele showed significantly increased (3-fold) basal phagocytotic activity compared to ATG16L1-T300 control monocytes. Both types of monocytes were hypersensitive to CSM, with significant reduction in phagocytosis detected already at 0,5% CSM, which was completely blunted at 10% CSM. However, the reduction in phagocytosis was much more pronounced in ATG16L1-T300A monocytes (-60%) compared to ATG16L1-T300 control monocytes (-15%).
In conclusion, we show that monocytes homozygous for the ATG16L1-T300A CD risk allele have increased basal phagocytotic activity, which is strongly repressed by cigarette smoke. A chronic imbalance between internalization (phagocytosis decreased) and digestion (autophagy increased) of bacteria may be one of the starting points of CD, which is initiated and/or aggravated by cigarette smoke.

Adrenergic modulation of inflammatory dendritic cells

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Introduction: Inappropriate antigen presenting cell (APC) reactivity can lead to pathogenic T cell polarisation and contribute to the pathogenesis of inflammatory bowel diseases (IBD). In the gut, APC such as resident dendritic cells (DC) are phenotypically and functionally shaped by epithelial and stromal cell derived signals. However in addition, the sympathetic nervous system (SNS) is increasingly recognized as an additional regulatory factor in APC functions. The SNS innervates the gut mucosa and gut associated lymphoid tissue. Aims and methods: The aim of this study was to asses if murine bone marrow derived DC (BMDC) are affected by sympathetic neurotransmitters and how adrenergic receptor expression is regulated in healthy and inflamed colons. Bone marrow was cultured for 7 days with GM-CSF to obtain immature DC (iDC). IDC were incubated for 15 minutes with epinephrine or with the beta2-adrenergic receptor (β2-AR) specific agonist salbutamol before 24 hours of stimulation with LPS. IL-12p70, IL-6, TNFα and IL-10 production in supernatant was measured by ELISA. Immunofluorescence stainings for the β2-AR and CD11c, CD11b as DC markers were performed. DC were analysed in colons from healthy, and chronic T cell transfer colitis in RAG1 $^{-/-}$ mice. Results: Short, 15 minutes incubation of BMDC with epinephrine or salbutamol (0.1 μM) prior to LPS stimulation of DC results in a decreased production of IL-12p70 (6 pg/ml vs 110 pg/ml, $p<0.0001$), IL-6 (5500 pg/ml vs 12000 pg/ml, $p<0.001$) and TNFα (1100 pg/ml vs 450 pg/ml, $p<0.001$) compared to vehicle treated DC. In contrast, IL-10 production increased 2 fold (320 pg/ml vs 150 pg/ml $p<0.001$). This effect is completely blocked by the general β-AR antagonist propranolol or by the β2-AR specific antagonist butoxamine.In control mice most CD11c+ cells are negative for β2-AR. However, in CD4+CD45RBhigh T cell-driven transfer colitis setting, we observed a significant increase of CD11c+ cells in the lamina propria of which are 90% CD11b+ and 40% β2-AR positive.
Conclusion: Stimulation of the β2-AR expressed by BMDC results in a significant anti-inflammatory cytokine profile compared to the inflammatory phenotype with high levels of IL-12p70, IL-6, TNFα and low IL-10 of vehicle treated BMDC. In T cell dependant colitis there is a significant increase of CD11c+CD11b+ DC in the lamina propria which express the β2-AR. Treating IBD patients with β2-AR agonists might have the same effect on inflammatory DC as in BMDC and could potentially ameliorate disease activity.

Effects of corticosteroids on interferon-α signaling and inhibition of hepatitis C infection by plasmacytoid dendritic cells

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Background/aims: Chronic hepatitis C virus (HCV) infection is one of the leading indications for liver transplantation, but outcomes are often compromised by re-infection of the graft. Several studies have indicated that the use of corticosteroid-based immunosuppression is a risk factor for severe HCV recurrence. The mechanism for the steroid-mediated effect on HCV is not fully elucidated, but recent studies using in vitro HCV models found no direct effect on viral replication. The success rate of interferon-a (IFN-α) based antiviral therapy is significantly lower post-transplantation than in the non-transplant HCV population; however the impact of steroids on the antiviral activity of IFN-α is unknown. Therefore, the aim of this study is to investigate the effect of steroids on the antiviral activity of IFN-α and the impact on the primary IFN-α-producing cells, the plasmacytoid dendritic cells (pDCs). Methods: As a model for HCV replication we used the Huh7 hepatoma cell line, stably transfected with the non-structural coding sequence of HCV directly coupled to a luciferase reporter gene (Huh7-ET), and treated with IFN-α in the presence or absence of different doses of prednisolone or dexamethasone. A Huh7 cell stably transfected with a luciferase gene under the control of an interferon response element (Huh7-ISRE-Luc) was used to assess effects on IFN-α signal transduction. To investigate the effects of steroids on pDCs, Huh7-ET cells were co-cultured with pDCs in the presence or absence of steroids, and conditioned media of cultured pDCs were collected. Results: HCV replication was inhibited by 10 IU/ml IFN-α by more than 99% of control levels. Treatment with increasing doses of dexamethasone or prednisolone did not significantly affect HCV replication. When combining IFN-α with dexamethasone or prednisolone, no interference with the inhibition of HCV replication by IFN-α was observed. Moreover, dexamethasone and prednisolone had no effect on IFN-α signal transduction as measured in Huh7-ISRE-Luc cells. However, when Huh7-ET cells were co-cultured with pDCs, a significant reduction of HCV replication was observed, which was almost completely reversed by treatment with steroids. HCV replication in Huh7-ET cells was inhibited by conditioned medium from cultured pDCs, but no inhibition was observed with medium from pDCs that were cultured in de presence of corticosteroids.

In conclusion: We found no evidence that corticosteroids interfere with signal transduction and antiviral action of IFN-α. However, steroids may affect HCV replication post-transplantation by reducing the antiviral capacity of pDCs.

Conditional activation of intestinal Hedgehog signaling inhibits the Interferon response

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Introduction: Indian Hedgehog (Ihh) is produced by epithelial cells of the intestine and signals to the mesenchyme in a paracrine manner. Subepithelial myofibroblasts, smooth muscle cells and myeloid cells have all been reported to be Hedgehog (Hh) responsive. Hh signaling results in the expression of mesenchymal factors that inhibit stem cell proliferation. In addition to its role in epithelial homeostasis, Hh has now also been identified as an anti-inflammatory mediator in the intestine. Moreover, genetic variants in the Hh pathway have been associated with the development of inflammatory bowel disease. Here we studied the effect of conditional activation of the Hh pathway on the intestinal mucosa in an unbiased manner and find that Hh signaling negatively regulates the Interferon response. Methods: We conditionally deleted the Hh receptor *Patched1* (*Ptch1*) in adult mice using *Rosa26CreERT2* mice. Eight-week-old mice were injected intraperitoneally with 1 mg tamoxifen for 5 days to induce *Ptch1* deletion. Both *Ptch1$^{flox/flox}$CreERT2$^{-/-}$* mice treated with tamoxifen and vehicle-treated *Ptch1$^{flox/flox}$ CreERT2$^{+/-}$* mice were used as controls. 19 days after recombination mice were sacrificed. RNA from colon was isolated and a gene array was performed (n=9). Immunostaining on paraffin embedded colon was performed using an anti-F4-80 antibody (T-2006, BMA Biomedicals). The response to Hh signaling was studied using Hh conditioned medium in primary macrophages and in Hh responsive C3H10T1/2 mesenchymal cells. Results: Gene arrays performed on colon of the *Ptch1* mutant mice show that most of the top down regulated genes upon activation of Hh signaling were genes involved in the Interferon response. Macrophages are major regulators of the Interferon response and we found that macrophages are lost from the lamina propria upon conditional activation of Hh signaling (12.84 ± 3.53 vs 5.30 ± 3.12, P = 0.001). However, in our experiments macrophages were unresponsive to Hh signaling in vitro. In Hh responsive fibroblasts we observed down regulation of the same Interferon response signature that was observed on whole mucosa in the conditional *Ptch* mutant mice.
Conclusion: Our findings show that Hh signaling suppresses the Interferon response. Our experiments identify two possible explanations for this effect, disappearance of macrophages from the mucosa and down regulation of the Interferon response in Hh responsive smooth muscle like cells.

Rapamycin inhibits innate and adaptive immune functions of human plasmacytoid dendritic cells

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Rapamycin is an immunosuppressive drug used to prevent liver transplant rejection and to treat (gastro-intestinal) cancers. Plasmacytoid dendritric cells (PDC) are important in innate immunity as they are the principal producers of IFN-α, and in adaptive immunity by presentation of antigens to T cells. PDC are critically involved in immunity to viral infections and in the pathogenesis of auto-immune disorders like Systemic Lupus Erythematosus (SLE). Here we report that innate and adaptive immune functions of human PDC are differentially regulated by Toll-Like Receptors (TLR) and CD40, and that rapamycin inhibits both innate and adaptive immune functions of PDC. Human PDC activated by TLR-7 or TLR-9 ligands produced high amounts of IFN-α, but exhibited a weak T cell stimulatory capacity. Conversely, PDC activated by CD40-ligation failed to produce IFN-α, but induced robust allogeneic T cell proliferation and effector functions, among which production of pro-inflammatory cytokines IFN-gamma, TNF-alpha and IL-17. Rapamycin inhibited production of IFN-α by PDC, and suppressed the capacity of PDC to stimulate allogeneic T cell effector functions. Reduction of T-cell stimulatory capacity was most pronounced when rapamycin was added during activation of PDC via CD40, and was associated with inhibition of CD40 expression on PDC.
Conclusions: Activation of human PDC via TLR stimulates their innate immune functions, while activation via CD40 stimulates their adaptive immune functions. Rapamycin inhibits both innate and adaptive immune functions of human PDC, and may therefore constitute a novel treatment option for SLE, but increase susceptibility to viral infections.

The formation of tertiary lymphoid tissue in colitis is under neuronal control

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Tertiary lymphoid tissue is lymphoid tissue which forms in adult life in response to chronic inflammation in broad range of tissues (i.e. lacrimal glands in Sjogrens Syndrome, in cardiac allografts and atheroscerosis). The formation of this tertiary lymphoid tissue has been shown to be dependent on the lymphotoxin (LT) / lymphotoxin-b receptor (LTbR) signaling axis. In short, LTbR expressed on stromal organizer cells is triggered by lymphotoxin (LT) expressed on lymphoid tissue inducer cells which leads to increased expression of homeostatic chemokines (i.e. CXCL13, CCL19 and CCL21) and adhesion molecules (i.e. VCAM, ICAM and MAdCAM) by stromal organizer cells. However in the context of the inflamed colon we have recently shown that the formation of this tertiary lymphoid tissue is independent of the LT/LTbR signaling axis. Intriguingly, we have also recently shown that electrical stimulation of the vagus nerve can lead to an increased expression of the organogenic chemokine CXCL13 in the intestine, highlighting the potential role of neuronal control of lymphoid tissue. To assess the potential role of neuronal control of tertiary lymphoid tissue formation in the inflamed colon surgeries were performed and the vagal innervation to the intestine was cut or left intact. Subsequently tertiary lymphoid tissue formation was induced by administration of 2% DSS in drinking water for 5 days, followed by a 30 day period on normal drinking water. For the detection of tertiary lymphoid tissue entire colons were sectioned and every 40th section was screened for lymphoid tissue. Immunofluorescence analysis was performed to confirm the presence of tertiary lymphoid tissue. For the quantification of chemokines and adhesion molecules, known to be involved in the formation of lymphoid tissue, real time PCR was performed on whole colon homogenates. Interestingly, the formation of tertiary lymphoid tissue in vagotomized animals was completely disrupted compared to the neuronally intact animals. Real time PCR analysis revealed that the disruption of tertiary lymphoid tissue in vagotomized animals was accompanied by a decrease in CXCL13, ICAM-1, and MAdCAM-1 compared to intact animals. Transcript levels of CCL19, CCL21, CXCL12 and VCAM remained unaltered between vagotomized and intact animals. These results suggest a neuronal control of the expression of both chemokines (CXCL13) and adhesion molecules (ICAM-1 and MAdCAM-1) known to be involved in the formation of lymphoid tissue.
In conclusion we are the first to show that the formation of tertiary lymphoid tissue, in the context of the inflamed colon in DSS induced colitis, is under neuronal control.

Fall incidents decrease after short-term oral nutritional intervention in malnourished elderly patients: a randomized controlled trial

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Falls are a common and serious cause of morbidity and mortality in elderly. This randomized controlled trial evaluates the effects of a short-term nutritional intervention on falls in malnourished elderly patients. Malnourished elderly patients (≥60 y) either received nutritional intervention (energy and protein enriched diet, oral nutritional support, calcium-vitamin D supplement, supported by dietetic counselling) or usual care (controls) for three months post-discharge. Number of fallers, fall incidents, serum vitamin D levels, and dietary intake were measured at admission and at three months after discharge. In total 210 patients were included. At three months, both energy intake (+280 kcal (95% CI 37 ; 524)) and protein intake (+11 g (95% CI 1 ; 25)) were significantly higher in intervention patients than in controls. Mean serum vitamin D levels were 65.7 nmol/L in the intervention group and 54.8 nmol/L in controls (+10.9 nmol/L (95% CI -20.8 ; -0.1)). 57 fall incidents had occurred, 16 in the intervention group (10 patients who had fallen) and 41 in the control group (24 patients who had fallen) (OR=0.36, 95% CI 0.16 ; 0.79). The mean number of fall incidents among the whole group was 0.16 (SD 0.57) in the intervention group and 0.39 (SD 0.84) in the control group (p=0.009). The mean number of fall incidents among patients who had fallen was 1.6 (SD 1.1) in the intervention group and 1.7 (SD 0.91) in the control group (p=0.550).
We conclude that three months post-discharge short-term multi-component nutritional intervention in malnourished elderly patients decreases the number of fallers and fall incidents.

The bioelectrical impedance phase angle as indicator of undernutrition and adverse clinical outcome in cardiac surgical patients

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In cardiac surgical patients, undernutrition increases the risk of adverse postoperative outcome. The bioelectrical impedance phase angle (PA; °) has been considered an indicator of undernutrition and clinical outcome in several patient populations, but is not yet studied in cardiac surgical patients. Therefore, we investigated whether the PA is an indicator of undernutrition, and adverse outcome after cardiac surgery. In this prospective cohort study, 325 patients undergoing cardiac surgery were included. Investigated were the associations between a preoperative low PA measured by bioelectrical impedance spectroscopy, and well-established indicators of undernutrition such as body mass index (BMI; kg/m^2), unintended weight loss (UWL), and fat free mass index (FFMI; kg/m^2). Also associations with muscle strength (handgrip strength (HGS; kg), immune function (CRP, albumin) and postoperative outcomes (postoperative infection, death, time of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), and hospital LOS), were investigated. A low PA (<5.38°) was present in 29.8 % (n=96). A low PA was associated with undernutrition (low BMI and low FFMI, $p<0.05$) and less muscle strength (HGS, $p<0.05$) but not with UWL or immune function. Furthermore, a preoperative low PA was associated with a prolonged postoperative LOS at the ICU and hospital, also after adjustment for other risk factors such as operative risk and severity of heart failure (adj. Hazard Ratio (HR): 0.68; 95%CI: 0.49-0.94; p=0.020 and adj. HR: 0.74; 95%CI: 0.55-0.99; p=0.048, respectively).
In conclusion, a preoperative low PA is associated with undernutrition and less muscle strength, and increases the risk of adverse postoperative outcome. The bioelectrical impedance PA might add benefit to identify undernourished patients admitted for cardiac surgery.

A 60% reduction in hospital admission rate of patients on home parenteral nutrition after introduction of taurolidine catheter locking: a follow-up of nearly 200.000 days

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The care for patients with severe long-term intestinal failure who are treated by means of home parenteral nutrition (HPN) is challenging due to the high complication rate, mainly in the form of catheter-related bloodstream infections (CRBSI). In a previous prospective open-label randomized controlled trial (RCT) in 30 HPN patients presenting with CRBSI we showed that catheter locking with 2% taurolidine (TaurosSept®) dramatically (90%) reduced re-infections compared with low-dose (150 U/ml) heparin. Our complete HPN population therefore switched to taurolidine locking in 2008.The fact that a blinded RCT is lacking urged us to compare population dynamics and hospital admission data in the pre (2006-2007) and post (2008-2011) taurolidine eras, also taking into account new patients who need in-hospital training as well as patients who use an arteriovenous fistula (AVF) for HPN administration without catheter lock.From 2006 towards 2012 the number of HPN-related admission days at our 15-bed clinical ward remained stable at 1439 ±167 days/year. Over this period, however, the population number more than doubled (adult HPN patients from 61 to 133, new patients per year from 13 to 27) and observation days (patients with a catheter, subcutaneous port or AVF) increased from 21,619 to 44,895 per year (overall 194,559). The number of HPN patients using an AVF decreased from 20 to 12 (33 and 9% of total HPN population, respectively). Most importantly, the ratio of hospital admission days per catheter day decreased by 60% from 0.090 in the two pre-taurolidine years to 0.036 thereafter, excluding patients who had in-hospital training and patients using AVF. During this period all treatment- and educational protocols for HPN patients other than catheter locking remained unaltered.In conclusion, our results strongly suggest that catheter locking with 2% taurolidine beneficially alters the course of long-term HPN treatment. Since in our population AVF are mainly used in patients in whom CVCs repeatedly proved ineffective, this decreased complication rate may have strong implications for the number of patients in whom creation of an AVF for HPN treatment will be considered in the future.

Use of parenteral nutrition in critically ill cardiovascular patients is related to higher mortality

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Adequate protein and energy intake is related to decreased mortality in ICU patients. Use of parenteral nutrition (PN) in critically ill patients is highly debated and associated with disruption of the intestinal mucosa, hyperglycemia and increased risk for nosocomial infection. The EPaNIC trial showed no advantage of early supplemental use of PN, day 1 versus day 8. A recent Supplemental PN RCT from Switzerland showed beneficial effects of supplemental PN from day 4. One of the main differences was the number of cardiovascular patients, 60% in the EPaNIC trial and only very few patients in the Swiss RCT. In a large cohort of critically ill patients with detailed monitoring of adequate protein and energy intake and who were all fed according our energy-protein targeted algorithm, we looked at diagnosis-specific effects of use of PN on outcome parameters. From a cohort of 2226 ICU patients diagnostic categories such as sepsis, respiratory insufficiency, post surgical, and cardiovascular failure, were analysed for outcome effects of PN use (any amount used during total period of mechanical ventilation). Effect was analysed by Cox regression analysis on ICU mortality with adjustment for common confounders such as sex, age, BMI, hyperglycemic index, APACHE II, and protein and/or energy target reached (yes/no). Hazard ratios (HR) with 95% confidence interval (CI) are presented for cardiovascular and non-cardiovascular patients. Results show that ICU mortality in critically ill cardiovascular patients with PN is higher compared to critically ill cardiovascular patients without PN (34.8% compared to 13.4%, HR: 2.49, CI: 1.47-4.22, p-value 0.001). This in contrast to all other diagnoses. Enteral nutrition use within the cardiovascular group was similar, with a mean of 0.5 liter PN in PN+ group. Therefore the PN+ received more adequate amounts of nutrition. However, there was no difference in energy or protein targets achieved between survivors and non-survivors in the PN+ group. These observations were similar for the non-cardiovascular group.
Conclusion: The use of parenteral nutrition is associated with adverse effects on out-come in critically ill cardiovascular patients. This should be confirmed by a randomized trial.

Coffee and tea consumption is not associated with colorectal cancer risk: results of a large prospective population-based cohort study

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Colorectal cancer (CRC) is one of the most common cancers in developed countries, which may partly be explained by lifestyle and environmental factors. Coffee and tea are the most widespread beverages and are highly consumed in developed countries. Epidemiologic findings on the association between coffee and tea consumption and CRC risk are inconsistent. Most prospective cohort studies found no association, whereas some case-control studies indicated an inverse association between both coffee and tea and CRC risk. These contradictive findings may partly be explained by differences in study design and study population. Further, due to a limited number of CRC cases in previous studies, seperate analyses for proximal, and distal colon, or rectal cancer are scarse. The aim of this study was to investigate the association between coffee, and tea consumption, and the risk of developing CRC at different subsites. We analyzed data from 477,071 participants (70.2% female) of EPIC cohort study conducted in 23 participating centers from 10 European countries. At base (1992-2000) a validated food-frequency questionnaire was used to assess coffee and tea consumption and other dietary factors. Quartiles were computed for different levels of consumption excluding non-consumers. Multivariable Cox proportional hazard models were used to estimate adjusted hazard ratio's (HR) and 95%-confidence intervals (95%-CI) for CRC and tumor subsites (i.e. proximal colon, distal colon, rectum), using non-consumers as the reference and adjusted for known risk factors. To adjust for international differences in coffee and tea consumption (e.g. serving size, brewing method), we stratified for study center. We also performed subgroup analyses by gender. After a median follow-up of 11.6 years (inter quartile range 10.1-12.6), 4,234 participants had developed a primary CRC. For tea consumption we found no association with CRC risk (HR 1.00, 95%-CI 0.91-1.10, for consumers vs. non-consumers) or different tumor subsites, and no significant differences were observed between men and women. Coffee consumption was not associated with CRC risk (HR 1.05, 95%-CI 0.91-1.22, for consumers vs. non-consumers) or different tumor subsites. However, female coffee consumers had an increased risk for developing rectal cancer (HR 1.54, 95%-CI 1.07-2.23) and HRs increased depending on the level of coffee consumption (P-trend 0.02) with a HR of 1.84 (95%-CI 1.22-2.77) in the upper quartile of coffee consumption.

In conclusion, tea and coffee consumption are not associated with risk of CRC. However, female coffee consumers may have an increased risk for developing rectal cancer compared to non-consumers.

Prospective evaluation of the prevalence of fat-soluble vitamin deficiencies and decreased bone mineral density in chronic pancreatitis

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Malabsorption of fat is frequently seen in patients with chronic pancreatitis (CP), due to the loss of exocrine pancreatic function. Consequently, these patients are at risk to develop deficiencies of the fat-soluble vitamins. Moreover, because of an impaired absorption of vitamin D and a reduced calcium intake, they may develop a decreased bone mineral density (BMD), resulting in osteopenia and osteoporosis. Although malnutrition is common in CP, there are limited data on the prevalence of fat-soluble vitamin deficiencies and low bone density. Therefore we evaluated this in CP patients, with and without exocrine pancreatic insufficiency. In a prospective cohort study we included all consenting CP patients who visited the outpatient clinic of the department of Gastroenterology of our tertiary referral center between March and November 2011. The pancreatic function was evaluated, both exocrine (by means of a fecal Elastase-1 test; normal value ≥ 0.2 mg/g) and endocrine (presence of diabetes). Serum concentrations of vitamin A, D, E, and K were determined. Furthermore, a densitometry was performed to assess BMD (osteopenia: T score -1 to 2.5; osteoporosis: T score < -2.5). Twenty-eight patients were included, of which 57% were male with a median age of 52 (range 22-69). CP was caused by alcohol in 50%, by idiopathic disease in 32%, and by other causes in 18%. Exocrine insufficiency was present in 19 patients (68%), of whom 14 used pancreatic enzymes, and diabetes was observed in 11 cases (39%). Vitamin A deficiency was not observed. A vitamin E, K, and D deficiency were present in respectively 2 (7%), 16 (57%) and 13 (46%) patients. In the subgroup of patients with exocrine insufficiency who did not use enzymes, the prevalence of vitamin deficiencies was even higher; 20% for vitamin E, 60% for vitamin K, and 80% for vitamin D. A decreased BMD was observed in 16 patients (57%), of whom 12 suffered from osteopenia (43%) and 4 from osteoporosis (14%). Again, the prevalence was even higher in the patients with untreated exocrine insufficiency; osteopenia in 60% and osteoporosis in 20%. CP patients have an increased risk to develop deficiencies of the vitamins E, D and K, and a decreased BMD, even if they do not have a clinical proven exocrine insufficiency. Therefore, CP patients should be routinely screened by laboratory testing and bone densitometry at regular intervals. In addition, to prevent complications, it is crucial that EPI patients are treated with an adequate dosage of enzymes, in order to abolish fat malabsorption.

Severe weight loss before radiotherapy is a major prognostic factor for survival in patients with head and neck cancer

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Rationale: Weight loss before radiotherapy is frequently observed in head and neck cancer patients. The objective of this study was to assess the relation between pre-radiotherapy weight loss and the 5 year overall and disease specific survival in a large group of head and neck cancer patients. Methods: Between 2000 and 2008, all newly diagnosed head and neck cancer patients (≥18 years) receiving radiotherapy, with or without surgery/chemotherapy, with curative intent were included. Previous weight loss, patient and tumour characteristics were recorded before radiotherapy. The association between weight loss before radiotherapy and 5 year overall and disease specific survival was investigated by Cox regression analyses, with adjustments for age, gender, tumour location, tumour stage and performance status. Results: Seventy percent of 1330 included patients were men. Most patients (48%) had a stage IV tumour, 17% stage III, 19% stage II, 15% stage I and 1% stage 0. Tumours were mainly located at the pharynx (32%) and larynx (32%). Before radiotherapy, 70% of patients had no weight loss, 16% had ≤5% weight loss, 9% had >5-10% weight loss and 5% had >10% weight loss. After 5 years, the overall survival rates for these groups were 70%, 58%, 46%, 41%, respectively ($p<0{\cdot}001$). Disease specific survival rates were 86%, 86%, 80% and 71%, respectively ($p<0{\cdot}001$). After adjustment for important socio-demographic and tumour-related confounders, >10% weight loss before radiotherapy remained significantly associated with a worse overall and disease specific survival (HR 1·8; 95%CI 1·2–2·7; $p=0{\cdot}007$ and HR 2·1; 95%CI 1·1–3·7; $p=0{\cdot}018$).
Conclusion: More than 10% weight loss before radiotherapy is independently associated with a worse 5 year overall survival and disease specific survival.

Overzicht standhouders voorjaarscongres NVGE, 22 en 23 maart 2012
B = Beneluxhal, D = Doorloop, K = Kempenhal

Abbott BV	K 17
Alvleesklier vereniging	B 14
AstraZeneca BV	B 20
Boston Scientific Nederland BV	K 11
Bristol Meyers	B 8
Cablon Medical	D 3
CameraPil BV	D 2
Cobra Medical BV	B 2
COOK Medical	K 14
Crohn&Colitis Ulcerosa ver.Nederland	B 12
Dr. Falk Pharma Benelux BV	K 15
Ella-CS	B 9
Endotechniek	K 10
Erbe Nederland BV	B 10
Eurosteriel Medical	B 18
Ferring BV	B 16
FMH Medical BV	B 5
Fresenius Kabi Nederland BV	B 21
Gilead Sciences Nederland BV	K 3
Hitachi Medical Systems	K 2
Janssen-Cilag BV	B 1
Medical Measurements Systems BV	K 4
Medicor	D 1
Merck Sharp&Dohme	B 23
Minigrip Nederland BV	K 9
Minntech BV	K 19
Norgine BV	B 4
Nutricia	K 6
Olympus	K 7
Pentax Medical	K 1
Pyramed Nederland	B 3
Rescoope BV	B 22
Roche	B 17
Siemens	K 5
Stichting Vreemde kronkels	B 15
Surgical Technologies BV	B 6
TIMM Health Care BV	B 7
TRAMEDICO BV	K 13
V&VN MDL	B 19
Vereniging Ziekte van Hirschprung	B 13
Vifor Pharma Nederland BV	K 16
Wassenburg Medical Devices BV	K 12
Zambon Nederland BV	K 18


B5
B6
B7
B8
B9
B10
B4
B19
B20
B18
B3
B17
B23
B22
B15
B13
B2
BENELUXZAAL
B16
B21
B1
B12
B14
D2
D1
D3
DOORLOOP
K6
K19
K18
K9
K5
K4
K7
K10
K3
K16
K17
K2
KEMPENZAAL
K11
K14
DIEZEZ
K1
K15
K14
K13
K12
DIEZEFOYER
Cell Biology
Metabolisme
Cancer
IBD
Immunologie
DIENS
PODIUM
BRABANTZAAL
Bar

Nederlandse Vereniging voor Gastroenterologie

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

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

Tevens wil ondergetekende zich aansluiten bij:

□ Sectie Gastrointestinale Endoscopie*
□ Netherlands Society of Parenteral and Enteral Nutrition*
□ Sectie Neurogastroenterologie en Motiliteit*
□ Sectie Experimentele Gastroenterologie*
□ Sectie Kindergastroenterologie*
□ Werkgroep IBD
□ Nederlandse Vereniging voor Gastrointestinale Chirurgie *(combinatielidmaatschap)*
contributiebedragen: graag aankruisen wat voor u van toepassing is
□ Specialisten € 90,00 (totaal € 140,00 incl. lidmaatschap NVGE € 50,00)
□ Assistenten i.o. € 25,00 (totaal € 75,00 incl. lidmaatschap NVGE € 50,00)

*Aanvullende lidmaatschappen van met * aangegeven secties zijn kosteloos*

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

Bank- / girorekening: Datum en handtekening:

Dit ondertekende formulier per post of fax (023 – 5513087)
sturen naar: Secretariaat NVGE, Postbus 657, 2003 RR Haarlem

Aanvullende informatie: De contributie van de Nederlandse Vereniging voor Gastroenterologie bedraagt € 50,00 per jaar.

NEDERLANDSE VERENIGING VOOR HEPATOLOGIE

Aanmeldingsformulier lidmaatschap

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

** Doorhalen wat niet van toepassing is.*

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

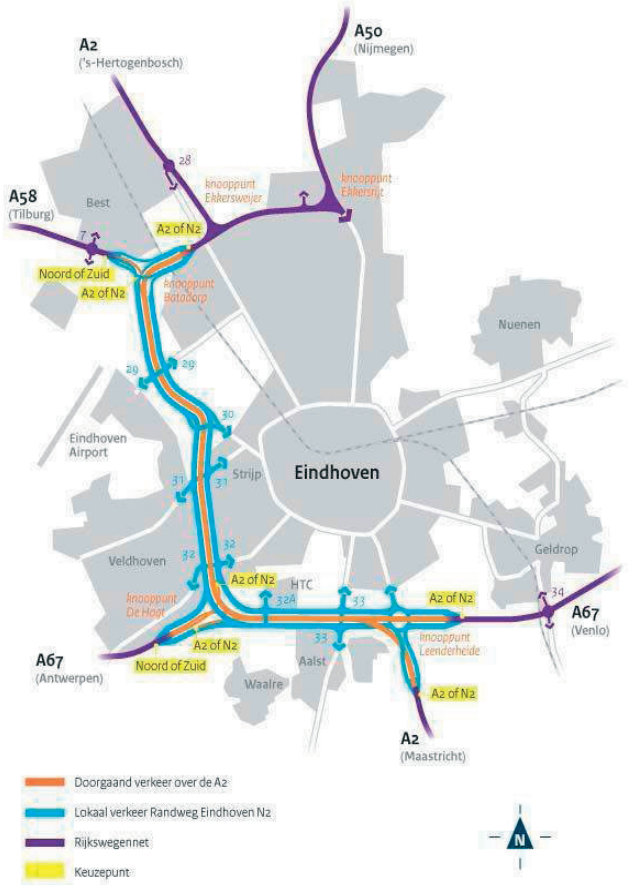
Bank- / girorekening: Datum en handtekening:

Dit ondertekende formulier per post of fax (023 – 5513087) sturen naar:
Secretariaat NVH, Postbus 657, 2003 RR Haarlem

Aanvullende informatie: De contributie van de Nederlandse Vereniging voor Hepatologie bedraagt € 35,00 per jaar.
Na toetreding als lid ontvangt u een factuur (conform de regels is volledige contributie verschuldigd in het jaar van toetreding).

Routebeschrijving NH Conference Centre Koningshof

Momenteel liggen er rondom Eindhoven twee wegen.
1. Het doorgaand verkeer dat richting Venlo of Maastricht moet neemt de oranje route (A2). Voor NH Koningshof moet je deze niet nemen. Het wordt aangegeven met de bewegwijzeringborden. Let op, dit is de middelste baan.
2. Voor het lokale verkeer rondom Eindhoven volgt de blauwe route (N2). Deze weg moet men nemen voor NH Koningshof. Hierbij moet u Eindhoven/Waalre/Veldhoven aanhouden. Vanuit het zuiden is dit identiek.



PER AUTO

VANUIT 's HERTOGENBOSCH:

- Volg de A2 richting Eindhoven
- Afslagroute 29 t/m 33 richting Waalre/Veldhoven
- Bij afslag 32 Veldhoven verlaat u de snelweg
- Onder aan de afslag gaat u rechtsaf en vervolgens volgt u de borden Koningshof
- Na ca. 3 km rechtdoor vindt u aan de linkerkant NH Koningshof.

VANUIT BREDA / TILBURG:

- Volg de A58 richting Veldhoven
- Volg de N2, afslagroute 29 t/m 33 richting Waalre/Veldhoven
- Bij afslag 32 Veldhoven verlaat u de snelweg
- Onder aan de afslag gaat u rechtsaf en vervolgens volgt u de borden Koningshof
- Na ca. 3 km rechtdoor vindt u aan de linkerkant NH Koningshof.

VANUIT VENLO:

- Volg de A67 richting Eindhoven
- Volg de N2, afslagroute 29 t/m 33 richting Veldhoven
- Bij afslag 32 Veldhoven verlaat u de snelweg
- Onder aan de afslag gaat u linksaf en vervolgens volgt u de borden Koningshof
- Na ca. 3 km rechtdoor vindt u aan de linkerkant NH Koningshof.

VANUIT MAASTRICHT:

- Volg de A2 richting Eindhoven
- Volg de N2, afslagroute 29 t/m 33 richting Waalre/Veldhoven
- Bij afslag 32 Veldhoven verlaat u de snelweg
- Onder aan de afslag gaat u linksaf en vervolgens volgt u de borden Koningshof
- Na ca. 3 km rechtdoor vindt u aan de linkerkant NH Koningshof.

VANUIT ANTWERPEN / TURNHOUT:

- Volg de A67 richting Eindhoven
- Bij afslag 32 Eersel verlaat u de snelweg
- Vervolg de route linksaf (3/4) op de rotonde richting Steensel
- Ongeveer 3 km na Steensel richting Veldhoven vindt u aan de rechterkant NH Koningshof.

PARKEREN

NH Conference Centre Koningshof beschikt over een uitgebreid gratis parkeerterrein.

ADRES

Locht 117, 5504 RM Veldhoven
040-253 74 75

PER OPENBAAR VERVOER:

- Bij aankomst per trein in Eindhoven Centraal Station verlaat u het perron rechtsaf richting busstation.
- Neem Buslijn 15 (directe lijn) of 149 of 150 en stap uit bij halte NH Koningshof. Duur van de rit bedraagt ongeveer 30 minuten.