Programma voorjaarsvergadering 17 en 18 maart 2016
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 vergaderingen tijdens voorjaarsvergadering:

Nederlandse Vereniging voor Gastroenterologie 17 maart,	11.30 uur – Brabantzaal
NVMDL i.o 17 maart,	12.00 uur – zaal 63+64
Nederlandse Vereniging voor Hepatologie 17 maart,	15.00 uur – Baroniezaal
Nederlandse Vereniging van Maag-Darm-Leverartsen 18 maart,	08.00 uur – zaal 82+83

INHOUDSOPGAVE **pag**

Vrijdag 18 maart 2016

Belangrijke mededeling
over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers aan de voorjaarsvergadering op 17 en 18 maart 2016

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.

De Geneesmiddelenwet 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 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 uiteraard voorkomen.

In verband met de Gedragscode Geneesmiddelenreclame van de CGR en de aan het NVGE-congres verbonden expositie van farmaceutische producten, medische instrumenten en voedingsmiddelen, zal bij uw congresregistratie via de NVGE-website worden gevraagd naar uw bevoegdheid om medicijnen voor te schrijven.

Alle congresdeelnemers dragen verplicht een congresbadge waarop behalve de naam ook beroep/functie staat aangegeven. Farmaceutische standhouders benaderen uitsluitend congresdeelnemers die de bevoegdheid hebben om receptgeneesmiddelen voor te schrijven of ter hand te stellen. Om dit extra te verduidelijken zal tijdens het voorjaarscongres worden gekozen voor verschillende kleuren congresbadges.

Uit het bovenstaande volgt dat aanwezige reclame-uitingen en merkproductinformatie van farmaceutische industrieën alleen gericht zijn 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) vertrouwen erop u met bovenstaande voldoende te hebben geïnformeerd.

Het bestuur van de NVGE

VOORWOORD

Hierbij treft u het volledige programma aan van het voorjaarscongres dat gehouden wordt op 17 en 18 maart a.s. in NH Conference Center Koningshof te Veldhoven. Anders dan gebruikelijk wordt ons congres deze keer niet vooraf gegaan door het cursorisch onderwijs, maar is dit onderwijs op vrijdag geïntegreerd in het programma. U dient hiervoor wel apart te registreren!

In het voorjaar is er altijd veel ruimte voor de presentaties van ingezonden klinische abstracts, naast een doorlopend DEGH programma op donderdag en vrijdag.
Daarnaast zijn meerdere symposia gepland. Op donderdag wordt het congres geopend met symposia van de sectie Oncologie over palliatieve zorg en een symposium van de NVGIC. Na de ledenvergadering en lunch is er onder meer een symposium over infectieuze aandoeningen, geopend door prof. dr. Ernst Kuipers met een state of the art lecture over *Helicobacter Pylori*. Tijdens dit symposium ook een voordracht over reinigen van endoscopen. Voorts deze middag symposia over TIPS (georganiseerd door de NVH) en T1 carcinomen (georganiseerd door de NVGIC in samenwerking met de sectie Endoscopie). 's Middags zijn er tevens Meet-the-Expert sessies over stents en levercirrose waar u kosteloos voor kunt inschrijven en een MLDS Career Development Grant Lecture. Tijdens de plenaire sessie wordt de NVGE Research Award voor het beste proefschrift uit 2015 uitgereikt door Prof. dr. ir. H.W. Verspaget, voorzitter van de jury. Hoogtepunt van de donderdag is de uitreiking van de Frieda den Hartog Jager prijs aan dr. E.A.J. Rauws, gevolgd door een erevoordracht. Aansluitend volgt de erevoordracht door Prof. dr. H.G. Gooszen.

Op de vrijdag start het programma met symposia van de sectie Endoscopie over kwaliteitsregistraties, en de NVH over hepatitis C. Aansluitend begint het cursorisch onderwijs over spoedeisende MDL-zorg. Parallel daaraan sessies met abstracts van de secties Endoscopie en Oncologie, het NESPEN symposium en het programma van de V&VN MDL, dit jaar in de Brabantzaal.

Het volledige programma, inclusief de abstracts vindt u eveneens op www.nvge.nl

Wij wensen u een plezierig congres!

Dr. J.J. Keller, secretaris NVGE
Dr. K. van der Linde, bestuurslid NVGE

Programma donderdag 17 maart 2016

Donderdag	Brabantzaal	Baroniezaal	Auditorium	Parkzaal
09.15 - 09.45	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie
09.45 – 11.30	Symposium Palliatieve Zorg *pagina 10*	DEGH-meeting, oral presentations (aanvang 10.30) *pagina 17*	Symposium NVGIC: Functionele . *pagina 14* Innovation room: zaal 82- 83	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie (aanvang 09.30) *pagina 21*
11.30 - 12.00	Ledenvergadering NVGE		Geen programma i.v.m. ALV van de NVGE	Geen programma i.v.m. ALV van de NVGE
12.00 - 13.00	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal
13.00 – 14.40 14.45	Minisymposium Infectieuze Aandoeningen *pagina 11* *MLDS Career Development lecture pagina 11*	DEGH-meeting, oral presentations *pagina 18*	Symposium NVGIC: Maligne Rectum (Symposium 2 – Lustrum NVCO) *pagina 15*	Vrije voordrachten Ned. Vereniging voor Gastrointestinale Chirurgie *pagina 24*
15.00 - 15.30	Theepauze	Theepauze + ALV NVH	Theepauze	Theepauze
15.30 - 17.00	TIPS symposium NVH *pagina 12*	DEGH-meeting, oral presentations *pagina 19*	Symposium NVGIC: Endoscopische behandeling van T1-carcinomen. *pagina 16*	Vrije voordrachten Sectie Neuro-gastroenterologie en Motiliteit *pagina 26*
17.00 - 17.30	Voordrachten President Select - *pagina 12*			
17.30 – 17.50	NVGE Research Award erevoordracht door de prijswinnaar			
17.40 – 18.05	Frieda den Hartog Jager prijs en lezing door Dr. E.A.J Rauws			
18.05 – 18.30	Lezing prof. dr. H.G. Gooszen			
18.30 - 19.30	Borrel in expositiehal			
19.30 - 22.00	Diner Genderzaal			
22.00 - 01.00	Borrel / Muziek in foyer			

Donderdag	Zaal 80 – Meet the expert - Cirrose	Zaal 81: Meet the expert - obstructiemanagement
13.00 – 14.00 14.00 – 15.00	Groep 1 - volgeboekt Groep 2 – volgeboekt *pagina 28*	Groep 1 - volgeboekt Groep 2 – volgeboekt *pagina 28*

Programma vrijdag 18 maart 2016

Vrijdag	Brabantzaal	Baroniezaal	Auditorium	Parkzaal
08.30 – 09.30	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie
09.30 – 10.30	Programma V&VN aanvang 10.00 uur *pagina 44*	Posterrondes DEGH zaal 19 en 20, aanvang 09.00 met ontbijt *pagina 30*	Symposium Hepatitis C anno 2016 *pagina 29*	Symposium: endoscopieregistraties zegening of nood-zakelijk kwaad? *pagina 36*
10.30 - 11.30	11.00 Koffiepauze	11.00 Koffiepauze	10.30 Koffiepauze expo	10.30 Koffie expo
11.30 - 13.00	Programma V&VN *pagina 44*	DEGH-meeting oral presentations *pagina 34*	Cursorisch onderwijs: Spoedeisende MDL-zorg *pagina 8*	Vrije voordrachten Sectie Gastrointestinale Endoscopie *pagina 36*
13.00 – 14.00	13.00 Lunch expohal	13.00 Lunch expohal	12.45 Lunch expohal	13.00 Lunch expohal
14.00 – 15.30	Programma V&VN *pagina 44*	DEGH-meeting oral presentations *pagina 34*	Cursorisch onderwijs: Spoedeisende MDL-zorg *pagina 9*	Vrije voordrachten Sectie Gastrointestinale Oncologie *pagina 38*
15.30 – 16.00	15.30 Thee Limburgfoyer	15.30 Thee Limburgfoyer	14.55 Thee bij de zaal	15.30 Thee bij Parkzaal
			Cursorisch onderwijs: Spoedeisende MDL-zorg *Pagina 9*	Geen programma in deze zaal
16.30			Einde cursus, thee/koffie bij de zaal	

Programma vrijdag 18 maart 2016
NVGE en NESPEN

Vrijdag	Zaal 80
09.30 – 10.30	Sessie met vrije voordrachten Nederlandse Vereniging voor Gastroenterologie *pagina 41*
10.30 – 11.00	Koffiepauze in de expositiehal
11.00	Symposium NESPEN met om 12.50 uur uitreiking vn de NESPEN abstract- en NESPEN proefschriftprijs *pagina 42*
13.00	Lunchbuffet in expositiehal
	In de middag geen programma in deze zaal

Vrijdag 18 maart 2016

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

Cursuscommissie
Prof. dr. U.H.W. Beuers, voorzitter, MDL-arts, AMC, Amsterdam
Mevr. dr. C.M. Bakker, MDL-arts, Atrium MC, Heerlen
Drs. K. van Hee, aios MDL, Radboud UMC, Nijmegen
Dr. J. Heisterkamp, chirurg, St. Elisabeth Ziekenhuis, Tilburg
Dr. M.A.J.M. Jacobs, MDL-arts, VUmc, Amsterdam
Dr. P.J.F. de Jonge, aios MDL, EMC, Rotterdam
Mevr. dr. A.M.J. Langers, MDL-arts, LUMC, Leiden
Dr. B. Oldenburg, MDL-arts, UMCU, Utrecht
Mevr. dr. R.E. Pouw, aios MDL, AMC, Amsterdam
Dr. B.J. Veldt, MDL-arts, Reinier de Graaf Gasthuis, Delft

Onderwerp: **Spoedeisende MDL zorg**

I. De gastrointestinale bloeding

Voorzitters: *U.H.W. Beuers, P.J.F. de Jonge*

11.00 – 11.05 Inleiding

11.05 – 11.25 Medicamenteuze therapie, stollingscorrectie, volumesubstitutie, bloedtransfusie
Dr. Jubi de Haan (EMC, Rotterdam)

11.30 – 11.50 Varicesbloeding
Dr. Eric T.T.L. Tjwa, MDL-arts (RUMC, Nijmegen)

11.55 – 12.15 Endoscopische therapie van bovenste en onderste GI-bloedingen
Dr. Hendrik M. van Dullemen, MDL-arts (UMCG, Groningen)

12.20 – 12.40 Interventionele therapie van GI-bloedingen
Dr. Arian R. van Erkel, radioloog (LUMC, Leiden)

12.45 – 13.15 Lunchbuffet expositiehal

II. Acute accidenten en de acute buik

Voorzitters: *B.J. Veldt, R.E. Pouw*

13.15 – 13.35 Bolusobstructie, corpora aliena, caustisch letsel
Dr. Maarten A.C. Meijssen (Isala, Zwolle)

13.40 – 14.00 Acute cholecystitis, acute cholangitis
Prof. dr. Laurens Stassen, chirurg (MUMC, Maastricht)

14.05 – 14.25 Acute diverticulitis
Prof. dr. Johan F. Lange, chirurg, (Erasmus MC, Rotterdam)

14.30 – 14.50 Voeding van de 'critically ill'
Prof. dr. B.J.M. Witteman, MDL-arts, Ziekenhuis Gelderse Vallei, Ede

14.55 – 15.15 Koffie/thee (in foyer bij Auditorium)

III. Preventie en behandeling van iatrogene complicaties

Voorzitters: *A.M.J. Langers, K. van Hee*

15.15 – 15.35 Slokdarmperforatie
Dr. Frank Vleggaar, MDL-arts (UMCU, Utrecht)

15.40 – 16.00 Complicaties van ERCP
Prof. dr. Marco J. Bruno, MDL-arts (EMC Rotterdam)

16.05 – 16.25 Perforatie na poliepectomie
Prof. dr. Paul Fockens, MDL-arts (AMC Amsterdam)

16.30 Einde programma

De cursuscommissie verwacht van de MDL-artsen i.o. dat ze de Cursus Klinische Hepatologie (NVH) tijdens de Dutch Liver Week éénmaal bezoeken in het tweede deel van de MDL-opleiding (jaar vier tot zes). Op het cursorisch onderwijs zijn conform de eisen van het Centraal Register Kort Beroepsonderwijs leveringsvoorwaarden van toepassing. Informatie vindt u op de onderwijspagina van www.mdl.nl en www.nvge.nl.

Donderdag 17 maart 2016

Symposium Palliatieve Zorg **Brabantzaal**

09.00 Registratie, koffie

Voorzitters: R.W.M. Schrauwen en K.M.A.J. Tytgat

09.45 Inleiding door de voorzitters

09.50 Inleiding palliatieve (MDL) zorg
Drs. B.S. Wanrooij, palliatieve zorg, AMC, Amsterdam

10.10 Ileus/peritonitis carcinomatosa
Dr. H. Boot, MDL-arts, Antoni van Leeuwenhoekhuis, Amsterdam

10.30 Na de cursus palliatieve zorg
Drs. M.I.E. Appels, MDL-arts, Rode Kruis Ziekenhuis, Beverwijk

10.50 Palliatie en de dokter
B.J. Giebner, humanistisch geestelijk verzorger, AMC, Amsterdam

11.10 MDL palliatie therapie
Dr. V.M.C.W. Spaander, MDL-arts, Erasmus MC, Rotterdam

11.30 Einde programma

Ledenvergadering **Brabantzaal**

11.30 Ledenvergadering Nederlandse Vereniging voor Gastroenterologie

12.00 Lunch in expositiehal

Minisymposium Infectieuze Aandoeningen **Brabantzaal**

Voorzitters: J.J. Keller en P.J. Wismans

13.00 State of the Art Lecture *Helicobacter Pylori*
Prof. dr. E.J. Kuipers, MDL-arts, voorzitter Raad van Bestuur, Erasmus MC, Rotterdam

13.25 Update desinfectie van endoscopen: nieuwe inzichten en regelgeving
J. Buijs, deskundige scopenreiniging en desinfectie, Erasmus MC, Rotterdam

13.40 Infectieuze diarree en diarree bij reizigers
Dr. P.J. Wismans, internist, Havenziekenhuis, Rotterdam

13.55 Parasitaire infecties: controversies, diagnostiek en behandeling
Dr. T. van Gool, arts-parasitoloog, AMC, Amsterdam

14.10 Recidiverende *Clostridium difficile* infectie
Dr. J.J. Keller, MDL-arts, MC Haaglanden, Den Haag

14.25 SOA's in de MDL-praktijk
Prof. J.F.W.M. Bartelsman, MDL-arts, Amsterdam

14.40 *Einde minisymposium*

MLDS Career Development Lecture **Brabantzaal**

Voorzitter: J.J. Keller

14.45 Genetic characterization of the progression of Intraductal Papillary Mucinous Neoplasm (IPMN) to invasive pancreatic carcinoma
Dr. L.A.A. Brosens, patholoog, UMC Utrecht

15.00 Theepauze expositiehal

TIPS Symposium — Brabantzaal

Voorzitters: U.H.W. Beuers en H.R. van Buuren

15.30 TIPS - state of the art
Prof. dr. M. Rössle, Praxiszentrum and University Hospital, Freiburg, Germany

16.00 TIPS: the procedure
Dr. A. Moelker, radioloog, Erasmus MC, Rotterdam

16.25 TIPS: complications and their treatment
Dr. M.J. Coenraad, MDL-arts, Leids Universitair Medisch Centrum

16.50 Discussion

Voordrachten President Select — Brabantzaal

Voorzitters: J.J. Keller en P.D. Siersema

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

17.00 Improved anastomotic leakage rates in patients following Ivor-Lewis esophagectomy with omental wrap and pleural flap (p. 48)
A.E. Slaman, J.A.H. Gooszen, M.I. van Berge Henegouwen, S.S. Gisbertz, Academisch Medisch Centrum, Amsterdam

17.10 CD44 and its splice variant CD44v6 as Potential Imaging and Treatment Targets for Colorectal Adenomas (p. 49)
E. Hartmans[1], V. Orian-Rousseau[2], A. Matzke-Ogi[3], A. Karrenbeld[4], D.J.A. de Groot[5], S. de Jong[5], G.M. van Dam[6], R.S.N. Fehrmann[*5], W.B. Nagengast*[*1], *Contributed equally, [1]Dept of Gastroenterology and Hepatology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands, [2]Institute of Toxicology and Genetics, Karlsruhe Institute of Technology, Karlsruhe, Germany, [3]Amcure GmbH, Eggenstein-Leopolshafen, Germany, [4]Dept of Pathology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands, [5]Dept of Medical Oncology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands, [6]Dept of Surgery, Nuclear Medicine and Molecular Imaging and Intensive Care, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands*

17.20 Bacterial contamination of reprocessed ERCP duodenoscopes in The Netherlands is widespread (p.50)

A.W. Rauwers[1], A.F. Voor in 't Holt[2], R. de Groot[2], J.G. Buijs[2], M.C. Vos[2], M.J. Bruno[1], [1]Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherands. [2]Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Prijsuitreikingen **Brabantzaal**

17.30 **Uitreiking NVGE Gastrointestinale Research Award 2015**
door de voorzitter van de jury, prof. dr. ir. H.W. Verspaget
gevolgd door erevoordracht door de prijswinnaar

17.40 **Uitreiking van de Frieda den Hartog Jager Prijs**
gevolgd door voordracht.

ERCP in Nederland
Dr. E.A.J. Rauws, MDL-arts, Academisch Medisch Centrum

18.05 **Lezing prof. dr. H.G. Gooszen, chirurg**
Chirurgie in 2025: *Nieuwe Verbintenissen: Ruimte door Beperkingen*

18.30 Einde programma, congresborrel in expositiehal

20.00 Diner in Beneluxzaal

Symposium Functionele coloproctologie

Voorzitters: J. Heisterkamp

10.00	Sacrale neuromodulatie voor incontinentie en obstipatie *Dr. J. Melenhorst, chirurg in opleiding en Dr. S.O. Breukink, chirurg, Maastricht UMC*
10.15	Rectopexie als behandeling voor functionele klachten *Dr. N.A.T. Wijffels, chirrug, Zuwe Hofpoort Ziekenhuis en St. Antonius Ziekenhuis*
10.30	Het Malone stoma *Spreker: to be announced*
10.45	De lange termijn uitkomsten van SECCA en pads bij faecale incontinentie *Dr. R.J.F. Felt-Bersma, MDL-arts, VU medisch Centrum Amsterdam*
11.00	Colonlavage bij faecale incontinentie *Dr. C. Smit, Reade, Amsterdam*
11.15	Samenvatting en discussie
11.30	Einde programma Voor de NVGE ledenvergadering kunt u zich begeven naar de Brabantzaal, aanvang 11.30 uur
12.00	Lunch in expositiehal

Symposium Maligne Rectum
Lustrum NVCO

Voorzitters: H. Rutten en D. Hilling

13.00	De term hybride doet ook zijn intrede in de coloproctologie *Dr. M. Vermaas, chirurg, IJsselland Ziekenhuis, Capelle a/d IJssel*
13.20	De uitkomsten van TEM na TME *C. Hoff, chirurg, Medisch Centrum Leeuwarden*
13.40	Niet standaard een ontlastend ileostoma meer? *Dr. J.W.T. Dekker, chirurg, Reinier de Graaf Gasthuis, Delft*
14.00	Ileostoma of transversostoma? *Dr. E.C.J. Consten, chirurg en F. Amelung, arts-onderzoeker, Meander MC, Amersfoort*
14.20	Behandeling van de perineale hernia na APR *H.J. Belgers, chirurg Zuyderland, Heerlen*
14.40	De toekomstige rol van de oncologische rectum chirurg *Prof. dr. G.L. Beets, chirurg, Amsterdam*
15.00	Theepauze expositiehal

Symposium Endoscopische behandeling van T1 carcinomen

Voorzitters: G. Beets en B.L.A.M. Weusten

15.30	T1 carcinomen, de rol van (aanvullende) chirurgie. *Drs. J.W.A. Leijtens, chirurg, Laurentius Ziekenhuis, Roermond*
15.45	T1 carcinomen: van herkenning naar resectie *Drs. P. Didden, MDL-arts, Erasmus MC, Rotterdam*
16.00	Endoscopische verwijdering van T1 carcinomen *Dr. L.M.G. Moons, MDL-arts, Universitair Medisch Centrum Utrecht*
16.15	Hoog risico colorectale poliepen in de pathologie *Dr. M.M. Laclé, patholoog, Universitair Medisch Centrum Utrecht* *Prof. dr. G.J.A. Offerhaus, patholoog, Universitair Medisch Centrum Utrecht*
16.45	T1 carcinomen, is er een rol voor sentinal node?" *Prof. dr. R.A.E.M. Tollenaar, chirurg, Leids Universitair Medisch Centrum*
17.00	Einde symposium *Voor het plenaire programma kunt u zich begeven naar de Brabantzaal*
18.30	Einde programma, congresborrel in expositiehal
20.00	Diner in de Beneluxhal

Voorzitters: Q. Pan en T. Vanwolleghem

10.30 Milestones in HCV research: From subgenomic replicon to cure
Dr. T. Vanwolleghem, MDL-arts, UZ Antwerpen

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

10.55 Neurons are permissive for hepatitis E virus infection (p. 51)
X. Zhou[1], F. Huang[2], L. Xu[1], B.C. Jacobs[3], W. Wang[1], Y. Wang[1], D. Sprengers[1], H.J. Metselaar[1], H.R. Dalton[4], N. Kamar[5], M.P. Peppelenbosch[1], Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, Netherlands. [2]Medical Faculty, Kunming University of Science and Technology, Kunming, China, [3]Dept of Neurology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands, [4]Cornwall Gastrointestinal Unit, Royal Cornwall Hospital & European Centre for the Environment & Human Health, University of Exeter Medical School, Truro, UK. [5]Dept of Nephrology and Organ Transplantation, CHU Rangueil, Toulouse cedex 9, France

11.07 PKCα / AP 1 drives transcription of interferon stimulated genes and mediates cell autonomous defense against hepatitis E virus (p. 52)
W. Wang, Y. Wang, X. Zhou, Y. Yin, Y. Debing, E. Metselaar, J.H. Brandsma, D. Sprengers, R.A. Poot, H.J. Metselaar, R. Smits, B. Berkhout, J. Neyts, M.P. Peppelenbosch and A. Pan, Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center

11.19 Drug drug interactions related to inhibition of the sodium taurocholate co transporting polypeptide (NTCP) by a novel anti HBV peptide (p. 53)
J.M. Donkers[1], M.J. Kwakkenbos[3], S. Duijst[1], S. Urban[4], R.P.J. Oude Elferink[1], S.F.J. van de Graaf[1,2], [1]Tytgat Institute for Liver and Intestinal Research & [2]Dept of Gastroenterology & Hepatology, AMC, Amsterdam, the Netherlands, [3]Aimm Therapeutics, Amsterdam, the Netherlands, [4] German Center for Infection Research, Heidelberg University, Heidelberg, Germany

11.31 Crosstalk between nucleotide synthesis pathways with cellular immunity in constraining hepatitis e virus replication (p. 54)
Y. Wang, W. Wang[1], L. Xu[1], X. Zhou[1], K. Felczak[2], L.J.W. van der Laan[3], K.W. Pankiewicz[2], D. Sprengers[1], H.J. Metselaar[1], M.P. Peppelenbosch[1] and Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]Center for Drug Design, University of Minnesota, Minneapolis, USA. [3]Dept of Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

11.43 Convergent transcription of interferon stimulated genes by TNF α and IFN α augments antiviral activity against HCV and HEV (p. 55)
W. Wang, L.. Xu, J.H. Brandsma, Y. Wang, M.S. Hakim, X. Zhou, Y. Yin, G.M. Fuhler, L.J.W. van der Laan, C.J. van der Woude, D. Sprengers, H.J. Metselaar, R. Smits, R.A. Poot, M.P. Peppelenbosch and Q. Pan, Erasmus Medical Center, Rotterdam

12.00 Lunchpauze

Voorzitters: H.S. Hofker en R. Shiri Sverdlov

13.00 Metagenomic analysis of the gut microbiota at a population scale
Prof. dr. M.H. Hofker, Hoogleraar Moleculaire Genetica, UMC Groningen

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

13.25 Congenital glycosylation defects in patients with unexplained elevated aminotransferases, steatosis and low ceruloplasmin (p. 56)
J.C. Jansen[1,2], M. van Scherpenzeel[2,3], D.J. Lefeber[2,3], J.P.H. Drenth[1], [1]Dept of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, [2]Translational Metabolic Laboratory, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, [3]Dept of Neurology, Donders Institute for Brain, Cognition and Behavior, Radboud University Medical Center, Nijmegen, The Netherlands

13.37 Significance of Integrin alpha 11 in phenotypic transformation of hepatic stellate cells in liver fibrosis (p. 57)
R. Bansal[1], S. Nakagawa[2], J. van Baarlen[3], S.L. Friedman[2], Y. Hoshida[2], J. Prakash[1], [1]Targeted Therapeutics, Dept of Biomaterials Science and Technology, MIRA Institute for Biomedical Technology and Technical Medicine, Faculty of Science and Technology, University of Twente, Enschede, The Netherlands. [2]Division of Liver diseases, Liver Cancer Program, Dept of Medicine Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Laboratorium Pathologie Oost Nederland, Hengelo, The Netherlands*

13.49 Indian Hedgehog inhibits an intestinal inflammatory response via suppression of stromal CXCL12 (p. 58)
B.F. Westendorp[1], N.V.J.A. Büller[1], M.E. Wildenberg[1], O. Karpus[1], V. Muncan[1], G.R. van den Brink[1], [1]Academic Medical Center, Amsterdam, The Netherlands

14.01 Similar depletion of the protective gut bacterium Faecalibacterium prausnitzii in psoriasis and Inflammatory Bowel Disease (p. 59)
H. Eppinga[1,2], C.J. Sperna Weiland[2], H.B. Thio[1], C.J. van der Woude[2], T.E.C. Nijsten[1], M.P. Peppelenbosch[2], S.R. Konstantinov[2], [1]Dept of Dermatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, [2]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

14.13 Intestinal microbiota regulate the inflammatory response of splenocytes (p. 60)
S. Katiraei[1], J.A. van Diepen[2], L.R. Hoving[1], F. el Bouazzouai[1], A.C.M. Pronk[1], M.G. Netea[2], K. Willems van Dijk[1,3] , V. van Harmelen[1], J.F.P. Berbée[3], [1]Dept. of Human Genetics, LUMC, Leiden; [2]Dept. of Internal Medicine, Radboud UMC Nijmegen; [3]Dept. of Medicine, Div. of Endocrinology, LUMC, Leiden; The Netherlands

14.25 Mycophenolic acid potently inhibits rotavirus infection with a high barrier to resistance development (p. 61)

Y. Yin[1], Y. Wang[1], W. Dang[1], L. Xu[1], X. Zhou[1], W. Wang[1], K. Felczak[2], L.J.W. van der laan[3], K.W. pankiewicz[2], A.A. van der Eijk[4], M. Bijvelds[1], D. Sprengers[1], H. de Jonge[1], M.P.G. Koopmans[4], H.J. Metselaar[1], M.P. Peppelenbosch[1] and Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands. [2]Center for Drug Design, University of Minnesota, Minneapolis, USA. [3]Dept of Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands. [4]Dept of Viroscience, Erasmus MC University Medical Center, Rotterdam, The Netherlands

14.37 Combined activity of NTCP and OATPs governs hepatic uptake of conjugated bile acids in vivo (p. 62)

D. Slijepcevic[1], J.M. Donkers[1], D. Tolenaars[1], D.R. de Waart[1], U. Beuers[1], R. Oude Elferink[1], A. Schinkel[2], S. Van De Graaf[1], [1]Tytgat Institute for Liver and Intestinal Research & Dept of Gastroenterology & Hepatology, AMC, Amsterdam, the Netherlands. [2]Division of Molecular Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

15.00 Theepauze en ledenvergadering NVH

DEGH oral presentations **Baroniezaal**

Voorzitters: K.F.J. van de Graaf en D.M.A.E. Jonkers

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

15.30 Nuclear localization of IMPDH2, the primary target of mycophenolic acid, constrains hepatocellular carcinoma (p. 63)

K. Chen[1,2], K. Sideras[1], B. Ma[1], W. Cao[1], L.J.W. van der Laan[3], D. Sprengers[1], R. Smits[1], H.J. Metselaar[1], J. Kwekkeboom[1], M.P. Peppelenbosch[1], Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC Cancer Institute, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [2]College of Life Science, Zhejiang Sci Tech University, Hangzhou, China, [3]Dept of Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

15.42 The dynamics of fast and slow cycling stem cells in liver homeostasis and injury (p. 64)

W. Cao[1], R. Smits[1], N. Tuysuz[2], K. Chen[1], M. Bolkestein[3], L.J.W. van der Laan[4], D. ten Berge[2], D. Sprengers[1], H.J. Metselaar[1], J. Kwekkeboom[1], M.P. Peppelenbosch[1] and Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Cell Biology, [3]Dept of Experimental Surgical Oncology, [4]Dept of Surgery, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

15.54 Portal vein embolization triggered liver regeneration is accelerated by the FXR agonist obeticholic acid (p. 65)

F.G. Schaap[1,], P.B. Olthof[2,*], C. van Himbeeck[1], F. Huisman[2], K.P. van Lienden[3], R.F. van Golen[2], M. Heger[2], J. Verheij[4], I.A. Leclercq[5], P.L.M. Jansen[1], T.M. van Gulik[2,*], S.W.M. Olde Damink[1,*], [1]Dept of Surgery, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands. Depts of [2]Surgery, [3]Radiology and [4]Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. [5]Laboratory of Hepato Gastroenterology, Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain, UCL, Brussels, Belgium. *Equally contributing first and senior authors*

16.06 WNT secretion is not required to sustain WNT/ β catenin signaling in β catenin mutant hepatocellular carcinoma cells (p. 66)

W. Wang, L. Xu, K. Jairam, D. Sprengers, M. Peppelenbosch, Q. Pan and R. Smits., Dept of Gastroenterology and Hepatology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands.

16.18 Obeticholic acid enhances liver regeneration in hepatectomized mice (p. 67)

K.M.C. van Mierlo[1], V. Lebrun[2], C. van Himbeeck[1], P.L.M. Jansen[1], I.A. Leclercq[2], F.G. Schaap[1], S.W.M. Olde Damink[1], [1]Dept of Surgery, NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands [2]Laboratory of Hepato Gastroenterology, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium

16.30 Under expression of PDL1, Galectin 9 and CD8 TIL in Hepatocellular Carcinoma is associated with worse patient survival (p. 68)

K. Sideras[1], K. Biermann[1], J. Verheij[2], R.B. Takkenberg[2], S. Mancham[1], B.E. Hansen[1], H.M. Schutz[1], R.A. de Man[1], D. Sprengers[1], S.I. Buschow[1], Q. Pan[1], T.M. van Gulik[2], T. Terkivatan[1], J.N.M. IJzermans[1], U.H.W. Beuers[2], S. Sleijfer[1], J. Kwekkeboom[1], M.J. Bruno[1], [1]Erasmus Medical Center Cancer Institute, Rotterdam, [2]Academic Medical Center, Amsterdam

17.00 Einde sessie

Voor het plenaire programma kunt u zich begeven naar de Brabantzaal

Vrije voordrachten Ned. Vereniging voor Gastroenterologie **Parkzaal**

Voorzitters: C.H.C. Dejong en J.J. Kolkman

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

09.30 Biomarkers in inflammatory bowel disease: serum calprotectin is not accurate in detecting disease activity (p. 69)

D.M. Hakvoort[1], A.C.O.G. Cabbolet[1], S.L. Giles[1], D.G.C. van der Lee[1], K.F. Bruin[1], M.W.M.D. Lutgens[1], B. Jakobs[2], R.J.F. Laheij[1], [1]Dept of Gastroenterology and Hepatology, St. Elisabeth TweeSteden Hospital, Tilburg, The Netherlands. [2]Dept of Clinical Chemistry and Haematology, St. Elisabeth – TweeSteden Hospital, Tilburg, The Netherlands.

09.40 The value of mercaptopurine therapy after failing azathioprine in inflammatory bowel disease patients (p. 70)

B. Meijer[1], M.L. Seinen[1], N. Leijte[1], C.J.J. Mulder[1], A.A. van Bodegraven[1,2,] K.H.N. de Boer[1], [1]Dept of Gastroenterology and Hepatology, VU University MC, Amsterdam, [2]Dept of Internal Medicine, Geriatrics and Gastroenterology, Zuyderland Medical Center, Sittard Geleen, The Netherlands.

09.50 Trans radial access for endovascular abdominal interventions: a safe and feasible technique (p. 71)

L.J.D. van Dijk[1], D. van Noord[1], J. Florie[2], M.J. Bruno[1] and A. Moelker[2], Depts of [1]Gastroenterology and Hepatology and [2] Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands

10.00 Postprandial flow measurements of the mesenteric arteries and portal vein using Magnetic Resonance imaging: a pilot study (p. 72)

L.J.D. van Dijk[1], M. Ouhlous[2], D. van Noord[1], A.C. de Vries[1], H.J.M. Verhagen[3], E.J. Kuipers[1,4], A. Moelker[2] and M.J. Bruno[1], Depts of [1]Gastroenterology and Hepatology and [2]Radiology and [3]Vascular Surgery and [4]Internal Medicine, Erasmus University MC, Rotterdam, The Netherlands

10.10 Bowel preparation for colonoscopy and risk of hypokalemia: a pilot study (p. 73)

A. Reumkens[1,2,3], S. Sanduleanu[2,4], B. Winkens[5,6], C.T. van Deursen[1], A.A.M. Masclee[2,3], C.M. Bakker[1,] [1]Dept of Internal Medicine and Gastroenterology, Zuyderland Medical Center, Sittard Heerlen, [2]Division of Gastroenterology and Hepatology, Dept of Internal Medicine, Maastricht University Medical Center, Maastricht, [3]NUTRIM, School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, Maastricht, [4]GROW, School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, [5]Dept of Methodology and Statistics, Maastricht University Medical Center, Maastricht, [6]CAPHRI, School for Public Health and Primary Care, Maastricht University Medical Center, Maastricht, the Netherlands

10.20 Proton pump inhibitors affect the gut microbiome (p. 74)

F. Imhann[1], M.J. Bonder[2*], A. Vich Vila[1*], J. Fu[2], Z. Mujagic[3], L. Vork[3], E.F. Tigchelaar[2], S.A. Jankipersadsing[2], M.C. Cenit[2], H.J.M. Harmsen[4], G. Dijkstra[1], L. Franke[2], R.J. Xavier[5], D. Jonkers[3#], C. Wijmenga[2 #], R.K. Weersma[1#], A. Zhernakova[2#] *Shared first authors # Shared last authors, [1]University of Groningen and University Medical Center Groningen, Dept of Gastroenterology and Hepatology, Groningen, the Netherlands, [2]University of Groningen and University Medical Center Groningen, Dept of Genetics, Groningen, the Netherlands, [3]Maastricht University Medical Center+, Division Gastroenterology Hepatology, NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht, The Netherlands, [4]University of Groningen and University Medical Center Groningen, Dept of Medical Microbiology, Groningen, the Netherlands, [5]Broad Institute of Harvard and MIT, Boston, Massachusetts, USA*

10.30 Evaluation of Paneth cell alterations after intestinal transplantation and during graft rejection (p. 75)

A.M. Kip[1], I.H.R. Hundscheid[1], L.J. Ceulemans[2], B. Boonen[1], H. Hartog[3], R. Brown[3], O. Corcos[4], F. Joly[4], G. Hertogh[2], G. Gupte[3], D. Mirza[3], C.H.C. Dejong[1], J. Pirenne[2], S.W.M. Olde Damink[1], K. Lenaerts[1], [1]Dept of General Surgery, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, The Netherlands; [2]University Hospitals Leuven, Leuven, Belgium; [3]Birmingham Children's Hospital and University Hospitals Birmingham, Birmingham, United Kingdom; [4]Beaujon Hospitals, Paris, France

10.40 A Multicentre Randomized Controlled Trial Evaluating E health for Children and Young Adults with Coeliac Disease – the CoelKids study (p. 76)

S.L. Vriezinga[1], A. Borghorst[1], M.E. van den Akker van Marle[2], M.A. Benninga[3], E.K. George[4], D.M. Hendriks[5], E. Hopman[6], T.G. de Meij[7], A.E. van der Meulen-de Jong[8], H. Putter[9], E.H.H.M. Rings[1,10], M.W. Schaart[1], J.J. Schweizer[1], M.J.M. Smit[5], M.M. Tabbers[3], M.E.I. Weijerman[1], M.M.S. Wessels[1,12], M.L. Mearin[1], Depts of Paediatrics[1], Dept of Medical Decision Making[2], Dietetics[6], Gastroenterology and Hepatology[8] and Medical Statistics[9], Leiden University Medical Centre, Leiden, and the Depts of Paediatrics of Emma Children's Hospital[3], Academic Medical Centre, Amsterdam, Medical Centre Alkmaar[4], Alkmaar, Juliana Children's Hospital[5], HagaZiekenhuis, The Hague, VU University medical center[7], Amsterdam, Sophia Children's Hospital[10], Erasmus Medical Centre, Rotterdam, Alrijne Hospital[11], Leiderdorp, Rijnstate Hospital[12], Arnhem, all in the Netherlands.

10.50 Development of a core outcome set for infant colic (p. 77)

N.F. Steutel[1,2], M.A. Benninga[1], M.W. Langendam[2], J.J. Korterink[1], F. Indrio[3], H. Szajewska[4], M.M. Tabbers[1], [1]Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital/ Academic Medical Center, The Netherlands [2]Dept of Clinical Epidemiology, Bioinformatics and Biostatistics, Academic Medical Center, The Netherlands [3]Dept of Pediatrics, Giovanni XXIII Hospital, Italy; [4]Dept of Pediatrics, The Medical University of Warsaw, Poland

11.00 Investigating the metabolic fingerprint of Celiac Disease – a prospective approach in the PreventCD cohort (p. 78)

F.F. Kirchberg[1], O. Uhl[1], M.L. Mearin[2], R. Auricchio[3*], G. Castillejo[4*], I.R. Korponay Szabó[5*], I. Polanco[6*], M. Roca[7*], C. Ribes Koninckx[8], S.L. Vriezinga[2*], K. Werkstetter[1*], B. Koletzko[1], C. Hellmuth[1], [1]Ludwig Maximilian's University, Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, University of Munich Medical Center, Munich, Germany, [2]Dept. of Pediatrics, Leiden University Medical Center, Leiden, The Netherlands, [3]Dept. of Medical Translational Sciences and European Laboratory for the Investigation of Food Induced Diseases, University Federico II, Naples, Italy, [4]Dept. of Pediatric Gastroenterology Unit, Hospital Universitari Sant Joan de Reus, URV, IIPV, Reus, Spain, [5]Celiac Disease Center, Heim Pál Children's Hospital, Budapest, Hungary, [6]Dept. of Pediatric Gastroenterology and Nutrition, La Paz University Hospital, Madrid, [7]U. Enfermedad Celiaca e Inmunopatología Digestiva, Instituto de Investigación Sanitaria La Fe, Valencia, Spain; [8]Dept of Pediatric Gastroenterology and Hepatology, La Fe University Hospital, Valencia,Spain; *PreventCD project*

11.10 **MLDS voordracht**

Human intestinal ischemia reperfusion Tales from the crypts (p. 79)

I.H.R. Hundscheid[1], L. Eijssen[2], Z. Soons[1], D.H.S.M. Schellekens[1], J.P.M. Derikx[1], J. Grootjans[3], G. van der Vries[4], M.A. Swertz[4], S.W.M. Olde Damink[1], C.H.C. Dejong[1], K. Lenaerts[1], [1]Dept of Surgery and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, [2]Dept of Bioinformatics BiGCaT, Maastricht University, Maastricht, [3]Dept of Gastroenterology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [4]Genomics Coordination Center Groningen and Dept of Genetics, University Medical Centre Groningen, Groningen, The Netherlands

11.20 **MLDS voordracht**

A Multicentre Randomized Controlled Trial Evaluating E health for Children and Young Adults with Coeliac Disease – the CoelKids study (p. 80)

S.L. Vriezinga[1], A. Borghorst[1], M.E. van den Akker van Marle[2], M.A. Benninga[3], E.K. George[4], D.M. Hendriks[5], E. Hopman[6], T.G. de Meij[7], A.E. van der Meulen-de Jong[8], H. Putter[9], E.H.H.M. Rings[1,10], M.W. Schaart[1], J.J. Schweizer[1], M.J.M. Smit[5], M.M. Tabbers[3], M.E.I. Weijerman[1], M.M.S. Wessels[1,12], M.L. Mearin[1], Depts of Paediatrics[1], Dept of Medical Decision Making[2], Dietetics[6], Gastroenterology and Hepatology[8] and Medical Statistics[9], Leiden University Medical Centre, Leiden; and the Depts of Paediatrics of Emma Children's Hospital[3] , Academic Medical Centre, Amsterdam; Medical Centre Alkmaar[4], Alkmaar; Juliana Children's Hospital[5], HagaZiekenhuis, The Hague; VU University medical center[7], Amsterdam; Sophia Children's Hospital[10], Erasmus Medical Centre, Rotterdam; Alrijne Hospital[11], Leiderdorp; Rijnstate Hospital[12], Arnhem, all in the Netherlands.

11.30 Einde programma

U kunt zich voor de NVGE ledenvergadering begeven naar de Brabant-zaal, aanvang 11.30 uur.

12.00 Lunch in expositiehal

Vrije voordrachten Ned. Vereniging voor Gastrointestinale Chirurgie — Parkzaal

Voorzitter: P. van Duijvendijk

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

13.00 Fecal incontinence treated by sacral neuromodulation: worldwide largest single center study (p. 81)
S.Z. Kuiper[1], P.T.J. Janssen[1], S.O. Breukink[1], J. Melenhorst[1], [1]Dept of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

13.10 Long term outcome of constipation treated by sacral neuromodulation (p. 82)
Y. Meyer[1], P.T.J. Janssen[1], J. Melenhorst[1], S.O. Breukink[1], [1]Dept of general surgery, Maastricht University Medical Center, The Netherlands

13.20 Long term outcomes of a Malone Antegrade Continence Enema (MACE) for the treatment of constipation or fecal incontinence in adults (p. 83)
R. Sturkenboom[1], A.A. van der Wilt[1], A. Ahmad[1], L.P.S. Stassen[1], C. Baeten[1], J. Melenhorst[1], S.O. Breukink[1], [1]Dept of Surgery, Maastricht University Medical Center, Maastricht

13.30 The effect of sarcopenia and visceral obesity on the inflammatory response in colorectal surgery (p. 84)
B.J.J. Smeets[1], D.J. Brinkman[1], E.C.J. Horsten[1], J.A. Langius[2], H.J.T. Rutten[1], W.J. de Jonge[3], M.D.P. Luyer[1], [1]Dept of Surgery, Catharina Hospital Eindhoven, [2]Dept of Nutrition and Dietetics, Internal Medicine, VU University Medical Center, Amsterdam, [3]Tytgat Institute for Intestinal and Liver Research, Academic Medical Center, Amsterdam, The Netherlands

13.40 Limited clinical value of CT colonography in obstructive colorectal cancer (p. 85)
J.F. Huisman[1], L.W. Leicher[1], E. de Boer[2], H.L. van Westreenen[3], J.W. de Groot[4], F.A. Holman[6], P.C. van de Meeberg[7], K.C.M.J. Peeters[6], M.N.J.M. Wasser[8], H.F.A. Vasen[5], W.H. de Vos tot Nederveen Cappel[1], [1]Dept of Gastroenterology and Hepatology, and [2]Dept of Radiology, and [3]Dept of Surgery, and [4]Dept of Medical Oncology, Isala clinics, Zwolle, Netherlands, [5]Dept of Gastroenterology and Hepatology, and [6]Dept of Surgery, [8]Dept of Radiology, Leiden University Medical Center, Leiden, Netherlands, [7]Dept of Gastroenterology and Hepatology, Slingeland hospital, Doetinchem, Netherlands

13.50 The added value of fluorescence imaging during laparoscopic resection of liver tumors (p. 86)
H.J.M. Handgraaf[1], L.S.F. Boogerd[1], H.D. Lam[1], V.A.L. Huurman[1], C.J.H. van de Velde[1], A.E. Braat[1] and A.L. Vahrmeijer[1], [1]Leiden University Medical Center, Dept of Surgery

14.00 External biliary drainage following major liver resection for perihilar cholangiocarcinoma: impact on development of liver failure and bile leakage (p. 87) *P.B. Olthof[1], R.J.S. Coelen[1], J.K. Wiggers[1], M.G.H. Besselink[1], O.R.C. Busch[1], T.M. van Gulik[1], [1]Dept of Surgery, Academic Medical Center – University of Amsterdam, Amsterdam, The Netherlands.*

14.10 Referral of patients with suspicion of perihilar cholangiocarcinoma to a tertiary center: a retrospective audit following introduction of a national management guideline (p. 88)

R.J.S. Coelen[1], J. Huiskens[1], O.M. van Delden[2], H. Klümpen[3], E.A. Rauws[4], T.M. van Gulik[1], [1]Dept of Surgery, Academic Medical Center, Amsterdam, [2]Dept of Interventional Radiology, Academic Medical Center, Amsterdam, [3]Dept of Oncology, Academic Medical Center, Amsterdam, [4]Dept of Gastroenterology, Academic Medical Center, Amsterdam, the Netherlands

14.20 Systematic review of resection rates and outcomes after FOLFIRINOX treatment in patients with locally advanced pancreatic cancer (p. 89)

M.S. Walma[a,], S.J.E. Rombouts[a,*], J.A. Vogel[b], L.B. van Rijssen[b], J.W. Wilmink[c], N. Haj Mohammad[d], H.C. van Santvoort[e], I.Q. Molenaar[a,#], M.G.H. Besselink[b,#] *Contributed equally #These authors share senior authorship, [a]Dept of Surgery, University Medical Center Utrecht, [b]Dept of Surgery, Academic Medical Center, Amsterdam, [c]Dept of Oncology, Academic Medical Center, Amsterdam, [d]Dept of Oncology, University Medical Center Utrecht, [e]Dept of Surgery, St. Antonius Hospital, Nieuwegein, The Netherlands*

14.30 Distribution of lymph node metastases in esophageal adenocarcinoma after neoadjuvant chemoradiation therapy: a prospective cohort study (p. 90)

H.T. Künzli[1], AS van Rijswijk[2], S.L. Meijer[3], E.D. Geijsen[4], M.I. van Berge Henegouwen[2], S.S. Gisbertz[2], Dept of Gastroenterology and Hepatology[1], Surgery[2], Pathology[3], and Radiotherapy[4], Academic Medical Center, Amsterdam, the Netherlands.

14.40 Preoperative chemoradiotherapy versus perioperative chemotherapy for patients with resectable esophageal or gastroesophageal junction adenocarcinoma (p. 91)

M.C.J. Anderegg[1], P.C. van der Sluis[2]*, J.P. Ruurda[2], S.S. Gisbertz[1], M.C.C.M. Hulshof[3], M. van Vulpen[4], N. Haj Mohammed[5], H.W.M. van Laarhoven[6], M.I. van Berge Henegouwen[1]#, R. van Hillegersberg[2]#, [1]Dept of Surgery, Academic Medical Center, Amsterdam, [2]Dept of Surgery, University Medical Center Utrecht, Utrecht, [3]Dept of Radiation Oncology, Academic Medical Center, Amsterdam, [4]Dept of Radiation Oncology, University Medical Center Utrecht, Utrecht, [5]Dept of Clinical Oncology, University Medical Center Utrecht, Utrecht, [6]Dept of Clinical Oncology, Academic Medical Center, Amsterdam, The Netherlands. *and # these authors contributed equally to this abstract.*

14.50 Feasibility of long course chemoradiotherapy plus surgery for patients with cT4b oesophageal carcinoma (p. 92)

M.C.J. Anderegg[1], J.P. Ruurda[2], S.S. Gisbertz[1], M.N. Sosef[3], B.P.L. Wijnhoven[4], M.C.C.M. Hulshof[5], J.J.G.H.M. Bergman[6], H.W.M. van Laarhoven[7], M.I. van Berge Henegouwen[1], [1]Dept of Surgery, [5]Radiotherapy, [6]Gastroenterology and [7]Medical Oncology, Academic Medical Center, Amsterdam, [2]Dept of Surgery, University Medical Center, Utrecht, [3]Dept of Surgery, Atrium Medical Center, Heerlen, [4]Dept of Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

15.00 Theepauze expositiehal

Vrije voordrachten Sectie Neurogastroenterologie en Motiliteit **Parkzaal**

Voorzitters: D.P. Hirsch en D. Keszthelyi

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

15.30 Amino acid based diet induces histological remission, reduces clinical symptoms and restores esophageal mucosal integrity in adult eosinophilic esophagitis patients (p. 93)

M.J. Warners[1,2], B.J. Vlieg–Boerstra[3], J. Verheij[4], M.T.J. van Ampting[5], L.F. Harthoorn[5], B.D. van Rhijn[6], W.J. de Jonge[2], A.J.P.M. Smout[1], A.J. Bredenoord[1], [1]Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, [2]Tytgat Institute for Liver and GI research, Academic Medical Center, Amsterdam, [3]Dept of Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Center, Amsterdam, and [4]Dept of Pathology, Academic Medical Center, Amsterdam, [5]Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, [6]Dept of Dermatology and Allergology, Utrecht, the Netherlands

15.40 Relative intercellular space area in gastroesophageal reflux disease: a new standardized method for the evaluation of the intercellular space diameter (p. 94)

N.F. Rinsma[1], L. van de Laarschot[1]*, J.M. Conchillo[1], A.A. Masclee[1], R.M. Farré[2], * both authors contributed equally to the study work. [1]Division of Gastroenterology Hepatology, NUTRIM, Maastricht University Medical Center, Maastricht, The Netherlands, [2]Translational Research Center for Gastrointestinal Disorders, Catholic University Leuven, Belgium. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, (Ciberehd), Instituto de Salud Carlos III, Spain.*

15.50 A randomized, phase I, double blind, crossover study on pharmacokinetics of peppermint oil capsules in healthy volunteers: colon targeted delivery versus enteric coating (p. 95)

Z.Z.R.M.Weerts[1], D. Keszthelyi[1], H.W. Frijlink[2], J.R.B.J. Brouwers[3], L. Vork[1], D.M.A.E. Jonkers[1], A.A.M. Masclee[1], [1]Gastroenterology Hepatology, Maastricht University Medical Center, Maastricht, [2]Dept of Pharmaceutical Technology and Biopharmacy, University of Groningen, [3]Dept of Pharmacotherapy and Pharmaceutical Care, University of Groningen, The Netherlands.

16.00 Effect of running on gastroesophageal reflux and reflux mechanisms (p. 96)

T.V.K. Herregods[1], F.B. van Hoeij[1], J.M. Oors[1], A.J. Bredenoord[1], A.J.P.M. Smout[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

16.10 Effect of Electrical Stimulation Therapy of the lower esophageal sphincter on postprandial reflux mechanisms in GERD patients (p. 97)

N.F. Rinsma[1], B.F. Kessing[3], N.D. Bouvy[2], M.I. van Berge Henegouwen[4], A.J. Smout[3], A.J. Bredenoord3, A.A. Masclee1, J.M. Conchillo1, Depts of 1Gastroenterology and Hepatology and 2General Surgery, Maastricht University Medical Center, Maastricht, Dept of 3Gastroenterology and Hepatology and 4General Surgery, Academic Medical Center, Amsterdam, The Netherlands.

16.20 Decreased esophageal barrier integrity correlates with esophageal eosinophilia and predicts disease activity in adult patients with eosinophilic esophagitis (p. 98)

M.J. Warners[1], A.J.P.M. Smout[1], A.J. Bredenoord[1], [1]Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, the Netherlands

16.30 Mucosal integrity and sensitivity to acid of the proximal esophagus in patients with gastroesophageal reflux disease (p. 99)

F.B. van Hoeij[1,2], P.W. Weijenborg[1,2], M.A. van den Bergh Weerman[3], R.M.J.G.J. van den Wijngaard[2], W.J. de Jonge[2], A.J.P.M. Smout[1] and A.J. Bredenoord[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, [2]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, University of Amsterdam, Amsterdam, [3]Dept of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

16.40 Management of recurrent symptoms after peroral endoscopic myotomy in achalasia (p. 100)

F.B. van Hoeij[1], F.A. Ponds[1], P. Fockens[1], B.A.J. Bastiaansen[1], J.E. Pandolfino[2], J.M. Sternbach[2], T. Rösch[3], A.J.P.M. Smout[1], A.J. Bredenoord[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, [2]Dept of Medicine, Northwestern Memorial Hospital, Northwestern University, Chicago, IL, USA, [3]Dept of Interdisciplinary Endoscopy, University Hospital Hamburg Eppendorf, Hamburg, Germany

16.50 The Secca® procedure in faecal incontinence: a randomized sham controlled clinical trial (p. 101)

A.P. Visscher[1], T.J. Lam[1], M.M. Meurs Szojda[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 sessie

Voor het plenaire programma kunt u zich begeven naar de Brabantzaal

Meet the Expert **Zaal 80**

Meet the expert sessie Cirrose*

Prof. dr. R.A. de Man, MDL-arts, Erasmus MC, Rotterdam
Prof. dr. J.P.H. Drenth, MDL-arts, Radboudumc, Nijmegen

groep 1: 13.00 – 14.00 uur
groep 2: 14.00 – 15.00 uur

* *vanwege de grote belangstelling is deze sessie alleen toegankelijk voor deelnemers die zich hiervoor tevoren hebben ingeschreven*

Meet the Expert **Zaal 81**

Meet the expert sessie Obstructie Management*

Prof. dr. P.D. Siersema, MDL-arts, Radboudumc, Nijmegen
Dr. J.E. van Hooft, MDL-arts, Academisch Medisch Centrum, Amsterdam

groep 1: 13.00 – 14.00 uur
groep 2: 14.00 – 15.00 uur

* *vanwege de grote belangstelling is deze sessie alleen toegankelijk voor deelnemers die zich hiervoor tevoren hebben ingeschreven*

HCV Symposium **Auditorium**

Behandeling Hepatitis C anno 2016

Voorzitter: R.J. de Knegt

09.30 Huidige 'standard of care' behandeling hepatitis C
Prof. dr. J.P.H. Drenth, MDL-arts, Radboudumc, Nijmegen

09.50 Behandeling van hepatitis C bij nierinsufficientie
Dr. K.J. van Erpecum, MDL-arts, UMC Utrecht

10.10 Behandeling van hepatitis C bij gecompenseerde en gedecompenseerde cirrose
Drs. M. van Tilborg, arts-onderzoeker, Erasmus MC, Rotterdam

10.30 Koffiepauze in de expositiehal

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

Onderwerp: **Spoedeisende MDL zorg**
Aanvang 11.00 uur.

I. De gastrointestinale bloeding
II. Acute accidenten en de acute buik
III. Preventie en behandeling van iatrogene complicaties

U vindt het volledige programma van de cursus op bladzijde 8 en 9.

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

Op het cursorisch onderwijs zijn conform de eisen van het Centraal Register Kort Beroepsonderwijs leveringsvoorwaarden van toepassing. Informatie vindt u op de onderwijspagina van www.mdl.nl en www.nvge.nl.

Poster rounds DEGH meeting *(including breakfast buffet)* **Zaal 19**

09.00 – 10.00

Chairs: A.A. te Velde, G. Bouma, R.S. Sverdlov and K.F.J. van de Graaf

1. The impact of liver resection on bile salt and FGF19 dynamics in humans

K.V.K. Koelfat[1], K.M.C. van Mierlo[1], J.G. Bloemen[1], A.K. Groen[2], P.L.M. Jansen[1], C.H.C. Dejong[1], F.G. Schaap[1], S.W.M. Olde Damink[1,3] ,[1]Surgery, Maastricht University Medical Center and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht, [2]Pediatrics, Laboratory of Medicine, University Medical Center Groningen, Groningen, Netherlands, [3]Institute for Liver and Digestive Health, University College London, London, United Kingdom

2. RIG-I inhibits hepatitis E virus replication by simultaneously activating JAK-STAT and NFkB pathways

L. Xu[1], W. Wang[1], X. Zhou[1], Y. Wang[1], Y. Yin[1], L.J.W. van der Laan[2], D. Sprengers[1], H.J. Metselaar[1], M.P. Peppelenbosch[1] and Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Postgraduate School Molecular Medicine, Erasmus MC University Medical Center, Rotterdam; [2]Dept of Surgery, Postgraduate School Molecular Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

3. Cross-presentation of HBV antigens by human dendritic cells to boost T cell responses in chronic HBV infection

Y. Dou[1], N. van Montfoort[1], A. van den Bosch[1], R.S. Hagedoorn[2], M.H. Heemskerk[2], A.J. Gehring[3], A. Bertoletti[4], S.I. Buschow[1] and A.M. Woltman[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, The Netherlands [2]Dept of Hematology, Leiden University Medical Center, Leiden, the Netherlands. [3]Molecular Microbiology & Immunology, Saint Louis University School of Medicine, St. Louis, USA [4]Emerging Infectious Diseases Duke-Nus Graduate Medical School, Singapore

4. The prebiotic inulin in combination with a high cholesterol diet induces liver inflammation in APOE*3-Leiden.CETP mice

L. Hoving[1], S. Katiraei[1], A. Pronk[1], M. Giera[3], V. van Harmelen[1], and K. Willems van Dijk[1,2], [1]Dept. of Human Genetics and Einthoven Laboratory for Experimental Vascular Medicine, [2]Dept. of Medicine, division Endocrinology, [3]Center of Proteomics and Metabolomics, Leiden University Medical Center, Leiden, The Netherlands.

5. Interferon regulatory factor 1 restricts hepatitis E virus replication by activating stat1 to induce antiviral interferon stimulated genes

L. Xu[1], X. Zhou[1], W. Wang[1], Y. Wang[1], Y. Yin[1], L.J.W. van der Laan[2], D. Sprengers[1], H.J. Mason[1], M.P. Peppelenbosch[1] and Q. Pan[1], [1]Dept of Gastroenterology and Hepatology, Postgraduate School Molecular Medicine, Erasmus MC University Medical Center, Rotterdam, [2]Dept of Surgery, Postgraduate School Molecular Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

6. Effects of healthy- and acute liver failure plasma on ifferentiated human heparg progenitor cells in monolayers and bioartificial

M. van Wenum[*1, 2], *R. Chamuleau*[2], *A. Jongejan*[3], *P. Treskes*[4], *S. Meisner*[2], *E. Hendriks*[1], *T. van Gulik*[1], *P. Moerland*[3], *R. Hoekstra*[1,2], [1]*Experimental Surgery,* [2]*Tytgat Institute for Liver and Intestinal Research,* [3]*Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands,* [4]*Hepatology Laboratory, University of Edinburgh, Chancellor's Building, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom*

7. Long term in vitro and in vivo replication of feces-derived genotype 3 hepatitis E virus without potent intracellular innate immune responses

M.D.B. van de Garde[1], *S.D. Pas*[2], *B.L. Haagmans*[2], *G. van der Net*[2], *R. de Man*[1], *A.D.M.E. Osterhaus*[2], *L. Gama*[3], *A. Boonstra*[1], *T. Vanwolleghem*[1,4], [1]*Dept of Gastroenterology and Hepatology,* [2]*Dept of Viroscience, Erasmus University Medical Center, Rotterdam, The Netherlands.* [3]*Dept of Molecular and Comparative Pathobiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.* [4]*Dept of Gastroenterology and Hepatology University Hospital Antwerp, Belgium*

8. New approaches to strengthen colonic anastomoses using butyrate; are intraluminal butyrine-eluting patches the answer?

J.W.A.M. Bosmans[1,2], *A.C.H.M. Jongen*[1,2], *B.T.C. Boonen*[1], *S. van Rijn*[1,2], *F. Scognamiglio*[3], *M.J.J. Gijbels*[4], *N.D. Bouvy*[1,2], [1]*Dept of Surgery, Maastricht University Medical Center, Maastricht,* [2]*NUTRIM School for Nutrition and Translation Research in Metabolism, Maastricht University, Maastricht,* [3]*Dept of Nanotechnology, University of Trieste, Italy.* [4]*Dept of Pathology, Maastricht University Medical Center, Maastricht, the Netherlands*

9. Profiling immunosuppressant mycophenolic acid identified as a potent inhibitor against norovirus replication

W. Dang, Y. Yin, Y. Wang, L. Xu, M.P. Peppelenbosch and Q. Pan, Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam

10. Unphosphorylated ISGF3 drives the basal transcription of interferon-stimulated genes to defend HCV and HEV infections

W. Wang, Y. Yin, L. Xu, Y. Wang, X. Zhou, D. Sprengers, H.J. Metselaar, M.P. Peppelenbosch and Q. Pan, Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

10.00 – 11.00

Chairs: A.A. te Velde, G. Bouma, R.S. Sverdlov and K.F.J. van de Graaf

1. Complement activation in patients with chemotherapy-associated steatohepatitis

J. Zhao[1], S.S. Rensen[1], C.P.H. Vreuls[2], C.H.C. Dejong[1,3], S.W. Olde Damink[1,4], [1]Dept of Surgery, Maastricht University Medical Centre, and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, [2]Dept of Pathology, Maastricht University Medical Centre, Maastricht University, [3]Grow School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands, [4]Institute for Liver and Digestive Health, University College London, London, United Kingdom

2. Sequence analysis for resistance monitoring following a single dose of RG-101, an anti-mir targeting microRNA-122, in chronic hepatitis C patients

M.H. van der Ree[1, 2], F. Stelma[1, 2], J.M.L. de Vree[3], S.B. Willemse[1], M. van der Valk[1,4], A.C. van Nuenen[2], A. Patick[5], P. Grint[5], S. Neben[5], A. Pavlicek[5], E. van der Veer[6], N.A. Kootstra[2], H.W. Reesink[1,2], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands, [3]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands, [4]Dept of Infectious Diseases, Academic Medical Center, Amsterdam, The Netherlands, [5]Regulus Therapeutics, San Diego, United States, [6]DDL Diagnostics Laboratories, Rijswijk, The Netherlands

3. In situ hypothermic perfusion with retrograde outflow during right hepatectomy, a randomized controlled trial

P.B. Olthof[1], M.J. Reiniers[1], R.F. van Golen[1], M. Heger[1], B. Mearadji[2], R. Bennink[3], J. Verheij[4], T.M. van Gulik[1], [1]Dept of Experimental Surgery, [2]Dept of Radiology, [3]Dept of Nuclear Medicine, [4]Dept of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

4. Pancreatic cell-derived factors induce NF-κB activation and activate the ubiquitin-proteasome system in skeletal muscle cells

D.P.J. van Dijk[1], R.D.W. Vaes[1], S.W.M. Olde Damink[1], C.H.C. Dejong[1], A.M.W.J. Schols[2], S.S. Rensen[1], R.C. Langen[2], [1]Dept of Surgery, Maastricht University Medical Centre, and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, [2]Dept of Pulmonology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands

5. Human liver CD8+ T cells have a tissue resident phenotype and differ from blood CD8+ T cells

F. Stelma[1,2], A. de Niet[1,2], M.J. Sinnige[2], K.A. van Dort[2], E.M.M. van Leeuwen[2], N.A. Kootstra[2], H.W. Reesink[1,2], [1]Dept of Gastroenterology and Hepatology, [2]Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands

6. NK cells from chronic HBV patients in different clinical phase exhibit altered gene expression profiles by RNA-Seq

J.Hou, R.A. de Groen, T. Vanwolleghem, G. van Oord, Z.M.A. Groothuismink, R. de Knegt, P.A. Boonstra, Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, The Netherlands

7. Caution should be taken when selecting glycerol as plasticizer in biomaterials designed for intra-abdominal use

J.W.A.M. Bosmans MD[1,2], A.C.H.M. Jongen[1,2], R.D.W. Vaes[1,2], F. Scognamiglio[3], M. Borgogna[3], A. Travan[3], M.J.J. Gijbels PhD[4], N. Hoebers[5], J.W. Jocken[5], N.D. Bouvy MD, PhD[1,2], [1]Dept of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands, [2]NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands, [3]Dept of Life Sciences, University of Trieste, Italy, [4]Dept of Pathology, Maastricht University Medical Center Maastricht, The Netherlands

8. Treatment with anti-miRNA122 RG-101 results in decreased IP-10 in patients with chronic hepatitis C

F. Stelma[1,2], M.H. van der Ree[1,2], M.J. Sinnige[2], J.M.L. de Vree[3], S.B. Willemse[1,2], A. van Vliet[4], J.U. de Haes[4], P. Grint[5], S. Neben[5], N.A. Kootstra[2], H.W. Reesink[1,2], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of and Experimental Immunology Academic Medical Center, Amsterdam, [3]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, [4]PRA Healthsciences, Zuidlaren, The Netherlands, [5]Regulus Therapeutics, San Diego, CA, USA

9. Extrahepatic cholestasis induces large scale alterations in the human liver transcriptome

F.G. Schaap[1], Z. Soons[1], L. Fischer[1], M.J. Jetten[2], D. Jennen[2], J.C. Kleinjans[2], P.L. Jansen[1], S.W. Olde Damink[1], [1]Dept of Surgery, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, [2]Dept of Toxicogenomics, Maastricht University, Maastricht, The Netherlands

10. Similar frequencies, phenotype and activation status of intrahepatic NK cells in chronic HBV patients after long-term treatment with tenofovir disoproxil fumarate (TDF)

L.L. Boeijen[1], M. van Campenhout[1], E.T.T.L. Tjwa[1], R. Zoutendijk[1], G.W. van Oord[1], R.J. de Knegt[1], H.L.A. Janssen[2], A.M. Woltman[1], A. Boonstra[1], [1]Dept. of Gastroenterology and Hepatology, Erasmus Medical Centre University Hospital, Rotterdam, The Netherlands, [2]Liver Clinic, Toronto Western & General Hospital, University Health Network, Toronto, Ontario, Canada

11. Development of a novel in vitro contractile smooth muscle system

R.D.W. Vaes[1], S.W.M. Olde Damink[1], S.S. Rensen[1], [1]Dept of General Surgery, Maastricht University Medical Centre and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands

DEGH oral presentations **Baroniezaal**

Voorzitters: D. Keszthelyi en R.P.J. Oude Elferink

11.30 Pain
Dr. D. Keszthelyi, MDL-arts i.o., Maastricht Universitair Medisch Centrum

11.55 The continuing mystery of cholestatic itch
Prof. dr. R.P.J. Oude Elferink, biochemicus, Academisch Medisch Centrum, Amsterdam

12.20 Battle beste Lever en Darmpublicatie van de NVH en SEG.
Tijdens de 'Battle' worden de winnaars van de Young Hepatologist Award van de NVH en Basale Junior Onderzoekers Prijs van de SEG gekozen uit twee maal drie presentaties van de genomineerden van 5 minuten.

13.00 Lunch in expositiehal

DEGH oral presentations **Baroniezaal**

Voorzitters: G. Bouma en M. van Engeland

14.00 New molecular insights in CRC and applicatition in clinical practice
Prof. dr. M. van Engeland, Professor Pathobiology of cancer, MUMC Maastricht

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

14.25 HOX gene expression in Barrett's esophagus resembles that of the colon, can be modulated by acid and bile exposure, and induces Barrett's specific gene products (p. 102)
V.T. Janmaat, A.P. Verhaar, M.J. Bruno, M.P. Peppelenbosch, M.C.W. Spaander, Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

14.37 HOXA9 is overexpressed in colonic adenomas and causes an increase in cell growth (p. 103)
P.H.A. Wisse, V.T. Janmaat, A.P. Verhaar, M.J. Bruno, M.C.W. Spaander, M.P. Peppelenbosch, Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

14.49 Endoglin expression on cancer-associated fibroblasts plays an important role in cancer progression and metastasis (p. 104)

M.J.A. Schoonderwoerd[1#], M. Paauwe[1#], A. Groenewoud[4], G.W. van Pelt[3], E.S.M. de Jonge-Muller[1], J.C.H. Hardwick[1], H.W. Verspaget[1], C.F.M.[3], B.E. Snaar-Jagalskar[4], P. ten Dijke[2], L.J.A.C. Hawinkels[1], Leiden University Medical Center, Dept. of [1]Gastroenterology- Hepatology, [2]Molecular Cell Biology, [3]Surgery; Leiden University [4]Cell Observatory Leiden, the Netherlands, [#] equal contribution

15.01 Grp78 heterozygosity in the intestinal epithelium protects against adenoma formation (p. 105)

J.F. van Lidth de Jeude[1], C.N. Spaan[1], B.J. Meijer[1], M.C.B. Wielenga[1], T. Soeratram[1], V. Muncan[1], G.R. van den Brink[1], J. Heijmans[1,2], [1]Tytgat institute for Liver and Intestinal Research and Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands

15.13 Loss of the Bone Morphogenetic Protein pathway in mesenchymal myofibroblasts initiates polyp formation in the mouse intestine (p. 106)

L.R.A. van der Burg1, P.W. Voorneveld1, C. Steenkamp1, J.A.D.E. Erinkveld1, E.S.M. de Jonge-Muller1, G.J. Offerhaus2, L.J.A.C. Hawinkels1, J.C.H. Hardwick1, 1Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, 2Dept of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

15.25 Einde programma

Symposium Sectie Gastrointestinale Endoscopie **Parkzaal**

Endoscopieregistraties: zegening of noodzakelijk kwaad?

Voorzitters: J.J.G.H.M. Bergman en M.A.J.M. Jacobs

09.30 De ERCP registratie; Een kwaliteit verhogend instrument
Dr. A.D. Koch, MDL-arts, Erasmus MC, Rotterdam

09.50 DRCE: Complicatieregistratie nieuwe stijl
Dr. W.R. ten Hove, MDL-arts, Alrijne Ziekenhuis, Leiden

10.10 Dutch Gastrointestinal Endoscopy Audit (DGEA)
Dr. M. Ledeboer, MDL-arts, Deventer Ziekenhuis

10.30 Koffiepauze expositie

Vrije voordrachten Sectie Gastrointestinale Endoscopie **Parkzaal**

Voorzitters: Y.C.A. Keulemans en T. Römkens

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

11.00 Long-term follow-up results of stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia (p. 107)
K. Belghazi[1], F.G.I. van Vilsteren[1], B.L.A.M. Weusten[2], S.L. Meijer[3], J.J.G.H.M. Bergman[1], R.E. Pouw[1], [1]Gastroenterology, Academic Medical Center, Amsterdam, [2]Gastroenterology, St Antonius Hospital, Nieuwegein, [3]Pathology, Academic Medical Center, Amsterdam, The Netherlands

11.10 Reducing patient's burden. A minimalistic approach to radiofrequency ablation in Barrett's epithelium achieving complete eradication (p. 108)
A.W. Gotink[1], P. Didden[1], M.J. Bruno[1], A.D. Koch[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam

11.20 Improved prediction of neoplastic progression in patients with Barrett's esophagus using specific histological criteria for low grade dysplasia (p. 109)
F.J.C. Ten Kate[1], D. Nieboer[4], S. van Olphen*[1,2], F.J.W. Ten Kate[3], M. Doukas[1], M.J. Bruno[2], M.C.W. Spaander[2], L.H.J. Looijenga[1], K. Biermann[1], [1]Dept of Pathology, Erasmus University Medical Center, Rotterdam, [2]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [3]Dept of Pathology, University Medical Center Utrecht, Utrecht, [4]Dept of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands *contributed equally to the work*

11.30 Stepwise development of a volumetric laser endomicroscopy prediction score and computer algorithm to detect Barrett's neoplasia using matched VLE-histology images of endoscopic resection specimens (p. 110)

A. Swager[1], F. van der Sommen[2], M.G.H. van Oijen[3], G.J. Tearney[4], C.L. Leggett[5], S. Zinger[2], S.L. Meijer[6], E.J. Schoon[7], P.H.N. de With[2], W.L. Curvers[7], J.J.G.H.M. Bergman[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands, [2]Dept of Electrical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands, [3]Dept of Medical Oncology, Academic Medical Center, Amsterdam, The Netherlands, [4]Dept of Pathology and Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA USA [5]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN USA, [6]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands, [7]Dept of Gastroenterology and Hepatology Catharina Hospital, Eindhoven, The Netherlands

11.40 Efficacy and safety of the CryoBalloon Focal Ablation System for the eradication of dysplastic Barrett's oesophagus islands (p. 111)

H.T. Künzli[1,2], D.W. Schölvinck[1,2], S.L. Meijer[2], C.A. Seldenrijk[1], J.J.G.H.M. Bergman[2], B.L.A.M. Weusten[1,2], [1]Sint Antonius Hospital, Nieuwegein, [2]Academic Medical Centre, Amsterdam

11.50 What should be the target diameter of endoscopic dilation of benign esophageal anastomotic strictures? (p. 112)

E.E. van Halsema, I.C. Noordzij, P. Fockens, J.J. Bergman, J.E. van Hooft, Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands

12.00 Early experience of Duodenal Mucosal Resurfacing treatment for Type 2 Diabetes when expanding from single to multiple sites (p. 113)

A.C.G. van Baar[1], J. Devière[2], G. Costamagna[3], M.P. Galvão Neto[4], L. Rodriguez[5], R.J. Haidry[6], J.J.G.H.M. Bergman[1]. On behalf of Revita-1 Investigators, [1]Dept of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands, [2]Dept of Gastroenterology, Erasme University Hospital, Brussels, Belgium, [3]Dept of Digestive Endoscopy, Policlinico Gemelli, Catholic University of Rome, Rome, Italy, [4]Dept of Surgery, Gastro Obeso Center, São Paulo, Brasil, [5]Dept of Surgery, Clinical Center for Diabetes, Obesity and Reflux, Santiago, Chile, [6]Dept of Gastroenterology, University College Hospital, London, United Kingdom

12.10 Cap-assisted endoscopy for a complete visualization of the ampulla of Vater and duodenal surveillance in patients with familial adenomatous polyposis (p. 114)

F.G.J. Kallenberg[1], B.A. Bastiaansen[1], E. Dekker[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, The Netherlands

12.20 Molecular-guided fluorescence endoscopy for colorectal polyp identification: a dose-escalation study with bevacizumab-800CW (p. 115)

J.J.J. Tjalma[1], E. Hartmans[1], P.B. Garcia Allende[2], M.D. Linssen[1], M. Koller[1], A. Jorritsma-Smit1, M.C. e Silva de Oliveira Nery[1], A. Karrenbeld[1], J.H. Kleibeuker[1], G.M. van Dam[1], D. Robinson[3], V. Ntziachristos[2], W.B. Nagengast[1], [1]University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [2]Technical University of Munich and Helmholtz Center Munich, Munich, Germany; [3]Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Vrije voordrachten Sectie Gastrointestinale Endoscopie **Parkzaal**

12.30 Comparison of colonoscopy, sigmoidoscopy and multiple rounds of FIT-based colorectal cancer screening: long-term follow-up (p. 116)

E.J. Grobbee[1], M. van der Vlugt[2]*, A.J. van Vuuren[1], A.K. Stroobants[3], R.C. Mallant-Hent[4], I. Lansdorp-Vogelaar[5], P.M.M. Bossuyt[6], E.J. Kuipers[1], E. Dekker[2], M.C.W. Spaander[1], [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Centre, Rotterdam, [2]Dept of Gastroenterology and Hepatology, Academic Medical Centre Amsterdam, Amsterdam, [3]Clinical Chemistry, Academic Medical Center Amsterdam, Amsterdam, [4]Gastroenterology and Hepatology, Flevoziekenhuis, Amsterdam, [5]Dept of Public Health, Erasmus University Medical Centre, Rotterdam, [6]Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, The Netherlands, * both authors contributed equally*

12.40 The extent of unnecessary surgery for benign rectal polyps in the Netherlands (p. 117)

L. van Nimwegen[1], L.M.G. Moons[2], J.M.J. Geesing[3], L. Arensman[4], M.M. Lacle[5], I.A.M.J. Broeders[6], P.P. Viergever[7], J.N. Groen[8], K. Kessels[9], M.P. Schwartz[1], [1]Dept of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, [2]Dept of Gastroenterology and Hepatology, University Medical Center, Utrecht, [3]Dept of Gastroenterology and Hepatology, Diakonessenhuis, Utrecht, [4]Dept of Pathology, Meander Medical Center, Amersfoort, [5]Dept of Pathology, University Medical Center, Utrecht, [6]Dept of Surgery, Meander Medical Center, Amersfoort, [7]Dept of Gastroenterology and Hepatology, MCA Gemini Group, Den Helder/Alkmaar, [8]Dept of Gastroenterology and Hepatology, St. Jansdal, Harderwijk, [9]Dept of Gastroenterology and Hepatology, Flevoziekenhuis, Almere, The Netherlands

12.50 Endoscopic full-thickness resection of colorectal neoplasias: Report on the first Dutch experience (p. 118)

J. Strebus[1], L. Hageman[1], B.W. van der Spek[1], G.D.N. Heine[1], M.E. Haverkort[2], [1]Gastroenterology & Hepatology, Noordwest Ziekenhuisgroep, Medisch Centrum Alkmaar, [2]Internal Medicine and Infectious Diseases, Medisch Centrum Haaglanden

13.00 Lunch in expositiehal

Vrije voordrachten Sectie Gastrointestinale Oncologie **Parkzaal**

Voorzitters: J.M. van Dieren en G.A. Schouten

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

14.00 Sytematic review on the Treatment of Isolated Local Recurrence of Pancreatic Cancer after Initial Curative Resection; Re-resection, Chemoradiotherapy and Stereotactic Body Radiation Therapy (p. 119)

V.P. Groot[1], H.C. van Santvoort[2], S.J.E. Rombouts[1], J. Hagendoorn[1], I.H. Borel Rinkes[1], M.G. Besselink[2], M. van Vulpen[3], I.Q. Molenaar[1], [1]Dept. of Surgical Specialities, UMC Utrecht Cancer Center, [2]Dept. of Surgery, Academic Medical Center Amsterdam, [3]Dept. of Radiation Oncology, University Medical Center Utrecht, The Netherlands

14.10 Locally advanced colon cancer; evaluation of current clinical practice and treatment outcome at a population level (p. 120)

C.E.L. Klaver[a], L. Gietelink[b,e], W.A. Bemelman[a] , M.W.J.M. Wouters[c,e], T. Wiggers[d], R.A.E.M. Tollenaar[b,e], P.J. Tanis[a]; on behalf of the Dutch Surgical Colorectal Audit Group, [a]Dept of surgery, Academic Medical Centre, University of Amsterdam, Amsterdam, [b]Dept of surgery, Leiden University Medical Centre, Leiden, [c]Dept of Surgical Oncology, the Netherlands Cancer Institute / Antoni van Leeuwenhoek hospital, Amsterdam, [d]Dept of Surgical Oncology, University Medical Center Groningen, Groningen, [e]Dutch Institute for Clinical Auditing, Leiden, The Netherlands

14.20 Short-course radiotherapy and chemoradiation have similar effects on quality of life in routinely treated rectal cancer patients during the first year (p. 121)

J.P.M. Burbach[1], A.M. Couwenberg[1], M. Intven[1], W.M.U. van Grevenstein[2], E.C.J. Consten[3], I.H.M. Borel Rinkes[2], M. van Vulpen[1], H.M. Verkooijen[4], [1]Dept of Radiation Oncology, UMC Utrecht, Utrecht, [2]Dept of Surgery, UMC Utrecht, Utrecht, [3]Dept of Surgery, Meander Medical Center, Amersfoort, [4]Clinical Epidemiology, Imaging Division, UMC Utrecht, Utrecht, The Netherlands

14.30 Endoscopic surveillance in individuals at risk for familial diffuse gastric cancer (p. 122)

R.S. van der Post[1], J. van Dieren[2], A. Grelack[3], N. Hoogerbrugge[4], J.H. van Krieken[1], L.E. van der Kolk[5], T.M. Bisseling[3], A. Cats[2], [1]Dept of Pathology, Radboud university medical center, Nijmegen, [2]Dept of Gastroenterology, Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam, [3]Dept of Gastroenterology, Radboud university medical center, Nijmegen, [4]Dept of Human Genetics, Radboud university medical center, Nijmegen, [5]Dept of Clinical Genetics, Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

14.40 Is distinction of risk groups based on family history in the screening in familial colorectal carcinoma necessary? (p. 123)

C.B. Langenhof[1,2], Y.J. van Herwaarden[1], C.M. Kets[3], L.A. Kiemeney[4], M.C.A. van Kouwen[1], T.M. Bisseling[1] , B.W.M. Spanier[2], [1]Dept. of Gastroenterology and Hepatology, Radboud University Medical Center Nijmegen, [2]Dept. of Gastroenterology and Hepatology, Rijnstate, Arnhem, [3]Dept. of Human Genetics, Radboud University Medical Center, Nijmegen, [4]Radboud university medical center, Radboud Institute for Health Sciences

14.50 Blockade of multiple co-inhibitory pathways can re-vitalize tumor-specific responsiveness of intra-tumoral T cells in liver cancer (p. 124)

G. Zhou[1], D. Sprengers[1], P.P.C. Boor[1], A. Pedroza-Gonzalez[1,4], H. Schutz[1], M. Doukas[3], W.G. Polak[2], D. Grunhagen[2], J. de Jonge[2], T.C. Khe Tran[2], T. Terkivatan[2], C. Verhoef[2], J.N.M. IJzermans[2], M. Bruno[1], J. Kwekkeboom[1], Depts of [1]Gastroenterology and Hepatology, [2]Surgery and [3]Pathology, Erasmus MC University Medical Center, Rotterdam, The Netherlands. [4]Laboratory of Immunology Research, FES-Iztacala, UNAM, Mexico

15.00 Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent (p. 125)

K. Parry[1†], E. Visser[1†], P.S.N. van Rossum[1,2], N. Haj Mohammad[3], J.P. Ruurda, R. van Hillegersberg[1], [1]Dept of Surgery, University Medical Center Utrecht, [2]Dept of Radiotherapy, University Medical Center Utrecht, [3]Dept of Medical Oncology, University Medical Center Utrecht, The Netherlands, [†] These authors share first authorship

Vrije voordrachten Sectie Gastrointestinale Oncologie **Parkzaal**

15.10 Palliative chemotherapy and targeted therapies for esophageal and gastro-esophageal junction cancer (p. 126)

V.T. Janmaat[1], E.W. Steyerberg[2], A. van der Gaast[3], R.H.J. Matthijssen[3], M.J. Bruno[1], M.P. Peppelenbosch[1], E.J. Kuipers[1], M.C.W. Spaander[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 Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands

15.20 Cost-effectiveness of Cetuximab for advanced esophageal squamous cell carcinoma (p. 127)

V.T. Janmaat[1], M.J. Bruno[1], S. Polinder[2], S. Lorenzen[3], F. Lordick[4], M.P. Peppelenbosch[1], M.C.W. Spaander[1], [1]Dept of Gastroenterology and Hepatology, [2]Dept of Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands, [3]Third Dept of Internal Medicine (Hematology/Medical Oncology), Technical University of Munich, Munich, Germany, [4]University Cancer Center Leipzig (UCCL), University Medicine Leipzig, Germany

15.30 Theepauze

Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie **Zaal 80**

Voorzitters: A.M.J. Langers en W.H. de Vos tot Nederveen Cappel

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

09.30 Predictors and trends in fecal hemoglobin concentration: long term follow-up of population-based FIT-screenees (p. 128)

E.J. Grobbee[1], E.H. Schreuders, B.E. Hansen, M.J. Bruno[1], I. Lansdorp-Vogelaar[2], M.C.W. Spaander[1], E.J. Kuipers[1], [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, [2] Dept of Public Health, Erasmus MC University Medical Centre, Rotterdam, The Netherlands

09.40 Detection of advanced colorectal lesions in asymptomatic individuals; comparison of FIT, clinical risk factors and stool DNA (p. 129)

J.E.G. IJspeert[1], L.J.W. Bosch[2], P.M.M. Bossuyt[3], V.H.M. Coupé[4], M. van Engeland[5], B. Carvalho[2], E.J. Kuipers[6], G.A. Meijer[2], E. Dekker[1], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, [2]Dept of Pathology, Netherlands Cancer Institute, Amsterdam, [3]Dept of Biostatistics and Epidemiology, Academic Medical Center, Amsterdam, [4]Dept of Biostatistics and Epidemiology, VU University Medical Center, Amsterdam, [5]Dept of Pathology, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, [6]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

09.50 Incidence and endoscopic appearance of colorectal neuroendocrine tumors: a population-based study (p. 130)

A. Reumkens[1,2,3], C.M.C. le Clercq[1,3,4], C.M. Bakker[3], B. Winkens[5,6], H.I. Grabsch[7], E.T. Keulen[3], A.A.M. Masclee[1,2], S. Sanduleanu[1,4], [1]Division of Gastroenterology and Hepatology, Dept of Internal Medicine, Maastricht University Medical Center, Maastricht, [2]NUTRIM, School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, Maastricht, [3]Dept of Internal Medicine and Gastroenterology, Zuyderland Medical Center, Sittard-Heerlen, [4]GROW, School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, [5]Dept of Methodology and Statistics, Maastricht University Medical Center, Maastricht, [6]CAPHRI, School for Public Health and Primary Care, Maastricht University Medical Center, Maastricht, [7]Dept of Pathology, Maastricht University Medical Center, Maastricht, The Netherlands

10.00 CT-colonography versus colonoscopy for detection of high-risk sessile serrated polyps (p. 131)

J.E.G. IJspeert[1], C.J. Tutein Nolthenius[2], E.J. Kuipers[3], M.E. van Leerdam[4], C.Y. Nio[2], M.G.J. Thomeer[5], K. Biermann[6], M.J. van de Vijver[7], E. Dekker[1], J. Stoker[2], [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, [2]Dept of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, [3]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, [4]Dept of Gastroenterology and Hepatology, Netherlands Cancer Institute, Amsterdam, [5]Dept of Radiology, Erasmus University Medical Center, Rotterdam, [6]Dept of Pathology, Erasmus University Medical Center, Rotterdam, [7]Dept of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie **Zaal 80**

10.10 RNF43 in serrated polyposis and serrated polyps (p. 132)
L.M. Koggel[1], Y.J. van Herwaarden[1], Ing. J. Salomon[1], E. Vink-Börger[2], J. Dijkstra[2], Dr. P. Dura[1], Dr. F.M. Nagengast[1], Dr. T.M. Bisseling[1], Prof. Dr. I.D. Nagtegaal[2], [1]Dept of Gastroenterology and Hepatology, Radboud university medical center, [2]Dept of Pathology, Radboud university medical center

10.20 The prevalence of APC and biallelic MUTYH mutations based on phenotype (p. 133)
S.S. Badal, S.W. ten Broeke, T. van Wezel, H. Morreau, M. Nieuwenhuis, F.J. Hes, H.F. Vasen, C.M. Tops, M. Nielsen, Dept of clinical genetics: S.S. Badal, S.W. ten Broeke, F.J. Hes, C.M. Tops, M. Nielsen, Dept of pathology, T.van Wezel, H. Morreau, Dept of gastroenterology and STOET: H.F. Vasen, Departement of STOET: M. Nieuwenhuis

10.30 Koffiepauze expositie

Symposium NESPEN **Zaal 80**

Voorzitters: C.F. Jonkers en G. Wanten

11.00 Eiwit- en energiebehoefte van zieke mensen
Dr. ir. P.J.M. Weijs, Lector Gewichtsmanagement, Hogeschool van Amsterdam en VU medisch centrum, Amsterdam

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

11.50 Diarrhea is a risk factor for liver injury and may lead to Intestinal Failure Associated Liver Disease in critical illness (p. 134)
N.R.C. Lefel[1], F.G. Schaap[2], D.C.J.J. Bergmans[1], S.W.M. Olde Damink[2], M.C.G. van de Poll[1,2], [1]Department of Intensive Care Medicine, Maastricht University Medical Center (MUMC+), [2]Department of General Surgery, MUMC+ and Nutrition and Toxicology Research Institute Maastricht (NUTRIM), Maastricht University

12.00 The effects of two weeks synbiotic supplementation on intestinal permeability: a randomized controlled trial (p. 135)
E. Wilms[1], F.J. Troost[1], A.A.M. Masclee[1], [1]NUTRIM School of Nutrition and Translational Research in Metabolism; Department of Internal Medicine, division of Gastroenterology-Hepatology, Maastricht University Medical Center+, Maastricht, The Netherlands

12.10 Voedingsinname, voedingstoestand en welbevinden bij 2 maaltijdconcepten
D. Dijkshoorn, arts-onderzoeker, Radboudumc, Nijmegen

12.20 Ondervoeding bij thuiswonende ouderen: onderliggende factoren en aanpak
R. van der Pols-Vijlbrief, diëtist onderzoeker VU Amsterdam

12.30 Nutrition and Pancreatic Surgery
Dr. A. Gerritsen, arts-onderzoeker, Academisch Medisch Centrum, Amsterdam

12.40 Sarcopenia: inventarisatie van kennis en Praktijk bij zorgverleners
E. Reijnierse, PhD student, VU medisch centrum, Amsterdam

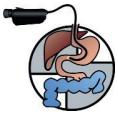
12.50 Uitreiking NESPEN abstractprijs en NESPEN proefschriftprijs

13.00 Einde symposium, lunch in de expositiehal

Vrijdag 18 maart 2016

Programma V&VN MDL **Brabantzaal**

v&vn
Beroepsvereniging van zorgprofessionals
Maag Darm Lever



Voorzitter: M. van Hout en E. Sprong

10.00	Opening
10.05	De spoedeisende slokdarm *Dr. L.M. Kager, MDL-arts, Noordwest Ziekenhuisgroep, Alkmaar*
10.30	Zelfdilatatie *Dr J.J.G.H.M. Bergman, MDL-arts, Amsterdam Medisch Centrum*
11.00	Koffiepauze
11.30	LEAN werken op de endoscopieafdeling *Y.J.M. Schaap en R. Tuinman, verpleegkundigen, Noordwest Ziekenhuisgroep*
12.00	'Er wordt te weinig naar de anus gekeken', met aansluitend een quiz *Dr. H.P.M. Festen, MDL-arts, Jeroen Bosch Ziekenhuis, Den Bosch*
13.00	Lunch in expositiehal

Middagprogramma Endoscopieverpleegkundigen **Brabantzaal**

Voorzitter: M. van Hout en E. Sprong

14.00	Voeden voorbij de maag: het hoe en waarom *Dr. A. Gerritsen, ANIOS chirurgie Gelre Ziekenhuis Apeldoorn*
14.30	Dilatatie bij stembandlozen *F. Stam, verpleegkundige, VU medisch centrum, Amsterdam*

Middagprogramma V&VN MDL **Brabantzaal**

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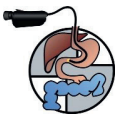
Beroepsvereniging van zorgprofessionals
Maag Darm Lever



15.00 Klachten en lokale afwijkingen van de insteekopening bij een PEG katheter;
micro organismen spelen geen rol
A. de Ruiter, verpleegkundig specialist MDL, Medisch Centrum Leeuwarden

15.30 Afsluiting

ABSTRACTS

Improved anastomotic leakage rates in patients following Ivor-Lewis esophagectomy with omental wrap and pleural flap

A.E. Slaman, J.A.H. Gooszen, M.I. van Berge Henegouwen, S.S. Gisbertz, Academisch Medisch Centrum, Amsterdam

Anastomotic leakage following esophagectomy is a major complication with serious consequences for patients. To prevent anastomotic leakage several techniques can be applied. In Ivor-Lewis esophagectomy the gastric tube is shorter and may be better vascularized than in McKeown esophagectomy. In addition, the anastomosis can be wrapped in omentum and concealed under a pleural flap. This study investigates which technique shows best results concerning the anastomosis following esophagectomy.All consecutive patients following esophagectomy were selected from a prospective database from February 2013 (first Ivor-Lewis esophagectomy) to December 2015 in a tertiary referral hospital. Patients were divided in 3 cohorts: McKeown esophagectomy (McKeown; complete time period), Ivor-Lewis esophagectomy without omental plasty and pleural flap (Ivor-Lewis; February 2013 to January 2014) and Ivor-Lewis esophagectomy with omental plasty and pleural flap (Flap&Wrap; January 2014 to December 2015). Anastomotic leakage, reoperation and mortality rates were compared between groups. Anastomotic leakage was diagnosed if proven by radiographic examination, if patients showed clinical manifestations (e.g. increased inflammation parameters, pulmonary insufficiency), and treatment was required.183 patients were included (71 McKeown, 37 Ivor-Lewis, 75 Flap&Wrap). The incidence of anastomotic leakage was 39.4% for McKeown, 32.4% for Ivor-Lewis and 5.3% for Flap&Wrap ($p<0.001$). Reoperation rates were 5.6%, 21.6% and 0%, respectively ($p<0.001$). The combined in-hospital and 30-day mortality rates were 4.2%, 2.7% and 0%, respectively ($p=0.212$).
Conclusion: The incidence of anastomotic leakage is significantly lower following Ivor-Lewis esophagectomy with omental wrap and pleuraplasty compared to Ivor-Lewis esophagectomy without anastomotic covering and also compared to McKeown esophagectomy.

CD44 and its splice variant CD44v6 as Potential Imaging and Treatment Targets for Colorectal Adenomas

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Colorectal cancer (CRC) is the third leading cause of cancer-related deaths worldwide. Early lesion detection, which is the most effective method for preventing CRC development, remains challenging. By fluorescently 'highlighting' specific molecular properties and enhancing optical discrimination, endoscopic molecular imaging has great potential for improving diagnostics. In addition to diagnostic purposes, molecular-targeted strategies can also be applied for personalizing treatment options, especially when considering high-risk patient populations. Though, in order to implement these molecular-targeted techniques effectively, target proteins that distinguish adenomas from normal tissue must be identified first.To identify adenoma-discriminating target proteins, we used the recently introduced Functional Genomic mRNA (FGM) profiling method. This method is able to identify functional genomic mRNA (FGmRNA) overexpressing genes in colorectal adenomas (n=47), compared to normal colon tissue (n=26). We validated the protein overexpression of the top identified genes via immunehistochemistry (IHC) in sporadic adenomas. Subsequently, we selected the most attractive target protein, namely CD44, and validated its expression in Lynch lesions. Finally, to evaluate the effect on adenoma formation, we treated $Apc^{Min/+}$ mice with a receptor-targeting peptide against the v6-splice variant protein of the CD44 gene. As a results, we identified 4,524 genes that show overexpression of FGmRNA in adenomas compared to normal tissue. We validated the protein expression of the top identified genes, AXIN2, KIAA1199, CD44, and JUN, showing clear protein overexpression in sporadic colorectal adenoma samples. Based on its protein cell surface localization and the level of overexpression, we identified CD44 as an attractive target protein in both sporadic and Lynch adenomas. In addition, treatment with a CD44v6 receptor-targeting peptide significantly reduced adenoma formation in an in vivo human colorectal adenoma model. In conclusion, we identified CD44 as an attractive target protein in both sporadic and high-risk Lynch adenomas. In addition, our results demonstrate the applicability of a small peptide drug, targeting its splice variant CD44v6, for molecular-targeted adenoma treatment strategies.

Bacterial contamination of reprocessed ERCP duodenoscopes in The Netherlands is widespread.

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Recent publications have reported multiple outbreaks involving multi-drug resistant microorganisms caused by contaminated Endoscopic Retrograde Cholangio-pancreatography (ERCP) endoscopes. Persistent contamination is attributed to the complex design of ERCP endoscopes (duodenoscopes) or breaches in the reprocessing process. In our centre an outbreak occurred in which the source was shown to be an Olympus TJF-Q180V duodenoscope. This is one of the latest generation duodenoscopes with a specific modified design. This finding questions at what scale failure of decontamination of duodenoscopes occurs and whether outbreaks are limited to specific scope types. The aim of this study was to determine the prevalence of bacterial contamination of reprocessed duodenoscopes in the Netherlands. All 71 Dutch ERCP centres were invited to sample 2 or more duodenoscopes. Local staff used a uniform sampling method explained by video instructions to assess 4 to 6 sites (i.e. protection cap, forceps elevator, flush of forceps elevator or air/water channels, flush and brush of suction and biopsy channel), depending on the scope type. The centrally cultured samples were considered positive for contamination in case of ≥20 colony forming units. Between June and December 2015, 60/71 (85%) Dutch ERCP centres responded and 664 samples of 134 duodenoscopes were processed. Twelve different scope types of 3 distinct scope manufacturers were sampled including 54/134 (40%) Olympus TJF-Q180V, 32/134 (24%) Olympus TJF-160VR, 8/134 (6%) Pentax ED-3490TK, 7/134 (5%) Pentax ED34-i10T and 4/134 (3%) Fujinon ED-530XT8 scopes. Twenty-five (42%) centres had 1 or more contaminated duodenoscope. Thirty-two (24%) duodenoscopes had 1 or more contaminated sample site. Sixteen (12%) duodenoscopes of 13 (22%) hospitals were contaminated with gastro-intestinal microorganisms, including Enterobacter cloacae, Escherichia coli, Klebsiella pneumonia and yeasts. Types of all 3 manufacturers were contaminated: Olympus with 14/54 (26%) TJF-Q180V and 11/32 (35%) TJF-160VR, Pentax with 1/7 ED34-i10T and Fujinon with 1/1 ED-530XT. 50/664 (7.5%) sample sites were contaminated of which the brush that was swiped through the suction and biopsy channel (16/50 - 32%) and forceps elevator (14/50 - 28%) were most often affected. Conclusions: In 42% of the Dutch ERCP centres at least 1 contaminated duodenoscope after reprocessing was detected. Of all duodenoscopes, 24% had 1 or more contaminated sample site. Positive culture results were not confined to a specific sample site or scope type. These results suggest that current duodenoscope reprocessing procedures are not adequate for the currently available duodenoscopes.

Neurons are permissive for hepatitis E virus infection

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Although hepatitis E virus (HEV) is thought to exclusively infect hepatocyte and cause hepatitis, neurological disorder has been described as an important extrahepatic manifestation. Because the mechanism of neuropathogenesis by HEV infection is largely unknown, this study aims to investigate whether HEV can directly infect neurons. HEV RNA positivity in cerebrospinal fluid (CSF) from patients with HEV-associated neurological disorders was retrospectively analyzed. HEV infection assays were performed in cell culture of human neuron cell lines and primary cells cultured from mouse brain, and in animal models of mouse and monkey. As clinical data retrieved from 3 cohorts of patients with HEV-associated neurological disorders, we found that several patients who had active infection shed virus into CSF. This suggested that HEV may directly infect the patient nervous system. In cell culture of 4 types of human neuron cell lines, embryonic stem cell-derived neural progenitor cells and fully differentiated neurons from embryonic stem cells, we confirmed the infectivity after inoculation of cell culture-derived HEV particles, determined by qRT-PCR of viral genome or immunohistochemical staining of the viral protein. Furthermore, HEV particles were produced by glioblastoma U87 cells upon electroporation of the full-length genomic HEV RNA. Inoculation of naive human hepatoma cells or neurons with U87 produced HEV particles resulted in active infection, demonstrating that these were infectious particles. U87 cells supported long-term replication and production of HEV, as tested for 30 days. Surprisingly, primary cerebellum and hippocampus cells cultured from mouse brain were also permissive for HEV infection. Therefore, we have inoculated mice with HEV particles and observed that viral protein and RNA were positive in brain tissues 3 days post-inoculation. More interestingly, in a monkey chronically infected with HEV for over 600 days but died expectedly, we have detected HEV in the brain tissue.

In conclusion, neurons are permissive for HEV infection by supporting virus entry, replication and production. Furthermore, this study has provided in vivo evidence that HEV may infect neurons in mouse, monkey and patients. These results will help to understand the mechanisms of HEV-caused neuropathogenesis.

PKCα / AP-1 drives transcription of interferon-stimulated genes and mediates cell-autonomous defense against hepatitis E virus

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Background & Aims: Protein kinases are enzymes that modify proteins by chemically adding phosphate groups (phosphorylation) and are considered pivotal regulators of almost all cellular processes. However, their involvement in viral infection is less well defined. This study aimed to identify kinase-mediated signaling pathways modulating hepatitis E virus (HEV) infection and to explore the feasibility of modulators of kinase activity as antiviral targets. METHODS: Human hepatoma Huh7 cell harboring sub-genomic HEV luciferase reporter or full-length infectious HEV genome was used. Result: Screening of a library containing 132 kinase inhibitors identified a Protein Kinase C (PKC) inhibitor that significantly promotes HEV infection. Consistently, RNAi mediated knockdown of PKCα, a key member of the PKC family, results in a significant increasement (2.25-fold) in HEV RNA levels. Conversely, over-expression of an active form of PKCα inhibited HEV replication by 49%. Phorbol-12-myristate-13-acetate (PMA) is a well-established PKC activator. As expected, treatment with PMA significantly inhibits HEV (by 68%), as well as rotavirus (70%), murine norovirus (31%) and even HIV replication. Strikingly, this correlates with the pound induction or antiviral interferon stimulated genes (ISGs) which are usually induced by interferons via activation of the interferon stimulated response elements (ISRE). Interestingly, in our experimental system PMA could potently transactivates ISRE and induces the expression or ISGs independent of the canonical elements of the interferon signaling. Knockdown of c-fos, a key component of the AP1 complex that's downstream or PKC, completely abolished the capacity or PMA to activate ISRE and to induce ISGs. Bioinformatics analysis reveals a consensus nucleotide sequence within the ISRE and AP1 DNA binding motifs in the promoter region. Further functional mutagenesis study and ChIP-Seq data set analysis reveal that the induction or ISGs via the Activator Protein 1 (AP-1) cascade. The AP-1 complex binds to ISRE and directly drives ISG transcription.
Conclusion: We identified PKC a as an important kinase in host defense against HEV. Activation ofPKC a provokes the AP-1 complex to directly drive the transcriptional activity of the ISRE motif, resulting in induction or antiviral ISGs..

Drug-drug interactions related to inhibition of the sodium taurocholate co-transporting polypeptide (NTCP) by a novel anti-HBV peptide

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In the liver, the sodium taurocholate co-transporting polypeptide (NTCP, SLC10A1) is the main transporter of conjugated bile acids (BA). Recently, NTCP was also identified as the entry receptor for the hepatitis B virus (HBV). Myrcludex-B, a synthetic peptide mimicking the NTCP-binding domain of HBV is currently in phase II clinical trials as a novel means to inhibit HBV entry. Myrcludex-B also inhibits NTCP-mediated bile acid uptake, but whether this affects the pharmacokinetics of other drugs is currently unknown. This study aimed to identify compounds interfering with BA transport and/or occupation of the HBV binding site of NTCP. To this end, two different approaches were used to screen 1280 FDA-approved compounds in U2OS-hNTCP cells: 1) uptake assays using tritium-labelled taurocholic acid, 2) competition assays with FITC-labeled Myrcludex-B. Effects of a selection of compounds on mouse NTCP, ASBT and cell viability was analysed by taurocholate uptake- and WST-1 assays, respectively. HBV viral entry inhibition was studied in HEPG2-hNTCP cells. Short term consequences of NTCP inhibition was studied in vivo by cannulation of the gallbladder and injection of radiolabeled taurocholate. BA and known NTCP inhibitors included in the screening library were amongst the top 100 hits, thereby validating both screening methods. From the largely overlapping top-hits, 12 were selected for follow-up studies. The most promising hits among these are Rosiglitazone (IC_{50} 5.1µM), Zafirlukast (IC_{50} 6.5µM), TRIAC (IC_{50} 6.9µM), Chicago Sky Blue 6B (IC_{50} 7.1µM), and Sulfasalazine (IC_{50} 9.6µM). All are effective in both human and mouse NTCP and largely ineffective for ASBT, a related BA transport protein. HBV infection in NTCP-expressing HepG2 cells was not inhibited at the aforementioned concentrations, whereas Myrcludex-B was effective to inhibit viral entry. In vivo, NTCP inhibition with Myrcludex-B showed decreased clearance of serum BA.
Conclusions: We established two complementary methods to screen for novel compounds that affect NTCP-mediated BA transport. Decreased NTCP-mediated BA transport was confirmed both in vitro and in vivo. As several of the identified compounds likely are transported via NTCP, this study identifies for which clinically relevant compounds Myrcludex B treatment could affect drug exposure or clearance.

Crosstalk between nucleotide synthesis pathways with cellular immunity in constraining hepatitis e virus replication

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Background and aims: Despite an global health issue, no approved drug is available for hepatitis E virus (HEV) treatment. Since viral replication heavily relies on the host cells to supply nucleosides, targeting nucleotide biosynthesis represents an attractive strategy for antiviral development. Given that the liver is a major site for nucleotide synthesis, we comprehensively profiled the role of purine and pyrimidine synthesis pathways in HEV cell culture models, aimed at identifying potential antiviral drug targets and understanding the crosstalk with cellular antiviral immunity. Methods: A subgenomic HEV replication model expressing luciferase reporter gene and a full-length infectious model were used. RESULTS: Supplementary exogenous guanosine promoted HEV replication in both subgenomic and infectious models, suggesting the importance of purine nucleotides in HEV infection. Surprisingly, we found that 3 pharmacological inhibitors targeting the 3 corresponding catalytic enzymes of primary purine nucleotide synthesis (inosine monophosphate) stimulates HEV replication. Consistently, down-regulation of these enzymes by RNAi enhanced HEV replication. In contrast, targeting the late step by 23 IMPDH inhibitors resulted in potent antiviral activity via nucleotide depletion. Furthermore, inhibition of pyrimidine pathway by targeting 2 catalytic enzymes resulted in potent anti-HEV activity, even though supplementation of uridine has no effect on HEV. Interestingly, all these inhibitors with anti-HEV activity concurrently triggered the induction of antiviral interferon-stimulated genes (ISGs), which was associated with nucleotide depletion. Thus, the interaction of nucleotide synthesis with cellular immune response provides a rational explanation as to their antiviral effects. Although ISGs are thought to be induced only via the JAK-STAT pathway, their induction by nucleotides synthesis inhibitors is through a non-canonical mechanism, since blockage of JAK-STAT cascade doesn't affect the induction of ISGs, as well as the anti-HEV activity. Conclusions: Selectively targeting host enzymes involved in nucleotide biosynthesis potently inhibits HEV replication. Furthermore, nucleotide biosynthesis pathways interact with cellular immune response that the pharmacological inhibitors exerting anti-HEV activity are capable of triggering antiviral ISG transcription. Thus, targeting nucleotide biosynthesis represents a viable option for antiviral drug development against HEV.

Convergent transcription of interferon-stimulated genes by TNF-α and IFN-α augments antiviral activity against HCV and HEV

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Background & aims: Interferon-alpha (IFN-a) has been used for decades to treat chronic hepatitis B and C, and as an off-label treatment for some cases of hepatitis E virus (HEV) infection. Tumor necrosis factor alpha (TNF-a) is another important inflammatory cytokine-which can interact with interferon signaling. Because interferon stimulated genes (ISGs) are the ultimate antiviral effectors of the interferon signaling, this study Aimed to understand the regulation of ISG transcription and the antiviral activity by IFN-a and TNF-a. Methods: HCV replicon cell and HEV models, and ISG transcription assay based on interferon-stimulated response element (ISRE) reporter were used. Clinically used TNF-a inhibitor (Humira) and serum samples from Crohn's disease patient's were also used. Results: Treatment of TNF- a significantly inhibited replication of HCV by 71 ± of 2.4% and HEV by 41 ± 4.9%.Consistently, serum from Crohn's disease patient's containing high levels of TNF-a also inhibited viral replication. Interestingly, TNF-a induced the expression of a panel of antiviral ISGs (18 out of 20 tested ISGs; by 2-11 fold). Blocking the TNF-a signaling by Humira Significantly abrogated ISG induction and its antiviral activity. Further loss-of-function assay Demonstrated That TNF-a induced ISGs expression is dependent on TNF receptor 1 and its downstream NF-k B pathway. Although ISRE element and the NF-k B DNA binding site motifs are distinctly activated by interferon or TNF-a, we surprisingly identified a consensus sequence within thesis two motifs. Chip-seq data analysis and mutagenesis assay Further Revealed That the NF-k B protein complex, the key element downstream of TNF-a signaling, directly binds to the ISRE motif in the ISG promoters and transcription Their Thereby drives. This process is independent of interferons and the classical JAK-STAT pathway. Importantly, When combined with IFN-a, TNF-a works cooperatively on ISG induction, explaining Their additive antiviral effects. Conclusions: TNF-a, via the activation of NF-k B cascade, can drive the transcription of antiviral ISGs through direct binding to ISREs. Further More, TNF-a also acts cooperatively with IFN-a in antiviral ISGs induction to exert additive antiviral effects. These findings providence new mechanistic insight into the crosstalk between thesis two antiviral cascades.

Congenital glycosylation defects in patients with unexplained elevated amino-transferases, steatosis and low ceruloplasmin

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Introduction: Congenital disorders of glycosylation (CDGs) are a heterogeneous group of autosomal recessive metabolic disorders with abnormal glycosylation as a hallmark. GI tract and liver symptoms are frequent but often secondary to more severe pathology. Here we show that mutations in CCDC115 and TMEM199 are pathogenic in twelve patients with a primarily liver phenotype and Golgi-localized glycosylation defects.Methods & ResultsAll patients (TMEM199-CDG: 5 pts., CCDC115-CDG: 8 pts.) showed an overlapping phenotype with elevated aminotransferases and bone-derived alka phosphatase, hypercholesterolemia and low ceruloplasmin. Liver biopsy indicated steatosis, fibrosis, cirrhosis and mild copper accumulation for some patients. Wilson Disease was discarded. In contrast to TMEM199-CDG, CCDC115- CDG patients also developed hepatosplenomegaly, hypotonia and psychomotor disability. End stage liver disease was seen for four CCDC115-CDG patients and necessitated liver trans-plantation. Age at diagnose varied from early infancy to adulthood, but CCDC115-CDG patients were diagnosed earlier in life. Disease gene identification was based on yeast homology. We identified yeast proteins involved in Golgi glycosylation and homeostasis, including proteins associated with the V-ATPase, an intracellular proton pump previously linked to abnormal glycosylation. TMEM199 and CCDC115 were identified as human homologs of two yeast V-ATPase assembly factors and have not been reported in literature before. Next, we searched raw exome sequencing data of a family where previous genetic diagnostics failed and found an homozygous missense mutation in poorly covered exon 1 of TMEM199. Further screening found seven more families with homozygous or compound heterozygous mutations segregating via an autosomal recessive inheritance.We analyzed glycosylation via mass spectrometry and found a pattern suggestive for a Golgi homeostasis defect. Additionally, we incubated patient-derived fibroblasts with fluorescent sialic acid. As sialic acid incorporation is the last step in glycopeptides synthesis this allowed us to determine glycosylation efficiency. After incubation, glycosylation efficiency was reduced for all patients. Transfection of patient-derived fibroblasts with wild-type TMEM199 or CCDC115 construct restored glycosylation efficiency. Additionally, we transiently transfected HeLa cells with V5-tagged constructs for IF and showed that both proteins are located in the ER-to-Golgi region. Conclusion: We identified two new disorders associated with unexplained elevated aminotransferases, low ceruloplasmin and steatosis in twelve patients with abnormal glycosylation. We propose a Golgi homeostasis defect as the cause. We suggest screening for glycosylation defects in patients with similar symptoms.

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Ook de allerbeste prestaties zijn altijd weer te overtreffen. Zolang je jezelf maar dwingt om tot het uiterste te gaan, je grenzen durft te verleggen en je techniek blijft perfectioneren. In het besef dat zelfs de kleinste vooruitgang al een wereld van verschil kan maken. Uit die gedachten halen wij onze inspiratie en gedrevenheid. Elke dag opnieuw zoeken we naar nóg betere oplossingen in de strijd tegen darm- en leverziekten. En daar boeken we nog steeds progressie. **www.drfalkpharma.nl**

Significance of Integrin alpha 11 in phenotypic transformation of hepatic stellate cells in liver fibrosis

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Liver fibrosis, characterized by the excessive accumulation of extracellular matrix (ECM) produced by proliferative and differentiated hepatic stellate cells (HSCs) or myofibroblasts, is the growing cause of mortality worldwide. Thus, understanding of the factors that induce HSCs differentiation is paramount to prevent the fibrotic process. Previous studies have shown that mechanical stress derived from the integrin-mediated interaction between ECM and the cytoskeleton promotes HSCs differentiation. In this study, we aimed to explore the significance of Integrin alpha 11 (ITGA11) in HSCs during liver fibrosis. ITGA11 expression and its correlation with fibrotic parameters were examined in fibrotic mouse livers, cirrhotic human livers and in TGFβ-activated human HSCs. To elucidate ITGA11 role in HSCs, ITGA11 expression was knocked-down using ITGA11-shRNA plasmid. Changes in HSCs morphology and fibrotic parameters were studied in ITGA11-KD (ITGA11 knock-down) HSCs using AFM, immunostainings, Quantitative real time PCR and RT2 profiler human fibrosis array. Furthermore, to assess its functional role, 3D-collagen gel contraction and wound healing assays were performed. ITGA11 expression was highly induced and correlated with increasing fibrosis in vivo in fibrotic mouse models. ITGA11 mRNA expression was significantly ($p<0.04$) increased at stage F3 or F4 (severe fibrosis) as compared to stage F0 or F1 (mild fibrosis) in NAFLD patients (n=32). ITGA11 expression was found to be co-localized with α-SMA positive HSCs in both mouse and human cirrhotic livers. Furthermore, very low expression of ITGA11 was found in normal mouse organs and healthy human organs tissue micro array (TMA). In vitro, ITGA11 expression levels were highly up-regulated in TGFβ-activated human HSCs while remained undetected in human hepatocytes and human monocytes. Following stable ITGA11-KD, 80% reduction in ITGA11 resulted in the drastic reduction in TGFβ-induced collagen I, α-SMA and vimentin expression. Strikingly, in RT2 profiler human fibrosis array, ITGA11-KD HSCs showed a significant reduction in 19 fibrosis-related genes. In the functional assays, ITGA11 knock-down resulted in attenuated would healing, reduced adhesion and impaired collagen contractility. Eventually, ITGA11 expression was found to be significantly up-regulated in different organ fibrosis in human patients suggesting ITGA11 regulates fibrosis development in different organs. Conclusion: These findings suggest that ITGA11 is a promising target in HSCs during fibrosis that regulates HSCs or myofibroblastic phenotypic transformation during fibrosis.

Indian Hedgehog inhibits an intestinal inflammatory response via suppression of stromal CXCL12

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Indian Hedgehog (IHH) is produced by the intestinal epithelium and signals to the mesenchyme. Hedgehog signaling plays an important role in the maintenance of intestinal homeostasis. Loss of IHH from the epithelium not only leads to an increase in stem cell proliferation but also activates a severe inflammatory response resulting in loss of villi and a substantial influx of immune cells suggesting the potential role of chemokines during this process. In addition, genetic variants in the Hedgehog pathway have been linked to the development of inflammatory bowel disease. Here we studied the mechanism behind the anti-inflammatory function of IHH. To investigate the expression of chemokines we performed a real-time quantitative PCR-array on C3H10T1/2 fibroblasts in which the Hedgehog pathway was activated. Among 84 chemokines, CXCL12 was prominently down regulated in the C3H10T1/2 cells upon stimulation of the Hedgehog pathway. A similar suppression of CXCL12 expression was seen in stimulated primary intestinal fibroblasts. We investigated the expression of CXCL12 by stromal cells in vivo by FACS-sorting intestinal immune, epithelial and stromal cells from wildtype mice. qPCR on RNA of the three cell populations showed exclusive expression of CXCL12 by the stroma. Furthermore, a sandwich ELISA was performed to measure chemokine levels in the supernatant of Hedgehog stimulated C3H10T1/2 fibroblasts and primary fibroblasts. We observed high protein levels of CXCL12 in the supernatant of these cells which could be suppressed by activating the Hedgehog pathway. To this end we performed a migration assay to study the migration of Jurkat T cells in response to the supernatant of Hedgehog activated C3H10T1/2 cells and primary fibroblasts. Migration of Jurkat T cells was preferentially towards the supernatant of unstimulated cells. Critically, migration towards supernatant of unstimulated C3H10T1/2 cells was inhibited when using a CXCL12 neutralizing antibody. Based on these data we conclude that epithelial derived Indian Hedgehog acts as an anti-inflammatory signal in the intestine by suppressing the expression of stromal CXCL12 and thereby inhibiting the migration of immune cells.

Similar depletion of the protective gut bacterium Faecalibacterium prausnitzii in psoriasis and Inflammatory Bowel Disease

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Psoriasis and Hidradenitis Suppurativa (HS) co-occur more often with Inflammatory Bowel Disease (IBD) than expected due to shared pathogenic and genetic features. It is known that IBD patients harbour an altered intestinal microbiome characterized by a depletion of Faecalibacterium prausnitzii and increase of Escherichia coli. At present, however, it is unclear whether a similar intestinal microbiome trend can be identified in IBD-associated skin disorders. We therefore investigated the F. prausnitzii and E. coli abundance in psoriasis and HS patients, with and without concomitant IBD. Using quantitative PCR, we compared the F. prausnitzii and E. coli abundance in the faecal samples from healthy controls (n=33) with samples from patients with psoriasis (n=29), IBD (n=31), concomitant IBD and psoriasis (n=13). Likewise, we analysed samples from patients with HS (n=17), and concomitant IBD and HS (n=17). Psoriasis patients harboured a significantly lower abundance of F. prausnitzii in their stool than healthy controls ($p<0.001$), which was similar to IBD patients. Together with the reduced F. prausnitzii levels, the psoriasis patients had a significantly higher abundance of E. coli ($p<0.001$). In HS patients, no significant difference in the abundance of F. prausnitzii or E. coli was demonstrated. There was no significant difference between Crohn's disease (n=24) and Ulcerative Colitis (n=7). It was apparent that faecal samples of patients with concomitant IBD and an associated skin disorder showed the greatest decrease of F. prausnitzii and the highest increase of E. coli. Conclusion The study demonstrates, for the first time, an IBD-like decrease of F. prausnitzii together with an increase of E. coli in psoriasis patients, supporting the presence of a gut-microbiome-skin axis in psoriasis and IBD.

Intestinal microbiota regulate the inflammatory response of splenocytes

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During bone marrow transplantation (BMT), hematopoietic stem cells are depleted by irradiation and subsequently replaced by bone marrow cells from healthy donors. After BMT, donor immune cells show hyper-responsiveness to inflammatory triggers, but the underlying mechanisms are unknown. Since BMT also affects the intestinal microbiota, we investigated whether microbiota play a role in the modulation of immune responses after BMT.Male WT mice underwent either BMT or a sham procedure. BMT mice were compared to other BMT mice that were co-housed with non-BMT control mice and to reference non-BMT non-co-housed mice. Cohousing results in mutual transfer of intestinal microbiota via natural coprophagy. After 24 weeks, both splenocytes and peritoneal cells were isolated and ex vivo stimulated with six different pathogenic stimuli (e.g. LPS, Pam3Cys, poly I:C) and cytokine secretion in the medium (e.g. TNF-α, IL-1α, IL-10, IL-22) was measured. Splenocytes derived from BMT mice showed increased cytokine secretion of TNF-α, IL-10 and IL-22 in response to various pathogenic stimuli ex vivo as compared to splenocytes from non-cohoused control mice. Interestingly, splenocytes from non-BMT mice that were co-housed with BMT mice showed the same cytokine response as splenocytes from BMT mice. BMT did not increase the basal and stimulated cytokine secretion of peritoneal cells ex vivo. Conclusions: We show that BMT increases the sensitivity of splenocytes for various pathogens. Importantly, this 'training' of splenocytes is transmitted from a BMT mouse to a non-BMT mouse via co-housing and thus seems to be mediated by the intestinal microbiota. Therefore, we conclude that microbiota play a role in the BMT-induced modulation of the immune response of splenocytes.

Mycophenolic acid potently inhibits rotavirus infection with a high barrier to resistance development

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Rotavirus infects the enterocytes of the small intestine and is one of the major causative agents of gastroenteritis. Recently it has become clear that rotavirus infection has emerged as an important cause of complications in organ transplantation recipients. Immunosuppressants used to prevent alloreactivity can also interfere with virus infection, but the direct effects of the specific type of immunosuppressants on rotavirus infection are still unclear. Hereto, we aimed to comprehensively profile the effects and mode-of-action of different types of immunosuppressants on rotavirus. Caco2 cell line, 3D model of human primary intestinal organoid, laboratory rotavirus strain (SA11), patient-derived rotavirus strain and five immunosuppressants including prednisolone (Pred), dexamethasone (Dex), cyclosporine A (CsA), tacrolimus (FK506) and mycophenolic acid (MPA) were used in this study. We found that steroids (Pred and Dex) and FK506 did not affect rotavirus infection. Treatment of SA11 rotavirus infected Caco2 cells with 1, 5, 10 µg/ml of CsA resulted in moderate inhibition of rotavirus replication without a clear dose dependence. Significant inhibition was only observed at 5 µg/ml, resulting in a 58 ± 9% reduction of viral RNA. Interestingly, the responsiveness of rotavirus to CsA was strictly regulated in an opposite direction by its cellular targets cyclophilin A (CypA) and B (CypB). Treatment with mycophenolic acid (MPA) at a clinically achievable concentration (10 µg/ml) profoundly inhibited rotavirus replication (99% inhibition of viral RNA) in Caco2 cells. This effect was further confirmed in primary organoids model with both laboratory and patient-derived strains. Importantly, continuous treatment with MPA for 30 passages did not attenuate its antiviral potency, indicating a high barrier to drug resistance development. Mechanistically, the antiviral effects of MPA act via inhibiting the IMPDH enzyme and resulting in guanosine nucleotide depletion. Conclusions: By profiling different immunosuppressants, we have identified MPA as a potent inhibitor of rotavirus infection with a high barrier to resistance development. Thus for transplantation patients at risk for rotavirus infection, the choice of MPA as an immunosuppressive agent appears rational.

Combined activity of NTCP and OATPs governs hepatic uptake of conjugated bile acids in vivo

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Humans with Na^+-taurocholate cotransporting polypeptide (NTCP) mutations or volunteers treated with Myrcludex B, a specific NTCP inhibitor currently in anti-HBV drug trials, show marked elevations in serum bile acid levels. Previously, we reported that NTCP knockout (KO) mice have an impaired hepatic uptake of conjugated bile acids (BAs). However, only a subset of NTCP KO mice shows hypercholanemia. What underlies the normalization of serum BA levels in NTCP KO mice is unknown. In this study, we investigated the in vivo contribution of murine Oatps to transport of conjugated BAs. Taurocholate clearance studies were performed in wild-type and Oatp1a/1b KO mice during gall bladder cannulation, by injection of radiolabeled taurocholate after receiving Myrcludex B (5 µg/g IV) or placebo. Myrcludex B was administrated for 2 hours or 5 days in Oatp1a/1b KO and Oatp1a/1b KO mice reconstituted with human OATP1B1. Bile acid levels in serum were quantified by HPLC. Messenger RNA was quantified by RT-qPCR. All NTCP KO mice show hypercholanemia at 4 weeks of age, and BA levels normalize in the majority of mice when reaching adulthood, suggesting partial redundancy of NTCP. The hypercholanemic adult mice display a complete absence of Oatp1a1. Oatp1a/b KO mice have slightly elevated serum unconjugated BA levels. In wild-type mice, injection of Myrcludex B results in delayed taurocholate clearance from the blood, but eventually all taurocholate is cleared from the blood. However, Myrcludex B completely inhibits active transport of all conjugated BA species in Oap1a/1b KO mice. Biliary excretion of taurocholate is <1% of the injected bolus after 1 hour of bile collection. Cyp7a1 mRNA levels are reduced after 5-day administration of Myrcludex B, likely caused by the significant induction of intestinal FGF15. Conclusions: This in vivo study shows the contribution of Oatps as well as Ntcp to hepatic uptake of conjugated bile acids. The data suggests that in humans, NTCP contributes relatively more to the hepatic uptake of conjugated BAs than it does in mice.

Nuclear localization of IMPDH2, the primary target of mycophenolic acid, constrains hepatocellular carcinoma

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Background & aims: Inosine monophosphate dehydrogenase (IMPDH) is a rate-limiting enzyme in purine-nucleotide synthesis. Mycophenolate mofetil (MMF)/Mycophenolic acid (MPA), a widely used immunosuppressant in organ transplantation, is a reversible and uncompetitive IMPDH inhibitor, preferentially targeting the IMPDH2 isoform. This study aimed to investigate the function of IMPDH2 in hepatocellular carcinoma (HCC) and its role in mediating the effects of MPA. Methods: Immunohistochemical (IHC) staining of IMPDH2 was performed in tissue microarrays of patient HCC tissue. Three HCC cell lines and immunodeficient mice were used for functional experiments. Retrospective analysis was performed to investigate the association of MMF therapy with HCC recurrence in liver transplantation patients.Results: Cytoplasmic IMPDH2 protein level was significantly lower in HCC tissues compared with adjacent liver tissues ($n = 131$, $P < 0.01$). High IMPDH2 level in tumor tissue was significantly associated with better cumulative survival ($n = 131$, $P < 0.01$). Conversely, down-regulation of IMPDH2 by RNAi in HuH7 cells significantly increased the ability of single cell colony formation in vitro ($n = 6$, $P < 0.01$), and the efficiency of tumor initiation (100% vs 67%) in mice. Furthermore, HuH7 cells with IMPDH2 down-regulation formed significantly larger tumors compared to the control group (1.40 g ± 0.23 vs 0.29 g ± 0.16, mean ± SEM, $n = 6$, $P < 0.01$). Interestingly, nuclear IMPDH2 was observed in a subset of patient HCC tissues, which was significantly associated with better cumulative survival ($n = 16$, $P < 0.05$). In HCC cell lines, MPA potently inhibited cell proliferation. In HCC related liver transplantation patients ($n = 42$), the use of MMF was significantly associated with lower recurrence rates ($P < 0.05$) and higher cumulative survival rates ($P < 0.05$). Mechanistically, the inhibitory effects of MPA on HCC cells were independent of cellular nucleotide synthesis. However, MPA was able to drive nuclear translocation of IMPDH2 forming rod/ring structures in the nucleus. Conclusions: High expression of IMPDH2, in particular its nuclear localization, is associated with less colony formation in cell lines, smaller and less aggressive tumors in mice and a better clinical outcome in HCC patients. The inhibitory effects of MMF/MPA on HCC is independent of cellular nucleotide synthesis, but likely attributed to its ability of driving nuclear translocation of IMPDH2. Key words: IMPDH2; MPA; HCC; Nuclear Localization

The dynamics of fast and slow cycling stem cells in liver homeostasis and injury

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Background & Aims: Adult liver stem cells are in general maintained in a quiescent/slow cycling state. However, a fast-cycling population marked by Leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) was recently identified as important liver stem cell. This study aimed to investigate the dynamics and functions of both fast- and slow- cycling stem cells in healthy/injured livers. Methods: The Lgr5 stem cells were investigated by using a diphtheria toxin (DT) receptor knock-in mice model with a GFP reporter and a lineage tracing mice model with a YFP reporter. Slow cycling stem cells were studied with a GFP based, Tet-on controlled transgenic mouse model. Results: We found that Lgr5 cells (GFP) are absent under normal conditions in healthy mice liver. With CCl_4 induced liver injury, less than 0.1% of Lgr5 cells emerged. Lgr5 cells formed organoids in 3D culture, demonstrating their stem cell property. However, during 25 days of follow-up, lineage tracing revealed that the offspring (YFP^+) derived from Lgr5 cells only had minor contribution (<1%) to injury recovery. Bile ducts isolated from healthy liver without Lgr5 cells also initiated organoids, and Lgr5 cells appeared during expansion. Surprisingly, Lgr5 cells depletion by DT did not influence organoid initiation, expansion and differentiation, indicating the existence of other important stem cell populations. Using the Tet-on regulated GFP transgenic mouse model, we found that a slow cycling population retaining GFP label (label retaining cells; LRCs) over 6 months in the homeostatic liver. LRCs localized around the portal triad, a recognized stem cell niche, but rapidly proliferated upon liver injury. Isolated LRCs initiated organoids, confirming their stem cell property. Furthermore, LRCs isolated from injured liver formed larger organoids compared to those from healthy livers (diameter measured at day 11 of culture: Normal vs Injury = 101 ± 21 vs 187 ± 35 μm, $P < 0.01$). More interestingly, isolated LRCs did not express Lgr5, but organoids derived from these cells started to express it during expansion, suggesting that LRCs may give rise to Lgr5 cells. Conclusion: Lgr5 cells are absent in homeostatic but emerged in injured liver, which is dispensable for injury recovery. In contrast, slow-cycling stem cells are present in homeostatic liver and respond to liver injury, and they can give rise to Lgr5 cells.
Keyword: Liver stem cells, Lgr5, Slow cycling stem cells, Fast cycling stem cells

Portal vein embolization-triggered liver regeneration is accelerated by the FXR agonist obeticholic acid.

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Bile salt signaling is required for compensatory liver regrowth following surgical loss of liver tissue. The bile salt receptor FXR plays an important role in this process. In this study we explored whether FXR is involved in the regenerative response following portal vein embolization (PVE), an intervention to increase future remnant liver volume in patients scheduled for extended liver surgery. Adult female rabbits received vehicle or the FXR agonist obeticholic acid (OCA; 10 mg/kg, daily oral gavage) for 7 days prior to, and after embolization of the cranial liver lobes. Effectiveness of PVE was confirmed by portography, and caudal liver volume (CLV) was analyzed by CT-volumetric analysis at days -7, -1, +3 and +7. Rabbits were sacrificed at day +3 and +7 (n=5-6 per group). Sera and tissues were harvested for analytical procedures. OCA induced a larger increase in CLV at day 3 after PVE (59.3±19.2% vs. 29.7±16.1% in controls, P=0.001), with both groups attaining a similar volume gain after 7 days. In both groups, PVE resulted in a similar pattern of serum bile salt elevation, with levels increasing after 3 hrs and normalizing at day +3. Analysis of tissues harvested at day +3, revealed that hepatic bile salt content was reduced (60.1 [16.0] vs 100.1 [75.1] nmol/g in controls; P=0.016) in the hypertrophied segments of OCA-treated animals. Reduced expression of the bile salt synthetic enzyme Cyp7a1 (-7.1 fold; P=0.004) and enhanced expression of the basolateral bile salt efflux pump subunit Slc51b (+6.5 fold; P=0.004) may have contributed to this lowering. Expression of Cdc25b, a phosphatase required for entry into mitosis, was elevated in the hypertrophic (+1.6 fold; P=0.006) but not atrophic (+1.1 fold; P=0.52) liver segments of OCA-treated animals. Cdc25b expression in the non-embolized segments correlated with FXR target genes Slc51b (ρ=+0.80, P=0.002) and Cyp7a1 (ρ=-0.62, P=0.033), and tended to be associated with percentual increase in CLV at day +3 (ρ=+0.57, P=0.055). OCA accelerated liver regeneration in the first 3 days after PVE in rabbits, with control and OCA-treated animals having a similar volume gain in the non-embolized segments after 7 days. Improved bile salt homeostasis and induction of proliferative genes (e.g. Cdc25b) may underlie the augmented growth rate in the initial phase after PVE. OCA treatment has potential in extending resectability and prevention of post-resectional liver failure.

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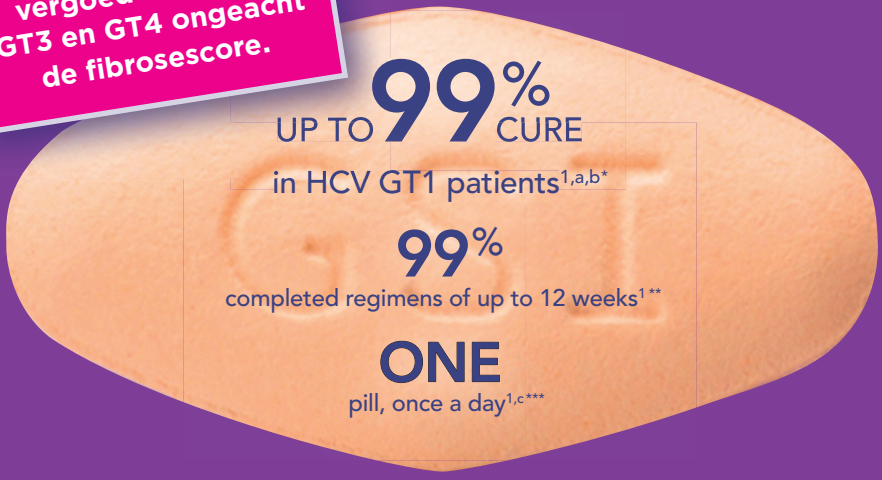

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[a] 99% cure rates were observed in the ION-1 study in previously untreated HCV GT1 patients treated with HARVONI for 12 weeks. Across the ION studies, SVR rates between 94–99% were observed in HCV GT1 patients treated with HARVONI for 8–24 weeks.[1]
[b] EASL define cure as SVR12.
[c] HARVONI offers a single-tablet, RBV-free regimen for the majority of HCV GT1 patients, excluding those with decompensated cirrhosis, or who are pre- or post-liver transplant.[1]

Referenties en productinformatie elders in deze uitgave.

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Wnt secretion is not required to sustain Wnt/β-catenin signaling in β-Ccatenin mutant hepatocellular carcinoma cells

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Aberrant activation of Wnt/β-catenin signalling plays a key role in the onset and development of many hepatocellular carcinomas (HCC), with around one-third of cases featuring activating β-catenin mutations. Previously, it was shown that colorectal cancers still partially depend on Wnt secretion to sustain optimal levels of β-catenin signalling, despite the presence of mutations that already hyperactivate the pathway. Here, we have investigated whether β-catenin mutation in HCC is sufficient to stimulate and maintain this pathway. Ten HCC cell lines of which three harboring a β-catenin mutation, were used to study the dependency on Wnt secretion and Wnt ligand binding. Eight CRC cell lines were used to compare the distinction between β-catenin mutant HCC and CRC cell lines. SiRNA mediated β-catenin knockdown showed the importance of β-catenin signalling for cell growth of most HCC cell lines. Using a β-catenin signalling reporter assay, all β-catenin mutant cell lines (SNU398, HepG2 and Huh6), Axin1 mutant PLC/PRF/5 and SNU182 presented with enhanced β-catenin signalling activity. Interestingly, the latter cell showed the highest expression of canonical Wnt ligands among all HCC cell lines, whereas only low level expression was observed in the β-catenin mutant ones. In accordance, β-catenin signalling and cell growth was not affected in these mutant cell lines by treatment with IWP12, an inhibitor of Wnt ligand secretion, while this was significantly reduced in SNU182 ($p < 0.01$). The mutant cell lines were also the least responsive to the activation by Wnt3a, when supplemented to the culture medium. In addition, one of four β-catenin mutant CRC cell lines, HCT116 sensitively responded to IWP12 and exogenous Wnt3a treatments, shown by activation of β-catenin signalling activity and stimulation of cell growth. Our results suggest that β-catenin mutation is adequate to sustain Wnt/β-catenin signalling activity, independent of Wnt secretion in HCC cell lines, different from CRC which is partially dependent on Wnt secretion. These observations provide a new perspective regarding the management of Wnt/β-catenin signalling inhibitors on different HCC subtypes.

Obeticholic acid enhances liver regeneration in hepatectomized mice.

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Animal studies demonstrated that tight control of bile salt homeostasis is required for efficient regeneration following partial hepatectomy (PH). Bile salt signaling via the intracellular bile salt receptor FXR is key to this homeostatic regulation. Impaired regeneration is observed in post-resectional liver failure, a potentially lethal complication of extended liver resection. The aim of the study was to explore whether FXR agonism can accelerate liver regeneration after PH. Adult male C57Bl/6 mice were pretreated for one week with the FXR agonist obeticholic acid (OCA; 10 mg/kg, daily oral gavage) or vehicle (0.5% methylcellulose) (n=13 per group). Five mice in each group were sacrificed at base to study efficacy of agonist pre-treatment, while the remaining mice underwent 70% PH and were sacrificed 48 hrs later. Prior to sacrifice, BrdU was administered i.p. to label S-phase cells. Tissues were harvested for histological (mitotic figures) and immunohistochemical (BrdU/Ki67) examination, transcript analysis and determination of bile salt content. Glycemia was monitored during the entire course of the experiment. Effectiveness of OCA pre-treatment was inferred from modulation of ileal (Fgf15, +12 fold, Slc51b, +2.0 fold; both $P<0.05$) and hepatic (Cyp8b1, -8.1 fold; $P<0.05$) Fxr target genes. OCA pre-treatment did not affect pre-operative body weight or glycemia course, or base bile salt levels in the circulation or liver. A transient drop in body weight and glycemia was observed in mice on day 1 after PH, with similar kinetics in the post-operative trajectory in both groups of mice. 48 hrs after PH, estimated liver mass recovery was somewhat reduced (69 vs. 62%; $P=0.02$) in OCA-treated animals. Mitotic figures (0.0 vs. 4.8; $P<0.001$) and percentage Ki67-positive hepatocytes (18.2 vs. 47.4%; $P=0.005$) were higher in OCA-treated animals. Hepatic expression of cell cyclins A2 (+4.2 fold; $P<0.05$) and B1 (+5.8 fold; $P<0.05$) was elevated in OCA-treated animals, with a tendency for elevated expression of a key regulator of proliferation, viz. Foxm1b (+2.3 fold, $P=0.07$). Bile salt content in the regenerated liver lobes was similar in both groups. Expression of bile salt synthetic genes Cyp7a1 (-6.3 fold; $P<0.05$) and Cyp8b1 (-37 fold; $P<0.05$) was reduced in OCA-treated animals. In conclusion, the aggregated data indicates that OCA enhances regeneration of the liver following PH. Time course analysis can provide further insight on Fxr dependent mechanisms of action in this model and clarify the involvement of bile salt homeostasis and/or a direct effect on cellular proliferation.

Under-expression of PDL1, Galectin-9 and CD8 TIL in Hepatocellular Carcinoma is associated with worse patient survival

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Hepatocellular carcinoma (HCC) is notoriously resistant to chemotherapy. Immunotherapy is a promising alternative as it can induce highly specific anti-tumor immune responses. Understanding the mechanisms by which HCC confers resistance against the immune system is crucial for the development of suitable immuno-therapeutics. The goal of this project was to examined the expression of the immune inhibiting molecules PD-L1, Galectin-9, HVEM, and IDO, as well as tumor CD8+ lymphocyte infiltration (CD8 TIL) in HCC. Tissues from 94 patients who underwent tumor resection at a Dutch institution were used to construct TMAs, with three 0.6mm cores from the tumorous area and two 0.6mm cores from the tumor-free liver (TFL) tissue, to form a discovery cohort. Tissues from an additional 60 resected patients from a second Dutch institution were used to construct similar TMAs to form a validation cohort. Follow up information on recurrence, death and known prognostic base clinicopathologic characteristics were collected. Standard immunohistochemistry using well-validated primary antibodies was performed. Scoring was performed by two independent investigators. In the discovery cohort low levels of tumor expression of PD-L1 ($p<.001$), Galectin-9 ($p=.001$) and HVEM ($p<.001$), as well as low CD8 TIL count ($p=.024$), were associated with worse HCC-specific survival. Expression of IDO did not show such associations. In multivariate analysis PD-L1, Galectin-9 and CD8 TIL count were not associated with clinicopathologic characteristics. The combination of PDL1, Galectin-9 and CD8+TIL also predicted HCC-specific survival independent of clinicopathologic characteristics ($p<.001$). Expressions of these same molecules in TFL tissue were not associated with HCC survival. These results were confirmed in the validation cohort were low tumor expression of PD-L1 ($p=.018$), Galectin-9 ($p=.047$) and low CD8+ TIL count ($p=.092$) were again associated with worse HCC-specific survival, and the combination of PDL1, Galectin-9 and CD8 TIL also predicted HCC-specific survival independent of clinicopathologic characteristics ($p=.024$). In addition, the results were internally validated in the first cohort using bootstrapping. In conclusion, low tumor expression of PD-L1 and Galectin-9, as well as low CD8 TIL count, are associated with worse HCC-specific mortality in patients with resected HCC. PD-L1 and Galectin-9 expression in tumors may be induced in response to immunologic pressure which may explain why their presence is associated with prolonged survival. PD-L1 and Galectin-9 may be promising immunotherapeutic targets in patients with tumors expressing these co-inhibitory molecules.

Biomarkers in inflammatory bowel disease: serum calprotectin is not accurate in detecting disease activity

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Endoscopy, the gold standard for monitoring inflammatory bowel disease activity is invasive. Therefore, non-invasive faecal calprotectin is used as a biomarker for disease activity. However, collecting a stool sample and bringing it to the laboratory, can be a hurdle for patients. Our study aim is to evaluate the accuracy of serum calprotectin ELISA as an alternative for faecal calprotectin in daily practice in detecting endoscopic or radiologic disease activity in patients who are suspected for a flare of disease. We performed a prospective cohort study in all consecutive patients who presented with clinical symptoms suspected for a flare of disease, at the outpatient clinic of our hospital between February 2015 and April 2015 in whom faecal calprotectin was determined. We studied the differences in measured serum calprotectin ELISA, faecal calprotectin Phadia, faecal calprotectin ELISA, C-reactive protein (CRP), leucocyte count and albumin in patients who had endoscopic or radiologic disease activity and those who had not. Of all 59 patients who were included in this study, 14 (23.7%) had endoscopic and/or radiologic disease activity. We found no significant difference in measured serum calprotectin ELISA between patients with and without endoscopic or radiologic disease activity (medians 264 versus 298; p = 0.87 with AUC 0.486). In faecal calprotectin ELISA our results were border not statistically significant (median 80 versus 40; p = 0.06 with AUC 0.669), this in contrary to the results we found in the other faecal calprotectin test (Phadia), in which we measured a significant difference in medians (890 versus 94; p =0.02 with AUC 0.701). We also tested CRP which showed a median of < 10 mg/L in both groups (p = 0.149), with an AUC of 0.587. Leucocyte count did not show a significant difference in means either (7.9 versus 7.4 x 10^9/L; p = 0.45; AUC = 0.534). In this study serum calprotectin ELISA is not an accurate biomarker in detecting endoscopic or radiologic disease activity.

The value of mercaptopurine therapy after failing azathioprine in inflammatory bowel disease patients

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Background Thiopurines have been widely accepted as immunosuppressive therapy in inflammatory bowel disease (IBD). Although considered as effective and relatively safe, many patients have to discontinue thiopurines due to intolerance or ineffectiveness. Few studies reported a beneficial switch from azathioprine (AZA) to mercaptopurine (MP) after development of adverse events (AEs). We assessed the value of MP therapy after failing AZA. Primary outcome is MP tolerance after AZA intolerance. Secondary outcome is clinical benefit of switching from AZA to MP, after AZA proved to be ineffective. Methods In this retrospective database study, we analyzed data from patients in whom AZA therapy failed due to adverse events (e.g. myelotoxicity, hepatotoxicity, pancreatitis or gastrointestinal(GI)-symptoms) or ineffectiveness (based on clinical symptom scales), who were subsequently treated with MP between 1998 and 2013 in our center. Results In total, 74 patients were included, of which 38 patients (51%) switched to MP due to intolerance of AZA. Intolerance reoccurred in 22 (58%) patients, the remaining 16 (42%) patients tolerated MP. Gastrointestinal problems (i.e. nausea or abdominal cramps) was the most reported AE. In 35%, the AE that led to discontinuation of MP was the same in AZA, which is in with the literature. AZA tended to be underdosed more often than MP (57% vs. 42%; p=0.12). A longer duration of AZA therapy was more common in MP tolerant patients (5.3 vs 1.2 months; p=0.04). Twenty-two patients (30%) had to stop AZA due to ineffectiveness. Eight (36%) patients benefited from a shift to MP after AZA ineffectiveness. Six out of these eight (75%) patients benefited from this switch by using allopurinol alongside MP. In all six patients, allopurinol was initiated due to ineffectiveness, identified by therapeutic drug monitoring (TDM) and based on a skewed thiopurine metabolism. Patients were more likely to benefit if the interval between both thiopurines was longer (4.4 vs. 0.01 months; p<0.05). The remaining 14 patients (19%) discontinued AZA for other reasons than intolerance or AEs (such as patient's request) or were lost to follow-up. Conclusions There is evidence that patients could benefit from a switch to MP after AZA therapy failed due to intolerance, however these numbers seem to be lower than previously suggested in the literature. This might be due to the fact that TDM is used in our center and therapy is adjusted based on metabolite levels. For patients ineffective on AZA, a switch to MP seems beneficial only when therapy is combined with TDM and initiation of allopurinol in patients with a skewed thiopurine metabolism.

Trans-radial access for endovascular abdominal interventions: a safe and feasible technique

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The number of endovascular abdominal interventions has increased over the past decades and is expected to increase even further in the near future. Examples of endovascular interventions in gastroenterology are trans-arterial chemoembolization (TACE) for hepatocellular carcinoma, mesenteric artery stent placement for occlusive chronic gastro-intestinal ischemia and embolization of hepatic artery aneurysms. The approach for endovascular abdominal interventions is mostly trans-brachial or trans-femoral. Previous reports about endovascular abdominal interventions report relatively high complication rates. Sana et al. reported in 43 patients (trans-brachial n=32) a minor complication rate of 25.6% (8 local hematoma, 1 dissection, 2 pseudo-aneurysms) and a major complication rate of 20.9% (1 pneumonia, 2 strokes, 1 spleen-infarction, 2 thrombosis, 1 AV-fistula, 2 nerve damages). In interventional cardiology nowadays, trans-radial access (TRA) is the preferred approach with low reported complication rates. Advantages of TRA are reduced radiation exposure to the interventionalist and no requirement of ultrasound for arterial puncture. Furthermore, no major anatomical structures with risk of damaging are nearby and collateral circulation exists via the ulnar artery. Finally, the closure device is inexpensive compared to femoral closure devices such as Angio-Seal and patients are permitted to mobilize immediately. TRA however requires longer catheters, especially in abdominal procedures, which can lead to difficulties in manipulation. Reports on endovascular abdominal interventions per TRA are lacking. We aimed to assess the feasibility and complication rate of TRA for endovascular abdominal interventions. We prospectively assessed the complication rates of patients who underwent endovascular abdominal intervention per TRA between November 2014 and November 2015. All patients had a normal modified Allen test result, a simple test to assess the adequacy of blood supply through the ulnar artery to the hand. Thirty-one patients (14 men, mean age 63.8±11.2 years) underwent 34 trans-radial endovascular abdominal procedures. Twenty-one (61.8%) interventions concerned a mesenteric endovascular procedure, 9 (25.6%) TACE and 4 (11.8%) an endovascular procedure of the hepatic artery. The minor complication rate was 8.8% (2 local hematoma, 1 cellulitis). There were no major complications. All patients were able to mobilize directly after the intervention. Conclusion: TRA for endovascular abdominal interventions showed to be a feasible and successful technique with a low complication rate. TRA may therefore be the preferred approach in endovascular abdominal interventions.

Postprandial flow measurements of the mesenteric arteries and portal vein using Magnetic Resonance imaging: a pilot study

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Patients with chronic gastro intestinal ischemia (CGI) suffer from severe postprandial abdominal pain due to insufficient postprandial increase of mesenteric blood flow, usually caused by atherosclerotic stenosis of the supplying gastrointestinal arteries. The diagnosis of CGI remains challenging as chronic abdominal pain due to other causes is common and stenosis of the mesenteric arteries are often asymptomatic due to extensive collateral circulation. Hence, a reliable non-invasive test to assess the hemodynamics of the mesenteric vessels is needed. In cardiovascular radiology, cardiac blood flow is measured using Magnetic Resonance (MR) imaging. The technique has not yet been explored to quantify intestinal blood flow. We aimed to determine the feasibility of flow measurements using MR imaging to assess the hemodynamics of the mesenteric arteries and portal vein and establish a set of reference values under fasting and feeding conditions in healthy volunteers. Nine healthy volunteers aged ≥ 50 years (3 male) underwent MR flow measurements of the abdominal aorta at a level just above the celiac trunk (AA), the celiac artery (CA), superior mesenteric artery (SMA), and portal vein (PV) on a 1.5 Tesla MR scanner during inspiration and expiration. An ECG-gated, velocity-encoded cine gradient-echo sequence was used to measure blood flow using a 32-channels surface coil. First, we performed MR flow measurements in fasting state. Consecutively, blood flow was assessed 10, 20, 30 and 40 minutes after oral intake of 400 mL (600 kcal) nutritional drink. Median blood flow in mL/stroke of the AA, PV and SMA increased significantly postprandially compared to baseline, both during expiration (AA 47.0 vs 58.2, p=0.028; PV 24.3 vs 40.3, p=0.008; SMA 4.9 vs 13.2, p=0.011) and inspiration (AA 38.2 vs 47.6, p=0.046; PV 21.6 vs 33.3, p=0.008; SMA 3.4 vs 14.3, p=0.021). Blood flow of the CA also increased postprandially, but these results were not statistically significant (expiration 10.1 vs 11.0, p=0.374; inspiration 7.7 vs 9.0 p=0.086). The relative increase in blood flow was most prominent in the SMA (expiration 169%, inspiration 321%) and these values overlap completely at base and maximal postprandial flow during inspiration and expiration. Conclusion: It is feasible to non-invasively assess the hemodynamics of the mesenteric arteries and portal vein using MR flow measurements. We have established a set of reference values under fasting and feeding conditions. Further research is needed for the applicability of this technique in the diagnostic work-up of CGI, starting with pre- and postprandial MR flow measurements in patients with CGI.

Bowel preparation for colonoscopy and risk of hypokalemia: a pilot study

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Bowel preparation for colonoscopy should not cause significant shift in systemic electrolyte concentrations. We recently reported two cases of severe postcolonoscopy hypokalemia with fatal consequences, prompting us to conduct a pilot study to explore the magnitude of and risk factors for hypokalemia associated with bowel preparation. We paid specific attention to higher risk subgroups, in particular diuretic users and hospitalized patients. From January 1 to December 31, 2014, we included all patients at higher risk for hypokalemia who underwent diagnostic, screening or surveillance colonoscopy at our institution. We defined this higher risk subgroup as diuretic users or hospitalized patients. We measured serum potassium levels before bowel preparation for colonoscopy. We recorded clinical information including demographic features, indication for colonoscopy and outcome of the examination, comorbidities and medication. In a random subset of patients who had normal serum potassium levels before bowel cleansing, serum potassium levels after bowel cleansing were also measured. Patients diagnosed with hypokalemia received potassium supplementation according to the standard local protocol. In total, 5515 colonoscopies were performed, of which 1823 procedures in diuretic users or hospitalized patients. Of these, 78 (4.3%) patients had hypokalemia before bowel cleansing (serum potassium level < 3.5 mmol/L), 1633 (89.6%) normal potassium levels (3.5-5.0 mmol/L) and 112 (6.1%) hyperkalemia (>5.0 mmol/L). Logistic regression model adjusted for age, gender, indication for colonoscopy, diuretics and setting showed that hospitalized patients were more likely to have hypokalemia than non-hospitalized patients (OR 0.34, [95% CI 0.20-0.57], $p<0.001$). Of the patients with normokalemia before bowel cleansing, 291 had also potassium controls after bowel cleansing, of whom 48 (16.5%) had hypokalemia. Eight patients had severe hypokalemia (mean 2.8 range, 2.7-3.0 mmol/L) before bowel cleansing, while 13 had severe hypokalemia (mean 2.8, range 2.2-3.0) after bowel cleansing. No serious adverse events occurred. In this pilot study, we found that hypokalemia already precedes colonoscopy in 4.3% (16.5% post-bowel cleansing) of patients receiving diuretics/ hospitalized patients. Severe hypokalemia was seen in 0.4% (4.5% post-bowel cleansing). No serious events occurred due to timely potassium supplementation. Prospective studies in random populations are required to identify subgroups in which careful monitoring of serum potassium levels can maximize the safety of colonoscopy.

Proton pump inhibitors affect the gut microbiome

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Proton pump inhibitors (PPI) are among the top ten most widely used drugs in the world. PPI use has been associated with an increased risk of enteric infections, most notably Clostridium difficile. The gut microbiome plays an important role in enteric infections, by resisting or promoting colonization by pathogens. In this study, we investigated the influence of PPI use on the gut microbiome. The gut microbiome composition of 1815 individuals, spanning three cohorts containing healthy individuals, Inflammatory Bowel Disease patients and Irritable Bowel Syndrome patients, was assessed by tag-sequencing of the 16S rRNA gene. The difference in microbiota composition in PPI users vs. non-users was analyzed separately in each cohort, followed by a meta-analysis. 211 of the participants were using PPI at the moment of stool sampling. PPI use is associated with a significant decrease in Shannon's diversity and with changes in 20% of the bacterial taxa (FDR < 0.05). Multiple oral bacteria were overrepresented in the fecal microbiome of PPI-users, including the genus Rothia (p=9.8x10-38). In PPI users we observed a significant increase in bacteria: genera Enterococcus, Streptococcus, Staphylococcus and the potentially pathogenic species Escherichia coli as well as a significant decrease in the genus Bifidobacterium and the family Ruminococcaceae. The differences between PPI users and non-users observed in this study are consistently associated with changes towards a less healthy gut microbiome. These differences are in with known changes that predispose to C. difficile infections and can potentially explain the increased risk of enteric infections in PPI users. On a population level, the effects of PPI are more prominent than the effects of antibiotics or other commonly used drugs.

Evaluation of Paneth cell alterations after intestinal transplantation and during graft rejection

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Intestinal transplantation (ITx) has evolved from an experimental procedure towards a clinical and life-saving treatment for patients with irreversible intestinal failure, but remains a challenging procedure. Acute rejection is the most common and life-threatening complication after ITx. Ischemia reperfusion (IR) injury plays a pivotal role in the cascade leading to rejection. We have shown that Paneth cells, important gatekeepers of the intestinal crypts, are highly susceptible to IR injury in humans. In a rat study, it was shown that Paneth cell antimicrobial peptide expression was significantly reduced in intestinal grafts undergoing acute rejection. Therefore, the aim of this study was to study Paneth cell homeostasis in IR injury and rejection in patients that underwent ITx. Archived endoscopic mucosal biopsies of 33 ITx patients from University hospitals Birmingham were used, and clinical information was collected. Biopsies were taken at transplant protocol-specified time points and whenever clinically indicated. Consecutive biopsies were double-stained for Paneth cell marker lysozyme and apoptotic marker M30 to visualize antimicrobial expression and Paneth cell loss at reperfusion (T0), and during the first week, the first month and the first year after ITx, as well as prior to, during, and after a rejection episode. The number of lysozyme-positive and lysozyme-positive/M30-positive cells per crypt, and lysozyme intensity were quantified. Within the first week after ITx, there was a significant decrease in lysozyme intensity ($P<0.05$), and a tendency towards lower Paneth cell number per crypt ($P=0.09$) compared to T0. Within the first year after ITx, the number of Paneth cells per crypt was comparable to T0, and significantly increased compared to the first week and month after ITX ($P<0.01$). Shortly before initiation of rejection, lysozyme intensity was significantly reduced compared with T0 ($P<0.01$). Higher lysozyme expression was observed after recovery of a rejection episode compared with levels prior to ($P<0.05$), and during rejection ($P=0.08$). Paneth cell numbers were significantly increased after recovery of a rejection episode compared with levels prior to, and during rejection ($P<0.05$). In conclusion, the current study shows reduced Paneth cell numbers and antimicrobial expression during the first week after ITx, as well as prior to, and during a rejection episode. These results suggest that Paneth cell alterations precede the onset of a rejection event. How these negative effects on Paneth cells relate to patient outcome and potential graft loss will be investigated in the next phase of the study.

A Multicentre Randomized Controlled Trial Evaluating E-health for Children and Young Adults with Coeliac Disease – the CoelKids study

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Our aim was to evaluate the effectiveness of on consultations for follow-up of children and young adults with celiac disease (CD). We designed a multicentre randomized controlled trial involving 304 patients aged ≤25 years with CD≥1 year, receiving on (N=156) or traditional consultation (N=148). On consultations included symptom questionnaires and home measurements of growth and anti-transglutaminase-type-2 antibodies (TG2A) using a point-of-care (POC) self-test. Both groups completed questionnaires concerning CD-specific health-related quality of life (HRQOL), gluten free diet adherence and patient-satisfaction. After 6 months, they performed the POC self-test and repeated HRQOL and patient-satisfaction questionnaires. The primary outcome was disease control, defined as negative TG2A. Secondary outcomes were CD-specific HRQOL, patient-satisfaction, and costs. Abdominal pain, lassitude and increased appetite were detected significantly more frequently in the on group than in controls. Growth problems were detected similarly in both groups. TG2A was positive in 2 on participants and 13 controls (POC vs. laboratory, p=0.003). CD-specific HRQOL (1=good; 5=poor) was similar in both groups, but improved after on consultation (3.25 to 3.16, p=0.013; vs. controls 3.10 to 3.23, p=0.810). Patient-satisfaction (1=low; 10=high) was 7.6 in the on group and 8.0 in controls (p=0.001). Mean costs in the on group were €202 less than in the control group (p<0.001). In conclusion, on consultations for children and young adults with CD are cost-saving and increase CD-specific HRQOL. Additionally, patients find these to be satisfactory. The discrepancy between the POC test and laboratory results suggests that the used POC test is not sensitive enough to detect low antibody levels and thereby unsuitable to monitor treated CD.

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Development of a core outcome set for infant colic

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Infant colic (IC) is a common functional gastrointestinal disorder with a worldwide prevalence of 5 – 25%. This self-limiting disorder can have negative long-term consequences, such as recurrent abdominal pain, migraine and even child abuse. Its etiology remains unknown, resulting in a wide variety in interventions and use of heterogeneous outcomes across therapeutic trials. Only a minority of trials reports parental perception as a primary outcome. Uniform definitions, outcomes, and validated instruments are needed to facilitate and improve evidence synthesis. The aim of this study is to develop a core outcome set for trials on IC. The Delphi technique was used to collect opinions of relevant stakeholders: 133 health care professionals (HCPs) were approached at pediatric conferences and 55 parents of infants with IC were approached at pediatric outpatient clinics. All were asked to list up to 5 outcomes they considered to be relevant in the treatment of IC. Outcomes mentioned by ≥ 10% of participants were forwarded to a shortlist. Outcomes on this shortlist were rated and prioritized by HCPs and parents. Treatment outcomes with the highest scores were included in the COS. In total, 86% of invited stakeholders contributed to the development of the final COS. Duration of crying, reduced family stress, sleeping time of infant, quality of life (of the family), infant discomfort and reduced hospital admission/duration were rated as most important outcomes in IC. In conclusion, this is the first COS that has been developed for IC. Researchers are encouraged to use this COS when setting up a new clinical trial on IC. It should serve as a minimum of outcomes to be measured and reported. This will benefit evidence synthesis, by enhancing homogeneity of outcomes, and enable evaluation of effectiveness in therapeutic trials of IC.

Investigating the metabolic fingerprint of Celiac Disease – a prospective approach in the PreventCD cohort

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In the development of Celiac Disease (CD) both genetic and environmental factors play a crucial role. The Human Leukocyte Antigen (HLA)-DQ2 and HLA-DQ8 loci are strongly related to the disease, however, HLA-DQ2 and HLA-DQ8 are necessary but not sufficient for the development of CD. Therefore, rising interest lays in examining the mechanisms from the early beginning. Differences in serum and urine metabolic profiles between healthy individuals and CD patients have been reported previously. We aimed to investigate if the metabolic pathways were already altered in young infants, preceding the CD diagnosis. Serum samples were available for 230 four months old infants of the PreventCD study, a multicenter, randomized, double-blind, dietary intervention study. They were all positive for HLA- DQ2 or HLA-DQ8 and had at least one first-degree relative diagnosed with CD. Amino acids were quantified after derivatization with liquid chromatography – triple quadrupole mass spectrometry (MS/MS) and polar lipid concentrations (lyso-phosphatidylcholines, phosphatidylcholines, and sphingomyelins) were determined with direct infusion MS/MS. We investigated the association of the metabolic profile with (1) the development of CD up to the age of 8 years (yes/no), (2) with the HLA-risk groups as defined in Vriezinga et al. (2014), (3) with the age at CD diagnosis, using linear mixed models and cox proportional hazards models. Gender, intervention group, and age at blood withdrawal were included as potential confounder. By the end of 2014, thirty-three out of the 230 children (14%) were diagnosed with CD according to the ESPGHAN criteria. Median age of all children that time was 6.5 years (IQR, 5.9 - 7.1). The frequencies of the five HLA-risk groups (ranging from high to low risk) were: 30 (14%), 18 (8%), 116 (52%), 10 (5%), 50 (23%). Median age at diagnosis was 3.4 years (IQR, 2.4 - 5.2). Testing each metabolite for a difference in the mean between healthy and CD children (1), we could not identify a discriminant analyte or a pattern pointing towards an altered metabolism (Bonferroni corrected $P > 0.05$ for all). Metabolite concentrations (2) furthermore did not differ across the HLA-risk groups. When including the age of diagnosis using (3) survival models, we found no evidence for an association between the metabolic profile and the risk of a later CD diagnosis. In conclusion, the metabolism of CD patients is not altered at young age. Our results suggest that pathways are affected only shortly before CD diagnosis and that furthermore the HLA-genotype does not influence the metabolic profile in young infants.

Human intestinal ischemia reperfusion - Tales from the crypts

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Previously, we demonstrated that the crypt region, and particularly Paneth cells, are affected in the ischemia-reperfusion-injured human small intestine. These cells contribute to host defense by producing antimicrobials and providing a niche for stem cells. Epithelial regeneration from the crypt region is critical for barrier maintenance after intestinal injury. Here, we unraveled the in vivo crypt epithelial response to ischemia-reperfusion injury in man. In 10 patients undergoing pancreaticoduodenectomy, a 6-cm segment of healthy jejunum, to be removed for surgical reasons, was subjected to 45 min of ischemia followed by reperfusion for 0, 30 and 120 min. In addition, a control sample not exposed to ischemia was harvested. Crypt epithelium was isolated from serial frozen sections of 10x4 intestinal specimens, using laser capture microdissection. RNA was harvested and RNA sequencing was used to quantify RNA transcripts. Differential gene expression was analyzed using DESeq2. PathVisio was used to perform pathway statistics. MaSigPro combined with Gene ontology (GO) analysis was applied to follow dynamic changes in gene expression over time. In total, 23,535 transcripts were found to be expressed in crypt epithelium. Known crypt-specific genes (DEF5A, DEF6A, OLFM4) were among the highest expressed, independent of condition. Compared with control, 4,858 genes were significantly changed (adjusted $P<0.05$), the majority during reperfusion. Significantly upregulated pathways after short reperfusion mainly involved cell proliferation, differentiation and cell fate determination (i.e. DNA damage response, Cell cycle, Notch signaling pathway, and BMP signaling and regulation). Downregulated pathways included mostly metabolic processes. After prolonged reperfusion, Apoptosis modulation and signaling, Senescence and autophagy, and MAPK signaling pathway were among the highly upregulated pathways, but also processes linked to tissue remodeling, such as Matrix metalloproteinases, and TGF beta signaling pathway. Shutdown of metabolic pathways remained after prolonged reperfusion. Data are in with the identified dynamic profiles, showing significant enrichment in GO terms Stress response and Cell death for the 99 genes belonging to the cluster of increased expression throughout reperfusion, and in GO term Cell motion of the 72 genes with increased expression only at prolonged reperfusion. In conclusion, this comprehensive analysis of the human intestinal epithelial crypt response to ischemia-reperfusion injury revealed consistently regulated cellular processes, providing leads for new therapeutic targets to protect the crypts and induce a regenerative response.

A Multicentre Randomized Controlled Trial Evaluating E-health for Children and Young Adults with Coeliac Disease – the CoelKids study

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Our aim was to evaluate the effectiveness of on consultations for follow-up of children and young adults with celiac disease (CD). We designed a multicentre randomized controlled trial involving 304 patients aged ≤25 years with CD≥1 year, receiving on (N=156) or traditional consultation (N=148). On consultations included symptom questionnaires and home measurements of growth and anti-transglutaminase-type-2 antibodies (TG2A) using a point-of-care (POC) self-test. Both groups completed questionnaires concerning CD-specific health-related quality of life (HRQOL), gluten free diet adherence and patient-satisfaction. After 6 months, they performed the POC self-test and repeated HRQOL and patient-satisfaction questionnaires. The primary outcome was disease control, defined as negative TG2A. Secondary outcomes were CD-specific HRQOL, patient-satisfaction, and costs. Abdominal pain, lassitude and increased appetite were detected significantly more frequently in the on group than in controls. Growth problems were detected similarly in both groups. TG2A was positive in 2 on participants and 13 controls (POC vs. laboratory, p=0.003). CD-specific HRQOL (1=good; 5=poor) was similar in both groups, but improved after on consultation (3.25 to 3.16, p=0.013; vs. controls 3.10 to 3.23, p=0.810). Patient-satisfaction (1=low; 10=high) was 7.6 in the on group and 8.0 in controls (p=0.001). Mean costs in the on group were €202 less than in the control group (p<0.001). In conclusion, on consultations for children and young adults with CD are cost-saving and increase CD-specific HRQOL. Additionally, patients find these to be satisfactory. The discrepancy between the POC test and laboratory results suggests that the used POC test is not sensitive enough to detect low antibody levels and thereby unsuitable to monitor treated CD.

Fecal incontinence treated by sacral neuromodulation: worldwide largest single center study

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Fecal incontinence (FI) is an embarrassing condition, which leads to social isolation. The first treatment option of FI is conservative therapy. If this fails, surgery is the next step. In the past, only invasive options like a colostomy were possible. In 1995 sacral neuromodulation (SNM) was introduced as a minimal invasive surgical therapy. The last 2 decades literature shows that it's a safe and effective option for treatment of FI. However, long outcome results of large patient cohorts with fecal incontinence treated by SNM are limited. This study shows the long term results of SNM for FI of a single high-volume center. All patients eligible for treatment of fecal incontinence with SNM between March 2000 and July 2015 were evaluated. Fecal incontinence was defined as involuntary fecal loss at least once per week. All patients underwent pre-operative work-up consisting of a defaecography, endo-anal ultrasound and a manometry. Besides they all filled in a 3 week bowel habit diary; objectifying decrease of involuntary fecal loss for the last 3 weeks, increase in time postponing defecation and decrease in defecation frequency. Post-operative follow-up was scheduled at 1, 3, 6 and 12 months after implantation and annually afterwards. Finally, all patients were asked to complete several quality of life questionnaires: Fecal Incontinence Quality of Life Score (FIQL), Short-Form 36 (SF-36) and the Vaizey-score. 374 patients were included (37 male) for a SNM screening-period after failing conservative treatment. In total, 334 (89.3%) patients received a permanent SNM. Mean age was 56.5 (17-82) years and mean follow-up was 85.1 months (3.0-183.4). Data showed a decrease in episodes of fecal loss per 3 weeks from 16.1(3.0-107.0) at base to 3.0 (0.0-24.0) after SNM ($p<0.001$). Time postponing defecation increased from 1.48 minutes at base (0.0-30.0) to 7.5 (0.0-90.0) minutes after SNM implantation ($p<0.001$). Defecation frequency decreased from 2.7 at base (0.3-10.0) to 1.87 (0.3-6.0) defecations per day after SNM implantation ($p<0.001$). SNM was removed due to unsatisfactory results in 63 patients (16.8%). Quality of life evaluation using the SF-36 at different time points during follow-up was not significantly different from the general Dutch population. The FIQL demonstrated no changes in quality of life during follow-up between different follow-up moments. Mean Vaizey score was 11.47 (1.0-22.0). Major incontinence, defined as a Vaizey score of >6, was seen in 103 (79.2%) patients. This study shows long-term efficacy for SNM in the treatment of fecal incontinence with a stable reduction of episodes of fecal loss up to 10 years.

Long-term outcome of constipation treated by sacral neuromodulation

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Constipation resistant for conservative therapy still poses a great therapeutical challenge. Surgical treatment consists of invasive procedures such as a Malone-stoma for antegrade enemas, ileostomy or subtotal colectomy, all associated with significant morbidities and impaired quality of life. Sacral neuromodulation (SNM) is a relative new, minimal invasive therapy modality for patients with constipation. Data on short-term follow-up are promising, however limited data regarding long-term follow-up are available. Long-term results of SNM for constipation in a single high-volume center were evaluated in this study. All patients treated with SNM for constipation between 2004 and 2014 were evaluated. Conservative treatment failed in all patients. Constipation was defined according to the accepted ROME III criteria: ≤ 2 bowel evacuations per week and/or straining to evacuate on >25% of all evacuation attempts and/or sensation of incomplete evacuation after defecation in >25% of all occasions. A preoperative work-up was conducted by a defaecography, an endo-anal ultrasound, a manometry and a 3-week bowel habit diary. The aboved mentioned ROME III endpoints were objectified in this diary. Besides, we asked all patients to fill in several questionnaires: Short-form 36 (SF-36), Cleveland Constipation Score (CCS) and a VAS-score. Post-operative follow-up was scheduled at 1, 3, 6 and 12 months after implantation and annually afterwards. In total, 180 patients refractory to conservative therapy were included (15 male) for SNM screening. 126 (70.0%) patients received chronic SNM. Mean follow-up was 47.4 months (3.0-146.6) and mean age was 39.8 (16-83.3) years. Data showed an increased defecation frequency per 3 weeks from 8.37 (0-74) at base to 19.0 (0-54) after SNM ($p<0.001$). Straining frequency per 3 weeks decreased from 9.6 (0-78) at base to 8.8 (0-98) after SNM ($p=0.83$). Sensation of complete evacuation per 3 weeks increased from 3.1 (0-75) at base to 5.8 (0-95) after SNM ($p=0.14$). Subjective rating of abdominal pain or bloating per 3 weeks decreased from 18.2 (0-42) at base to 10.1(0-37) after SNM ($p<0.001$). CCS decreased from 17.8 (11-27) at base to 8.6 (2-20) after SNM ($p<0.001$). Laxatives and/or enemas remain necessary for 32 patients (25.4%). The SNM-system was removed in 34 patients (25.4%) due to unsatisfactory results. Quality of life assessment using SF-36 showed no difference with the general Dutch population at any moment during follow-up. This study shows fair long-term efficacy of SNM in the treatment for therapy resistant constipation.

Long-term outcomes of a Malone Antegrade Continence Enema (MACE) for the treatment of constipation or fecal incontinence in adults

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The aim of the study is to evaluate the long-term outcomes of a Malone Antegrade Continence Enema(MACE) procedure for constipation or fecal incontinence in adults. If sacral nerve stimulation fails and/or the patient does not prefer a more invasive solution for therapy resistant constipation or fecal incontinence, a Malone stoma could be an option. This retrospective single center study assessed the outcome and quality of life of patients who underwent a MACE procedure between 1997 and 2014. The long-term outcome and the quality of life was objectivated by following questionnaires: SF-36, the current pain level by using the Visual Analogue Scale, Karnofsky scale and Cleveland Clinic Constipation Score or Vaizey Survey, objectivating constipation and fecal incontinence respectively. By using the continence scale by Malone, the overall success rate of the MACE was calculated. Complications were described using the Clavien-Dindo classification. Of the 22 patients who were eligible for inclusion, a response rate of 81.8% was achieved. 18 patients were included; 13 patients with constipation and 5 with fecal incontinence. The mean age was 44 years (S.D. 18.4). The mean follow up was 39 months (S.D. 25.8). According to the Malone continence scale we found an overall success rate of 61.1%. At final assessment the MACE is still functioning in 5 patients (39%) with constipation and in 3 patients (60%) with fecal incontinence. Quality of life of the patients with a MACE was not significantly different compared to the general Dutch population. 50% of all patients (n=9) developed a postoperative complication. Six of these 9 patients developed a major complication. Two patients were reoperated due to stenosis or leakage of the MACE.

In conclusion, the MACE can be effective for the management of constipation and fecal incontinence in adults and could be indicated in patients who prefer no more invasive surgical procedures or a definite stoma. However the success- and morbidity rate should be discussed with the patients thoroughly preoperatively.

The effect of sarcopenia and visceral obesity on the inflammatory response in colorectal surgery

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Sarcopenia and visceral obesity (VO) have been suggested to increase postoperative complications in colorectal surgery by altering the inflammatory response. However, clinical evidence to support this hypothesis is scarce. Here, we investigate the effects of sarcopenia and VO on inflammation and complications following colorectal surgery. A post-hoc analysis was performed in a randomized placebo-controlled trial, in which perioperative gum chewing reduced postoperative complications and inflammation. Sarcopenia and VO were assessed using computed tomography image analysis. Plasma concentrations of interleukin (IL) 8 and soluble tumor necrosis factor receptor 1 (TNFRSF1A) were measured preoperatively and 4 hours after start of surgery. C-reactive protein was determined in plasma via an immunoturbodimetric assay. Clinical data were prospectively registered in a database. In 79 patients, IL-8 was increased in patients with versus without sarcopenia before surgery (0 [0-6.01] vs 0 [0-0] pg/ml, p = 0.011) and after surgery (352 ± 268 vs 239 ± 211 pg/ml, p = 0.048). TNFRSF1A was increased in patients with versus without VO before surgery (0.49 [0.28-1.36] vs 0.40 [0.25-1.19] ng/ml, p = 0.036). Linear regression analysis identified gum chewing (p = 0.034) and sarcopenia (p = 0.034) as independent predictors of postoperative IL-8 concentrations. Gum chewing reduced postoperative IL-8 (215 ± 204 vs 376 ± 249 pg/ml, p = 0.016) and TNFRSF1A (0.75 [0.59-0.94] vs 0.92 [0.70-1.04] ng/ml, p = 0.044) in patients with VO. Sarcopenia and VO did not increase postoperative complications. Sarcopenia increases IL-8 before and early after colorectal surgery, while VO may increase preoperative TNFRSF1A. Gum chewing may reduce the postoperative inflammatory response in patients with VO.

Limited clinical value of CT- colonography in obstructive colorectal cancer

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Background In patients with obstructive colorectal cancer (CRC), visualisation of the entire colon prior to surgery is performed to exclude synchronous double tumours. Therefore, most centers combine CT- colonography (CTC) with the staging CT scan. Aims of our study were to evaluate the yield and clinical implications of CTC in these patients. Methods In this multicenter study, patients with obstructive CRC that underwent CTC and subsequent surgery between April 2013 and October 2015 were included. The outcome of the CTC, its influence on the surgical treatment plan as decided by a multidisciplinary team, and the final pathology report were evaluated. Results 161 patients with obstructive CRC were included. Nine (5.6%) synchronous cancers proximal to the obstructive tumor were suspected with CTC. In 5 of 9, outcome of CTC changed the surgical treatment plan. In 3 of these 5 patients, an extended resection was performed and definitive histology showed 3 synchronous adenocarcinomas (two of three T3 and both visible on staging CT as well and one T2 tumor). In the other two patients the result of CTC was false positive and consequently an unnecessary extended resection was performed in one patient. In the other patient only one tumour was manifest during surgery and the surgeon decided not to perform an extended resection, also post-operative colonoscopy did not reveal a secondary tumour. In the other four of nine patients the CTC did not change the primary surgical plan because the tumor was located within the scheduled resection (right sided (extended) hemicolectomy n=3 and left sided hemicolectomy n=1). Conclusion The yield of CTC was relatively low (7/161, 4.3%). In only three patients (1.9%) CTC correctly changed the primary surgical plan, but in two of these cases the tumour was also visible on the staging CT- scan. Therefore, the clinical value of CTC in obstructive CRC appears to be limited.

The added value of fluorescence imaging during laparoscopic resection of liver tumors

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Recurrence-free survival after resection of primary and metastatic liver tumors is still rather short. Up to 69% of patients with colorectal liver metastases develops recurrent disease and the majority even within 1 year. These high numbers are not entirely explained by incomplete resections, but support the hypothesis that malignant lesions are missed during surgery. Current modalities, such as CT, MRI and laparoscopic ultrasonography (LUS) all have limitations. Fluorescence imaging using indocyanine green (ICG) is an innovative technique enabling real-time intraoperative identification of subcapsular liver tumors. Defective biliary clearance in the transition area between tumor and normal liver tissue and in primary liver tumors results in ICG retention, which can be visualized using a fluorescence imaging system. The aim of the current study was to determine sensitivity of fluorescence imaging for detection of hepatic tumors and to show its added value during laparoscopic resection of liver tumors. Ten mg ICG was intravenously administered one day prior to surgery in patients undergoing resection of primary or metastastatic liver tumors. Fluorescence imaging was performed using the Karl Storz HD fluorescence laparoscope. A total of 21 patients is already included; colorectal liver metastases (n=11), hepatocellular carcinoma (n=5), uveal melanoma liver metastases (n=2), breast cancer liver metastases (n=2) and cholangiocarcinoma (n=1). All patients provided informed consent. Two patients were excluded because their procedure was postponed several days, resulting in low fluorescence signals. A total of 41 lesions, including 25 malignant tumors, were resected in the remaining 19 patients. Of all lesions, sensitivity of the imaging methods was: 79% (CT), 84% (MRI), 60% (inspection), 88% (LUS), 92% (fluorescence imaging). Three additional malignancies (in 2 patients) were identified by fluorescence imaging only. All malignancies could be detected by combining LUS and fluorescence imaging. Positive predictive values were: 76% (CT), 84% (MRI), 58% (inspection), 82% (LUS) and 82% (fluorescence imaging). This study shows the added value of fluorescence imaging during laparoscopic resections of several types of liver tumors. Fluorescence imaging is an easy, effective and safe method. The only requirement is a fluorescence laparoscopic imaging system and ICG. Large series will have to determine if fluorescence imaging truly improves patient outcome, but based on our results we believe this technology should be part of laparoscopic resection of liver tumors.

External biliary drainage following major liver resection for perihilar cholangiocarcinoma: impact on development of liver failure and bile leakage

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Background: Preoperative biliary drainage is considered essential in perihilar cholangiocarcinoma(PHC) requiring major hepatectomy with biliary-enteric reconstruction. However, evidence for postoperative biliary drainage is currently lacking. This study investigated the impact of postoperative external biliary drainage on the development of post-hepatectomy liver failure(PHLF) and biliary leakage. Methods: All patients who underwent major liver resection for PHC between 2000 and 2015 were retrospectively analyzed. The presence of a postoperative external biliary drain was examined and related to postoperative morbidity and mortality, especially biliary leakage and PHLF according to the International Study Group of Liver Surgery (ISGLS) criteria. Results: Eighty-nine out of 125 (71.2%) patients had postoperative external biliary drainage. Base and operative characteristics of the drain and no-drain groups were similar. The overall rate of postoperative complications (Clavien-Dindo Grade III-V) was similar between both groups (52.8% versus 55.6%) but PHLF (ISGLS grade B/C) was more prevalent in the drain group (29.2% versus 5.6%; P=0.004). There was no difference in the occurrence of bile leakage (ISGLS grade B/C) in both groups (31.5% versus 36.1%) and no risk factors for biliary leakage could be identified. On multivariable analysis, postoperative external biliary drainage was identified as an independent risk factor for PHLF (odds ratio 10.33(2.12-50.36); P=0.004), along with preoperative cholangitis and a small future liver remnant. Conclusions: External biliary drainage following major hepatectomy for PHC is associated with an increased incidence of PHLF. As evidence of such drains in the prevention of bile leakage in these patients is lacking, their use should be carefully considered.

Referral of patients with suspicion of perihilar cholangiocarcinoma to a tertiary center: a retrospective audit following introduction of a national management guideline

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Perihilar cholangiocarcinoma (PHC) is a relatively rare tumor requiring a complex treatment strategy. Discrepancies are often noted between management in local hospitals, where patients are initially presented, and the eventual treatment plan in specialized centers. Recently, guidelines have been established that provide recommendations on appropriate management of PHC including resectability assessment and indications for early referral. An important recommendation is not to attempt biliary drainage in patients with suspected PHC. The aim of this study was to evaluate whether referring centers adhere to these recommendations following implementation in 2013. Data were analyzed from all consecutive PHC patients referred to our center between June 2013 and July 2015. Frequency and quality of biliary drainage and imaging at referring centers were assessed. Technical success of biliary drainage was defined as successful bile duct cannulation with achievement of internal biliary drainage. Therapeutic success was defined as a minimum 20% decrease in total bilirubin within one week and drainage of the future liver remnant for potentially resectable tumors. A total of 139 patients with suspected PHC were referred within the study period. In 54% of patients, endoscopic biliary drainage was attempted at local hospitals with a technical and therapeutic success rate of 77% and 49%, respectively, and a complication rate of 44%. Endoscopic retrograde cholangiopancreatography was performed in 10 patients with a seemingly malignant stricture on imaging but without signs of jaundice. In 57% of patients who underwent computed tomography (CT), the used technique was found inadequate for resectability assessment, requiring additional imaging. Magnetic resonance imaging (MRI) was performed in 43% of patients. Eleven patients did not undergo CT or MRI prior to endoscopic drainage. Among 85 (61%) patients considered potentially resectable at our center, 70% of patients with a drainage attempt prior to referral required new procedures before laparotomy. Patients that initially underwent inadequate drainage had significantly more procedures and had a three-week prolonged waiting-time until laparotomy. Conclusion: Suboptimal adjustment remains between management of PHC in referring centers and eventual treatment strategies despite available guidelines, calling for the need of implementation of national health care pathways.

Systematic review of resection rates and outcomes after FOLFIRINOX treatment in patients with locally advanced pancreatic cancer.

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Objective: FOLFIRINOX has demonstrated to prolong survival in patients with metastatic pancreatic cancer but may also benefit patients with LAPC. Previous studies combined results in patients with LAPC and border resectable disease, which hampers the interpretation of resection rates in LAPC patients. The aim of this review is to provide an overview of the (R0) resection rate and clinical outcomes after FOLFIRINOX induction chemotherapy for solely locally advanced pancreatic cancer (LAPC). Methods: A systematic search in PubMed, Embase and the Cochrane library was performed to identify clinical studies published up to August 31st 2015, on FOLFIRINOX for LAPC. Primary outcome was the (R0) resection rate. Other outcomes of interest were treatment regimens, response rate, overall survival (OS), progression free survival (PFS) and toxicity. Results: Fourteen studies involving 365 patients were included. Four studies investigated FOLFIRINOX alone (n = 40) and 10 FOLFIRINOX plus radiotherapy (RT) (n = 325). All studies described FOLFIRINOX modifications or dose reductions in up to 65% of patients. Total response rate after FOLFIRINOX was 23%, resection rate 13% with 70% R0 resections and a median OS of 15.7 months was reported. After FOLFIRINOX plus RT, these outcomes were 30% and 33% , with 78% R0 resections and a improved median OS up to 25 months. Total grade 3-4 toxicity of FOLFIRINIOX was 19% (34/178) and combined with CRT 31% (37/119). Conclusions: FOLFIRINOX treatment seems feasible and safe in patients with LAPC with promising (R0) resection rates and survival. Outcomes seem to improve further when combined with RT, but at the cost of increased toxicity.

Distribution of lymph node metastases in esophageal adenocarcinoma after neoadjuvant chemoradiation therapy: a prospective cohort study

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The distribution of lymph node metastases (LNM) in esophageal adenocarcinoma (EAC) is not well studied. Distribution of metastatic lymph nodes (LNs) may be influenced by tumor location, invasion depth and neoadjuvant chemoradiation therapy (CRT). For the extent of the radiation field, as well as the extent of the lymphadenectomy it is essential to elucidate the distribution pattern of LNM. Aim of our study was to evaluate the distribution pattern of LNM in patients with an EAC after neoadjuvant CRT, and to evaluate the location of LNM in relation to the Clinical Target Volume (CTV) of the radiation field. Between April 1st, 2014 and August 8th 2015, all patients with an EAC undergoing esophagectomy in combination with a 2-field lymphadenectomy were included. Lymph node stations according to the 7th edition of the AJCC classification were excised and separately sent for histopathological examination. The relation between the location of LNM and the CTV was documented by a radiation oncologist, who was blinded for the location of LNM. Patients were excluded if they were diagnosed with an esophageal squamous cell or cardia carcinoma, when no neoadjuvant CRT was administered, or when a salvage or transhiatal resection was performed. Fifty patients (41 male, median age 64 years) were included. A distal and mid EAC was diagnosed in 47 and 3 patients, respectively. A total of 1794 LNs were resected, with a median of 36 (IQR 26-43) LNs per patient. LNM were found in 30 patients (60%) with a median of 3 tumor-positive LNs (range 1-54). Of the total of 164 tumor-positive LNs in the 30 patients with LNM, 107 (65%) were located in the CTV. LNM were observed most frequently in the LNs around the left gastric artery (40%, 12/30 patients), celiac trunk LNs (30%, 9/30), in the paraesophageal LNs (27%, 8/30), in the left paracardial LNs (27%, 8/30), and in the high paratracheal LNs (23%, 7/30). Twelve out of 30 patients (40%) diagnosed with LNM, had tumor-positive LNs both above and below the diaphragm. Conclusion: Esophageal adenocarcinoma frequently metastasizes to both the mediastinal and abdominal lymph node stations. Left gastric artery and celiac trunk lymph nodes have the highest risk for LNM in patients with a distal EAC. Distant nodal metastasis to high paratracheal lymph nodes were also frequently observed in distal EAC, which confirms that LNM distribution pattern in EAC is unpredictable. After neoadjuvant CRT a high percentage of positive lymph nodes are found outside the CTV.

Preoperative chemoradiotherapy versus perioperative chemotherapy for patients with resectable esophageal or gastroesophageal junction adenocarcinoma

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This study compares neoadjuvant chemoradiotherapy (nCRT) to perioperative chemotherapy (pCT) for patients with resectable esophageal or gastroesophageal junction adenocarcinoma. Toxicity, postoperative complications, pathological response and survival were compared between groups. 313 patients with resectable esophageal or gastroesophageal junction adenocarcinoma who were treated in 2 high volume centers with either nCRT (carboplatin/paclitaxel/41.4Gy, n = 176) or pCT (epirubicin, cisplatin and capecitabine, .n = 137) were retrospectively analyzed and compared. The ability to deliver all planned preoperative cycles was higher in the nCRT group (92.0% versus 76.6%, p = 0.000). nCRT was associated with a higher rate of grade 3-4 esophagitis (p = 0.000). pCT was associated with a higher rate of grade 3-4 thromboembolic events (p = 0.000), febrile neutropenia (p = 0.038), nausea (p = 0.001), vomiting (p = 0.001), diarrhea (p = 0.001), hand foot syndrome (p = 0.005), mucositis (p = 0.005), cardiac complications (p = 0.002), and electrolyte imbalances. Postoperative cardiac complications were higher in the nCRT group (17.4% versus 6.9%, p = 0.006). All other postoperative complications were comparable. The pathologic complete response (pCR) rate was 15.1% following nCRT and 6.9% following pCT (P = 0.000). Radicality of surgery was comparable (R0: 93.0% versus 91.6%, p = 0.644). Median overall survival was 35 months after nCRT versus 36 months after pCT (p = 0.747). Conclusion: nCRT and pCT lead to comparable outcomes in terms of radical resection rates and overall survival. However, neoadjuvant chemoradiotherapy is associated with less toxicity and higher pCR rates.

Feasibility of long-course chemoradiotherapy plus surgery for patients with cT4b oesophageal carcinoma

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Treatment of cT4b (unresectable) oesophageal carcinoma usually consists of definitive chemoradiotherapy (dCRT). However, outcome after dCRT in these patients is poor. The aim of this study was to assess the feasibility of oesophagectomy following long-course chemoradiotherapy in patients with cT4b oesophageal cancer. Patients with cT4b oesophageal carcinoma, as determined by endoscopic ultrasound and (PET-)CT, were eligible for this study. After written consent patients were treated with weekly carboplatin+paclitaxel with 50.4 Gy radiotherapy in 28 fractions for 5.5 weeks followed by a transthoracic oesophagectomy if feasible. From July 2011 through March 2013, 17 patients were enrolled. Six patients did not undergo surgery because of detection of distant metastases during/after CRT (n=3), unwillingness to undergo surgery (n=1), death before dCRT started (n=1) or revision of histology (n=1: neuroendocrine tumour). Of the 13 patients who completed dCRT, 3 patients experienced major hematologic toxicity (grade 3). A radical (pR0) resection was achieved in 9 of 11 patients. Postoperative complications occurred in 9 patients. A reoperation was performed in 2 patients and 2 patients died in hospital after surgery (due to massive bleeding and pulmonary embolism). In 3 of the 9 patients without in-hospital mortality recurrent disease was detected after a mean interval of 17 months. Median overall survival in these 9 patients was 26.2 months. Conclusions: In a small majority of patients with cT4b oesophageal carcinoma R0 resection can be accomplished after chemoradiotherapy. However, this treatment is associated with considerable complications and should therefore only be executed on physically fit patients.

Amino acid-based diet induces histological remission, reduces clinical symptoms and restores esophageal mucosal integrity in adult eosinophilic esophagitis patients

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The pathophysiology of eosinophilic esophagitis (EoE) is mainly driven by food allergy, whereby an increase in mucosal permeability might facilitate transepithelial allergen flux in the esophagus. Dietary treatment with elimination of disease-triggering allergens is a promising treatment option since it can provide a long-term and drug-free solution. Studies on the effect of elemental diets in adults are scarce and unpalatability makes adherence challenging. The aim of this study was to assess the effect of a ready-to-drink amino acid-based formula (Neocate, Nutricia) on eosinophilic inflammation and to study its effect on the integrity of esophageal mucosa. Additionally, adherence to this formula was evaluated. In this prospective study 21 adult patients with active EoE, confirmed by biopsy specimen with ≥15 eosinophils per high power field (HPF), were included. Patients underwent endoscopy before and 4 weeks after diet. Clinical disease activity and patient's adherence to the diet were evaluated by questionnaires. Histological disease activity and endoscopic signs ,using EoE Reference Score for Endoscopic Abnormalities (EoE-EREFs), were scored by physicians blinded to the patient's disease status. The esophageal mucosal impedance (MI) and resistance were measured by electrical tissue impedance spectroscopy (ETIS) in vivo, and by transepithelial electrical resistance (TER) in vitro. Ussing chambers were used to estimate esophageal permeability by measuring transepithelial flux of fluorescently-labelled molecules rhodamine (40 kDa) and fluorescein (0.3 kDa). All measurements were compared to 8 age-matched healthy controls. Peak eosinophil count decreased significantly after the diet from 40 to 9 per HPF ($p<0.001$). In total, 17 (81%) of the included patients completed the diet, 12 (71%) patients showed complete histological response (≤15 eosinophils) and another 4 (24%) patients showed partial histological response (≥50% decrease). Symptoms decreased substantially and 15 patients (88%) became completely asymptomatic ($p<0.001$). A strong improvement of endoscopic signs was observed ($p<0.001$). Esophageal permeability decreased and MI increased significantly after treatment ($p<0.05$), and both values were comparable to those seen in healthy controls. Although the TER improved significantly after diet ($p<0.005$), it did not reach levels similar to those in HC. Conclusion: This study strongly indicates that in adults with EoE, a ready-to-drink amino acid-based diet reduces eosinophilic inflammation, induces clinical remission and restores the esophageal mucosal integrity. Patient's adherence to this diet is better than previously described.

Relative intercellular space area in gastroesophageal reflux disease: a new standardized method for the evaluation of the intercellular space diameter

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Dilation of intercellular spaces (DIS) in esophageal mucosa is considered as an early histological marker for impaired mucosal integrity in patients with gastroesophageal reflux disease (GERD). Evaluation of intercellular space diameter (ISD) in esophageal biopsies is classically performed by placement of 10 random transects in 10 transmission electron microscopy (TEM) photographs per subject. This method is time consuming and may not take the irregularity of the delineation of the intercellular space fully into account. In the present study we present the "relative intercellular space area" as an alternative method for the evaluation of ISD and compare it to the classical method. Methods: 21 patients with chronic GERD (13 male, mean age 54 (range 28-77) and 10 healthy controls (5 male, mean age 35 (range 21-65)) were enrolled. Esophageal biopsies from macroscopically normal mucosa were obtained during endoscopy at 5 cm above the gastroesophageal junction and prepared for TEM. TEM-photographs were obtained from the basal layer of the epithelium. ISD was assessed in 10 TEM-photographs per subject using the classical (ISDc) method and in 3 TEM-photographs using the alternative (ISDa) method by two investigators. ISDa was assessed by measuring the area of the intercellular space around the cells divided by its corresponding length, using custom-written image analysis software in IGOR Pro (WaveMetrics Inc., Oregon, USA). Correlation of ISD values obtained with both methods as well as intra- and interobserver agreement were evaluated. Results: ISDa-values showed a high correlation with corresponding ISDc-values (r:0.81, p<0.001). However, ISDc-values were significantly larger when compared to ISDa-values (1.35 µm ± 0.05 vs. 0.90 µm ± 0.04, p<0.001). Both methods showed an excellent intraobserver agreement, with comparable Ä¸-values (ISDa: 0.91 and ISDc: 0.92). Interobserver agreement of both methods was good, with comparable Ä¸-values (ISDa: 0.81 and ISDc 0.80). The analysis per microphotograph using the ISDa method was more time consuming (ISDa: 119 s ± 8 vs. ISDc: 63 s ± 2, p<0.001). Comparing the time consumption of the full analysis (10 microphotographs per subject with ISDc versus 3 microphotographs with ISDa), ISDa was less time consuming (ISDa: 350 s ± 13 vs. ISDc: 628 s ± 15, p<0.001). Conclusion: Evaluation of the intercellular space diameter using the relative intercellular space area showed a high intra- and interobserver agreement and a strong correlation with ISD values obtained with the classical assessment. We conclude that this less time consuming method can be used to reliably assess the intercellular space diameter in GERD patients.

A randomized, phase I, double-blind, crossover study on pharmacokinetics of peppermint oil capsules in healthy volunteers: colon-targeted-delivery versus enteric-coating.

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Peppermint oil (PO) has been shown to reduce abdominal pain in patients with Irritable Bowel Syndrome (IBS). Menthol, the main constituent of PO, induces intestinal smooth muscle relaxation and desensitizes nociceptive nerve afferents. Enteric-coated (EC PO) capsules that release PO mainly in the small intestine are commercially available. In order to increase local, colonic anti-nociception, a colon-targeted-delivery peppermint oil (CTD PO) capsule has been developed. The aim of this study was to compare pharmacokinetic parameters of both formulations and to evaluate safety and tolerability.
In this randomized, double blind, placebo-controlled study, subjects received 182 mg of either EC PO or CTD PO in a crossover design with >14 days washout period in between. After base measurements and drug administration, blood samples to determine menthol-glucuronide (menthol is rapidly metabolized to menthol-glucuronide), blood pressure and heart rate measurements were collected at several time points. Side effects were evaluated using questionnaires. The primary outcome was T_{max}: time to reach peak menthol-glucuronide concentration in plasma. Eight healthy volunteers (50% female), aged between 20 and 65 years (median 22.2, IQR 20.8-28.8) were included. The T_{max} of CTD PO was significantly longer (in all volunteers) compared to EC PO with a median (IQR) of 360 (360-405) versus 180 (120-180) minutes, respectively, $p<0.05$. The Area Under the menthol-glucuronide plasma concentration time Curves were smaller with a median (IQR) of 2331µg*h/L (2006-2510) for CTD compared to 2623µg*h/L (2471-2920) for EC capsules, $p<0.05$. No significant differences were found in peak concentrations and elimination half-lives. No differences in vital signs or side effects were observed between both regimens. Remarkably, subjects noticed alterations in fecal odor after CTD PO but not after EC PO, again pointing to more distal delivery with CTD PO. In conclusion, the CTD PO has a significantly delayed peak menthol-glucuronide concentration, and is thereby assumed to release peppermint oil in the more distal part of the intestine. This may enhance therapeutic efficacy of PO as the application of the CTD results in increased exposure to the colonic mucosal afferents. These results encourage our randomized controlled trial with CTD PO in IBS patients.

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Effect of running on gastroesophageal reflux and reflux mechanisms

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Symptoms of gastroesophageal reflux disease (GERD) are common among athletes and can have a negative impact on athletic performance. It has been shown that strenuous exercise can induce excessive reflux, both in patients with GERD and in asymptomatic healthy subjects, suggesting that strenuous physical activity can be a risk factor for GERD. Currently, the mechanisms underlying excess reflux during exercise are still poorly understood. The aim of our study was to investigate the effect of exercise on reflux severity and to examine the underlying reflux mechanisms. Both a high-resolution manometry (HRM) and a pH-impedance catheter were placed in healthy subjects with frequent physical activity. A meal was given after placement of both catheters after which base pH, impedance and pressure signals were recorded for 30 minutes while the subject was standing. Following this, subjects ran on a treadmill for 30 min at 60% of maximum heart rate, followed by a short rest period and another 20 min period of running at 85% of maximum heart rate. In the last few minutes of each period, ten standardized 5-ml water swallows took place to quantify esophageal motility. Ten healthy sporty volunteers (4 females, age 21-41) were included in the study. Exercise led to a higher percentage of time with a pH<4 (medians: rest; 0%, 60% HRmax; 0.69% (p=0.018), 85% HRmax; 0.87% (p=0.018). A higher frequency and duration of reflux episodes was noted during exercise. Moreover, exercise resulted in a significantly lower distal contractile integral (medians: rest; 407 mmHg·s·cm, 60% HRmax; 144 mmHg·s·cm, 85% HRMax; 32 mmHg·s·cm (p=0.047)), decreased duration of peristaltic contractions, and shorter distal latency. The average and maximum abdominal pressure both significantly increased during exercise, while the minimal esophagogastric junction pressure significantly decreased. Importantly, the percentage of transient lower esophageal sphincter relaxations (TLESRs) which resulted in reflux significantly increased during exercise and all but one reflux episode occurred during TLESRs. In 6 subjects (60%) a hiatus hernia was detected during the exercise period but not during rest. Conclusion: Running induces gastroesophageal reflux almost exclusively through TLESRs. These are not more frequent during exercise, but are more often associated with a reflux episode, possibly due to an increased abdominal pressure, the up and down body movement, a change in esophagogastric junction morphology and a decreased esophageal clearance during exercise.

Effect of Electrical Stimulation Therapy of the lower esophageal sphincter on post-prandial reflux mechanisms in GERD patients

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Background: Two open-label trials have shown that Electrical stimulation therapy (EST) of the lower esophageal sphincter (LES) (LES-EST) significantly improves esophageal acid exposure and symptoms in GERD patients. However, the underlying antireflux mechanism(s) of LES-EST remain(s) unclear. The aim of this study is to evaluate the effect of EST on postprandial reflux mechanisms, especially on transient LES relaxations (TLESRs). Methods: We studied 10 chronic GERD patients with abnormal acid exposure (pH<4.0 during > 6% of time) and hiatal hernia <3 cm (3 males; mean age 53, range 32-66 yrs). Bipolar stitch electrodes and a pulse generator (EndoStim BV, The Hague, Netherlands) were implanted during laparoscopic surgery. LES-EST was delivered at 20 Hz, 220 μs, 5 mA in 12 30-minute sessions. Postprandial reflux mechanisms were studied before and 3 months after EST-implantation, using a combined stationary high-resolution manometry (HRM) and impedance-pH monitoring. Patients consumed a standardized high caloric (500 kCal) meal (cheeseburger, crisps and 200 ml orange juice), followed immediately by a 90-minute measurement. Patients remained in a semi-recumbent position during the measurement and were not allowed to sleep.
Results: The majority of postprandial reflux episodes occurred during TLESRs, both before (77%) and after (63%) EST-implantation. After LES-EST, a significant reduction in the total number of TLESRs (from 9.1 (4.0) to 5.6 (3.2), p<0.01) and in the number of TLESRs associated with reflux episodes (from 6.7 (4.1) to 3.8 (3.6), p=0.04) was observed. Total postprandial reflux episodes were not significantly altered by LES-EST (from 9.0 (5.1) to 6.8 (6.1), p=0.14); however, the number of reflux episodes facilitated by TLESRs was significantly reduced (7.0 (3.6) to 3.9 (3.4), p=0.03). The number of reflux episodes induced by other mechanisms (such as abdominal straining or swallow-induced) were unaffected by the treatment. EST showed no effect on the duration of TLESRs (from 17.5 (4.3) s to 14.4 (5.7) s, p=0.14) nor on LES resting pressure (from 19.2 (11.3) mmHg to 21.1 (14.9) mmHg, p=NS). Conclusion: Electrical stimulation therapy of the LES reduced the total number of postprandial TLESRs as well as the number of TLESR-associated reflux episodes in GERD patients. These results suggest that the effect of LES-EST on acid exposure and GERD symptoms is primarily TLESR-mediated.

Decreased esophageal barrier integrity correlates with esophageal eosinophilia and predicts disease activity in adult patients with eosinophilic esophagitis

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In patients with active eosinophilic esophagitis (EoE) the esophageal barrier integrity is decreased. It has been suggested this could facilitate transmucosal allergen passage, and provoke allergic inflammation. The precise association between esophageal barrier integrity and disease activity, defined as the presence of more than 15 eosinophils per high power field (HPF), is unknown. The aim of this study was to determine whether a decreased esophageal integrity is correlated with esophageal eosinophilia and whether esophageal barrier integrity predicts disease activity in adult patients with EoE. We included 39 EoE patients (74% male) with a median age of 45 years (interquartile range 32-48 years). All patients underwent an endoscopy at base and in patients with active EoE (≥15 eosinophils per HPF) a second or third endoscopy was performed 4-6 weeks after treatment (pharmaceutical or dietary). In total 96 endoscopies were performed, 65 in patient with active EoE and 30 in EoE patients in remission. Esophageal barrier integrity was measured by multiple techniques: during endoscopy mucosal impedance (MI) was measured by electrical tissue impedance spectroscopy (ETIS) and in Ussing chambers transmucosal electrical resistance (TER) and the flux of small (0.3 kDa) fluorescein and large (40 kDa) rhodamine molecules through esophageal biopsies were measured. In patients with active EoE compared to patients in remission, TER and MI were significantly decreased ($p<0.001$) whereas permeability for fluorescein and rhodamine was significantly increased ($p<0.001$). Peak eosinophil count was negatively correlated with MI ($r = -0.578$, $p<0.001$) and TER ($r = -0.610$, $p<0.001$), and positively to transepithelial flux of fluorescein ($r = 0.483$, $p<0.001$), and rhodamine ($r = 0.460$, $p<0.001$). To distinguish patients with active EoE from patients in remission the optimal cut-off values using ROC curves were 82.62 ($â„¦\cdot cm^2$) for TER (sensitivity 89% and specificity 64%), 5879.50 ($\Omega \cdot m$) for MI (sensitivity 78%, specificity 76%), 998.15 ($\mu mol/cm^2/h$) for fluorescein (sensitivity 60%, specificity 80%), and 14.96 ($\mu mol/cm^2/h$) for rhodamine (sensitivity 68%, specificity 83%). All measurements of esophageal barrier integrity were found to have high positive (between 80% and 87%) and moderate negative (between 55% and 76%) predictive values for histologically defined disease activity. In conclusion, in adult EoE patients a decreased mucosal integrity correlates strongly with esophageal eosinophilia. Additionally, esophageal mucosal barrier integrity measures are able to predict disease activity.

Mucosal integrity and sensitivity to acid of the proximal esophagus in patients with gastroesophageal reflux disease

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Reflux episodes that extend to the proximal esophagus are more likely to be perceived. This suggests that the proximal esophagus is more sensitive to acid compared to the distal esophagus. Our hypothesis is that the enhanced sensitivity of the proximal esophagus can be related to more pronounced impairment of mucosal integrity in this part of the esophagus. Therefore, this study aimed to assess acid sensitivity and mucosal integrity of the proximal and distal esophageal segments separately in patients with gastroesophageal reflux disease (GERD) and to investigate the relationship between these parameters. We included patients with heartburn and evidence of GERD on ambulatory pH-impedance measurement. After PPI washout of 7 and 10 days respectively, an esophageal hydrochloric acid perfusion test measuring segmental acid sensitivity proximally and distally in the esophagus (3 and 18 cm above the Z-line) and an upper endoscopy with biopsies at both levels were performed. During endoscopy, electrical tissue impedance spectroscopy was performed at the two levels and biopsies were taken from macroscopically unaffected mucosa. Biopsies were used to measure dilation of intercellular spaces with transmission electron microscopy as a morphological measure of impaired integrity and to investigate transepithelial electrical resistance and transepithelial fluorescein permeability in Ussing Chambers as a functional measure of mucosal integrity. We included 12 GERD patients (mean age 48 years, range 28-65, M:F 4:7). Lag time to heartburn perception was shorter after proximal acid perfusion (mean (95% CI) 0.8 minutes (0.16 - 1.44)) than after distal acid perfusion (3.5 minutes (2.2 - 4.8)); log rank $p < 0.01$. In vivo extracellular tissue impedance was significantly lower in the distal esophagus (mean (95% CI) 4914 Ω.m (3206 - 8705)) compared to the proximal esophagus (8926 Ω.m (5805 - 14069)); $p < 0.01$. Transepithelial fluorescein permeability was significantly higher in the distal than the proximal segment (median 2051 $nmol \cdot cm^{-2} \cdot h^{-1}$ and 368 $nmol \cdot cm^{-2} \cdot h^{-1}$); $p < 0.05$. Transepithelial electrical resistance, intercellular space ratio and maximum heartburn intensity were not significantly different between the proximal and distal esophagus. Conclusion The proximal segment of the esophagus in GERD patients off PPI is more rapidly sensitive to acid perfusion while the distal esophagus shows a more pronounced impairment of mucosal integrity. These findings suggest that the enhanced sensitivity to acid in the proximal esophagus is not explained by increased mucosal permeability.

Management of recurrent symptoms after peroral endoscopic myotomy in achalasia

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Peroral endoscopic myotomy (POEM) is an emerging, minimally invasive treatment for achalasia. It is a safe procedure, with a very good short-term success rate. Still, failure after POEM treatment with persistent or recurrent symptoms does occur. It is currently not known how these patients can be managed best. The objective of this study was to investigate the efficacy of different retreatments for achalasia patients suffering from recurrent symptoms after POEM and to identify predictors of success of retreatment after POEM. In three tertiary care hospitals in Europe and the USA all achalasia patients with recurrent or persistent symptoms after POEM (Eckardt symptom score > 3) were identified between 2011 and 2015. Retreatment success was defined as an Eckardt score ≤ 3 persisting for at least six months. Retreatment failure was defined as Eckardt > 3, also if patients developed recurrent symptoms after a symptom-free period. From a cohort of 418 patients that underwent POEM, we identified 44 achalasia patients (14 females; mean age 42 years, range 17-84) with an Eckardt > 3 after POEM. Achalasia subtype distribution before any treatment was: type I in 24 patients (55%); type II in 15 patients (34%); and type III in 5 patients (11%). Before POEM, most patients had either received no treatment (22 patients; 51%) or pneumodilatation (16 patients; 37%). Median relapse time of symptoms after POEM was 6 months (IQR 3-16). The majority of patients (36 patients; 85%) received one or more retreatments after POEM (Table 1). The other eight patients started a modified diet or refused treatment. Overall, in 18 patients (50%), the final retreatment was effective for at least six months, but efficacy differed for the choice of treatment. Laparoscopic Heller myotomy was effective in 63% of patients, and re-POEM in 56% of patients. Pneumatic dilatation (PD) with a 30 mm balloon was never long-term effective, PD 35 mm was effective in 23% of patients. When PD 35 mm was not effective, PD 40 mm also was not effective. No complications of retreatments occurred. Using logistic regression analysis, no independent predictors of retreatment success could be identified. Conclusion In our cohort of patients with POEM failure, laparoscopic Heller myotomy and re-POEM showed a modest efficacy, whereas pneumodilatation showed a poor efficacy. No independent predictors of retreatment success were identified.

The Secca® procedure in faecal incontinence: a randomised sham controlled clinical trial.

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Background: Controlled delivery of radio frequent energy (Secca) has been suggested as treatment for faecal incontinence (FI). Objective: The aim of this study was to determine whether clinical response to Secca procedure is superior to response to sham in patients with fecal incontinence. Design: randomised sham controlled clinical trial Setting: outpatient clinic Patients and methods: 40 patients with faecal incontinence in which full conservative management had failed where randomised to receiving either Secca or sham procedure. Interventions: 2008-2014 Main Outcome Measures: FI was scored using the Vaizey incontinence score (VS) at base and at 6 months. Impact of FI on quality of life was measured using the faecal incontinence quality of life scale (FIQL). Anorectal endosonography and manometry was performed at base and at 3 months. Results: After Secca the VS decreased a mean 3.6 points, from 17.7 (SD 3.1) to 14.1 (SD 4.1), $p < 0.001$. In patients undergoing sham VS decreased a mean 1.2 points from 17.6 (SD 3.0) to 16.4 (SD 4.4), $p = 0.01$, difference between groups, $p = 0.002$. There were no alterations in anorectal endosonography or manometry. There were no serious complications. In the FIQL scores, coping improved in both groups. There were no improvements in depression, embarrassment or lifestyle. Conclusion: The secca procedure decreases experienced faecal incontinence, however the majority of patients remained moderately to severely incontinent of faeces.

HOX gene expression in Barrett's esophagus resembles that of the colon, can be modulated by acid and bile exposure, and induces Barrett's specific gene products.

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HOX genes encode master regulators of anterior to posterior specification in organogenesis and tissue homeostasis. The 3' to 5' sequence of HOX genes corresponds to the sequence in which they act along the anterior to posterior axes of the body. This property is termed collinearity and links clustering to function. HOX collinearity has not been thoroughly investigated in the human gut. The morphology of metaplastic Barrett's Esophagus (BE) resembles a posterior phenotype, as observed in the colon. Therefore, the aim of this study was to characterize HOX expression in BE and along the gut. Furthermore, potential causes and consequences of HOX gene aberrations were investigated. Expression of 39 HOX genes was determined by RT-qPCR in tissues taken from 9 locations along the gut of 3 control patients and in squamous and BE tissues of 13 BE patients. Squamous esophageal cell lines HET-1A and EPC2-hTERT were exposed to acid and bile to simulate gastro esophageal reflux disease (GERD). HOXA13 RNA-ISH was performed and HOXA13 was transduced and overexpressed in EPC2-hTERT. HOX cluster gene expression differed significantly along the gut. In general, HOX gene expression was highest in the colon with exception of the expression of the HOXC cluster. HOXA cluster gene expression was the highest compared to other clusters. The most posterior highly expressed HOX cluster members in the esophagus of the control patients were A7, B7, C8, and D8 and in the rectum A13, B13, C10, and D13. BE tissue was characterized by upregulation of HOXA10, 11, and 13, B3, 6, 7, 8, 9, and 13, and C6, 9, 10, and 11. Downregulated in BE were HOXA1, 4, and 7. For clusters A and B, the HOX pattern observed in BE was similar to that seen in colon epithelium. HOXA and B cluster expression patterns adhere to the collinear property and have similar expression patterns in BE when compared to the colon. Therefore, the posterior members of these clusters could well be responsible for the posterior morphology observed in BE. HOXA13, highly overexpressed in BE, was chosen for further studies. HOXA13 mRNA was visualized in the epithelial cells of BE tissue. Exposure of two esophageal cell lines to acid and bile led to up regulation of HOXA13. Furthermore, induced overexpression of HOXA13 in turn upregulated expression of KRT7 and COX2, both involved in BE. Conclusion - HOX gene collinearity is present along the adult human gut. HOX gene rearrangements are found in BE, resulting in a colon like HOX expression pattern. Acid and bile exposure leads to upregulation of the posterior HOXA13 in an in vitro GERD model. Furthermore, HOXA13 overexpression induces BE specific gene products.

HOXA9 is overexpressed in colonic adenomas and causes an increase in cell growth

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Colonic adenomas are premalignant epithelial tumors with glandular origin. Identifying the molecular aberrations in this tissue may help to understand its malignant potential and could lead to better understanding of colorectal cancer development.The mammalian HOX clusters encode regulators of embryonic anterior to posterior specification and are important for the formation of tissues, structures and organs. Besides a function in embryology, HOX genes act as oncogenes in various situations. For example, HOXA13 overexpression predicts poor outcome for patients with cancer of the esophagus, stomach, and liver. In colon cancer, literature provides evidence for an upregulation of HOXA9 in (pre)malignant tissue. Interestingly, in a portion of acute myeloid leukemias (AML) a translocation encoding the NUP98-HOXA9 oncogene gives overexpression of HOXA9. This HOXA9 expression is the factor most strongly correlated with poor prognosis in AML. HOXA9 also promotes epithelial ovarian cancer growth. Therefore, the aim of this study was to compare the expression of HOXA9 between colonic adenoma tissue and location matched control colon tissue and, if increased expression was present, to evaluate potential effects of increased HOXA9 expression on cell growth.
Biopsy samples from colon tubular adenomas and location matched colon tissue were collected in patients undergoing colonoscopy. RT-qPCR was used to quantify the expression of HOXA9 in relation to UBC, TPT1, GAPDH, and RP2. Data were analyzed using the efficiency$^{\Delta\hat{a}^{\dagger}\hat{a}^{\dagger}Ct}$ method. In addition, Caco-2 cells were transduced with HOXA9 using a lentiviral vector, enabling inducible expression. An empty vector was used as a control. An automatic cell counter and MTT assay were used to determine cell number and total cell pool. RT-qPCR was used to analyze expression of genes described as being regulated by HOXA9 in the literature. HOXA9 expression in tubular adenomas of the colon was significantly increased compared to location matched control tissue, in with previous reports in literature ($p=0.04$). HOXA9 overexpression in Caco-2 cells led to increased cell numbers when assessed with an automatic cell counter ($p=0.004$) and to increased metabolic activity, and thus total cell pool, when assessed with an MTT assay ($p<0.001$). Downregulation of tumor suppressor genes and upregulation of oncogenes were found in the model system as a result of HOXA9 overexpression. Conclusion: HOXA9 expression is increased in colonic adenomas. The overexpression of HOXA9 is an early event in colonic oncogenesis and leads to growth of the cell pool. Further research is needed to establish its role in cancer progression and prognosis.

Endoglin expression on cancer-associated fibroblasts plays an important role in cancer progression and metastasis

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The contribution of the tumor microenvironment has become recognized as a major factor influencing colorectal cancer (CRC) growth and invasiveness. The tumor microenvironment consists of endothelial cells, immune infiltrate and cancer associated fibroblasts (CAFs). Endoglin, a transforming growth factor-ß (TGF-ß) co-receptor is highly expressed on angiogenic endothelial cells in solid tumors. Therefore, targeting endoglin is being explored in clinical trails for anti-angiogenic therapy. However, endoglin is not only expressed on angiogenic endothelial cells, but we observed endoglin expression on CAFs at the invasive border of CRC. In this project, the pathophysiologic significance of endoglin with respect to CAFs was explored. High endoglin expression on CAFs at the invasive border was significantly associated with decreased metastasis-free survival of stage I/II CRC patients. CAFs isolated from CRC patients expressed high levels of endoglin and showed invasion through a collagen-I matrix. Treatment with TRC105, an endoglin neutralising antibody, inhibited migration towards tumor cells in vitro. The importance of endoglin for CAFs was further confirmed by experiments showing that shRNA mediated knockdown of endoglin in CAFs results in a lethal phenotype. Therefore, we used mouse embryonic fibroblasts (MEFs) isolated from endoglin LOXp mice. CRE-Recombinase-mediated deletion of endoglin in MEFs resulted in less migration in transwell migration assays. To study the role of endoglin in a tumor model, we established a novel solid tumor model in zebrafish incorporating fibroblasts in the tumor microenvironment. Mouse MC38 CRC cells were injected in the heart cavity (not into circulation) of zebrafish embryos, in presence or absence of MEFs. Co-injection of endoglin-expressing MEFs and MC38 cells resulted in a significant decrease in survival and was accompanied by an increase in CRC cells infiltrating the liver. Next we generated a fibroblast-specific endoglin knockout mouse. Colorectal tumors were chemically induced by azoxymethane, while tumor formation was accelerated by dextran sodium sulphate-induced colitis. Surprisingly, fibroblast-specific deletion of endoglin led to significantly more tumors in the distal part of the colon. Further studies indicate an increase in infiltrating immune cells in the knockout group compared to the wildtype animals. Together our data suggest a potential important role of endoglin on CAFs in CRC, both in cross talk with epithelial cancer cells and with infiltrating immune cells.

Grp78 heterozygosity in the intestinal epithelium protects against adenoma formation

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In the intestinal epithelium, differentiation of stem cells is required for normal organ function. Perturbed stem cell differentiation underlies tumorigenesis. We have previously shown that endoplasmic reticulum (ER) stress, by knockout of the critical chaperone Grp78, results in forced differentiation of intestinal epithelial stem cells and may thereby protect against tumorigenesis. ER stress induced stem cell differentiation occurs through activation of the unfolded protein response (UPR). However, since no stem cells remain upon deletion of Grp78, this situation is incompatible with normal organ function. Previously, Grp78 heterozygosity has been used to induce moderate levels of ER stress. We set out to determine the phenotype of heterozygous deletion of intestinal epithelial Grp78 and its possible effects on adenomagenesis. We generated animals in which injections with tamoxifen resulted in heterozygous deletion of Grp78 specifically from intestinal epithelial cells (IEC, $Grp78^{fl/+(IEC)}$). For adenoma induction we used $Apc^{fl/+(IEC)}$ animals, that develop adenomas throughout the intestinal tract after recombination. To monitor recombination efficacy, we crossed LacZ reporter alleles into all mice. Upon staining with X-gal, all recombined cells become blue. We first analyzed the phenotype of $Grp78^{fl/+(IEC)}$ animals and Grp78 wild type littermate controls during homeostasis. Counting X-Gal stained sections, recombination in all animals was excellent with >95% of crypts recombined. Compared to controls, proliferation in $Grp78^{fl/+(IEC)}$ animals was unaltered, as judged by BrdU incorporation. Gene-expression analysis by means of quantitative RT-PCR showed no change in mRNA levels of stem cell markers Lgr5, Olfm4 or Ascl2 compared to controls. We found no changes in the expression of a set of UPR target genes showing that heterozygous deletion of Grp78 has no observable phenotype in a situation of homeostatic epithelial turn over. We next analyzed adenoma numbers in $Grp78^{fl/+}$-$Apc^{fl/+(IEC)}$ animals and $Apc^{fl/+(IEC)}$ controls. After 100 days, $Grp78^{fl/+}$-$Apc^{fl/+(IEC)}$ animals had a marked reduction in adenoma burden compared to $Apc^{fl/+(IEC)}$ mice (1.43 vs. 3.33; $P = 0.0054$). Conclusion: Heterozygous deletion of Grp78 from the intestinal epithelium results in unaltered proliferation and expression of stem cell markers. However, adenomagenesis is markedly reduced in compound heterozygous $Grp78^{fl/+}$-$Apc^{fl/+(IEC)}$ animals. These results show that deletion of a single Grp78 allele results in protection against intestinal tumorigenesis without affecting the healthy stem cell pool.

Loss of the Bone Morphogenetic Protein pathway in mesenchymal myofibroblasts initiates polyp formation in the mouse intestine

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Bone Morphogenetic Protein (BMP) signalling is essential for intestinal homeostasis. BMP pathway mutations cause Juvenile Polyposis Syndrome leading to hamartomatous polyps with an abundant mesenchymal component in addition to the epithelial alterations. In contrast, in adenomatous polyps the neoplastic epithelial cells are the predominant component. BMP receptor 1a (BMPR1a) knockout in both the intestinal epithelium and mesenchyme in mice initiates hamartomatous polyp formation, while specific epithelial BMPR1a knockout does not. This suggests that mesenchymal BMPR1a loss may be crucial for polyp formation but how this occurs and which mesenchymal cells are responsible is unknown. This study aims to identify whether disruption of BMP signalling specifically in various intestinal mesenchymal cell types leads to polyp formation. VeCad-Cre*BMPR1a-floxed (BMPR1a knockout in endothelial cells) and SM22-Cre*BMPR1a-floxed (BMPR1a knockout in myofibroblasts) were bred. These mice were also crossed with a YFP reporter. To induce recombination Tamoxifen was administered for 5 consecutive days. The mice were sacrificed at 1 month, 6 or 12 months after induction. Cre-negative BMPR1a-floxed mice injected with Tamoxifen served as controls. Immunohistochemistry was performed to investigate recombination (YFP, SM22, CD31 & BMPR1a), proliferation (Ki67), BMP signalling activity (pSMAD1,5,8), Wnt signalling (β-catenin) and cell markers (αSMA & Vimentin). Conditional knockout (cKO) of BMPR1a in endothelial cells did not induce polyp formation in the intestine, but minor epithelial changes including increased crypt fissioning were seen. Loss of BMPR1a in endothelial cells was complete in the cKO-group after 1 month but reappeared partly after 6 months and completely after 12 months. In contrast, cKO of BMPR1a in myofibroblasts showed a high number of polyps compared with the control group (median cKO=23 vs control=0, p=0.006) after 6 and 12 months. Most polyps were present in the small intestine and showed a serrated phenotype including a saw tooth configuration, crypt dilatation and crypt elongation. Increased proliferation and an expanded mesenchymal component were seen in some of these polyps. Endothelial specific knockout of BMPR1a did not cause polyp formation in the intestine of mice whereas myofibroblast-specific BMPR1a-knockout caused a serrated polyposis phenotype. Mesenchymal intestinal myofibroblasts form the crypt sheaths and are critical for cross-talk between the mesenchyme and epithelium and thus intestinal homeostasis; studies are ongoing to investigate the molecular mechanism that contributes to polyp formation upon loss of BMP signalling in myofibroblasts.

Long-term follow-up results of stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia.

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Stepwise radical endoscopic resection (SRER) allows for complete ER of Barrett's esophagus (BE) with early neoplasia. This approach has been shown very effective in reaching complete eradication of high-grade dysplasia (HGD) or early cancer (EC) (CE-neo) in 98% and all intestinal metaplasia (CE-IM) in 85% of patients. Aim of this study was to report the long-term follow-up (FU) results after successful SRER. We screened all patients treated with SRER in two centers between 2001-2014, for BE ≤5cm with HGD/EC, without signs of invasion >T1sm1, G3/G4 differentiation, lymph-vascular invasion or irradical deep resection margins in ER specimens. All patients who had endoscopic and histologically confirmed CE-IM/CE-neo after SRER were included for evaluation of long-term FU. All information from FU reports was collected and entered in a database. Duration of FU was calculated from last treatment till last FU endoscopy. Primary outcomes: recurrence of HGD/EC and of IM combined with visible BE. Secondary outcomes: Buried Barrett's (BB) in neosquamous biopsies and IM in biopsies obtained distal to the neo-z-line. Seventy-three patients were included (64 men, mean age 66 yrs, median BE C2M3). Worst base pathology: HGD, n=50; EC, n=23. Median FU was 76 mo with a median of 6 endoscopies. Recurrence of HGD/EC was observed in 1 patient (1.4% overall, 0.2% per patient year) after 129 mo FU (T1bN0M0 treated with curative surgery). Recurrence of IM in endoscopically visible BE was observed in 22% of patients (n=16, of which 2 had LGD) after a median FU of 31 mo. In all cases the extent of recurrence was limited to small (<1 cm) islands or tongues. Histological recurrence without visible BE was found in 25 patients: 3 patients had BB (4% overall, 0.7% per patient year); 24 patients (33%) showed IM in biopsies distal to a normal appearing neo-z-line. A finding of IM of the neo-Z- was reproduced in 50% of patients and BB in none of the patients. Additional treatment was performed in 8 patients: esophagectomy for T1b cancer, ER of small island with LGD (n=1), APC for small islands (n=5), RFA for LGD in the neo-z- (n= 1). CE-neo and CE-IM (excluding IM in the neo-z-line) at the last FU endoscopy was seen in 100% and 96% respectively. Conclusion: The 6-year follow-up results of this study show that after successful SRER of BE ≤5cm recurrence of HGD/cancer is rare (1% overall, 0.2% per patient year). Recurrence of endoscopically visible BE with IM or LGD was found in 22% of patients and was generally confined to small islands or tongues. Buried glands were rare (0.7% per patient year) and just as IM of the neo-z- (33% of cases) of insignificant importance.

Reducing patient's burden. A minimalistic approach to radiofrequency ablation in Barrett's epithelium achieving complete eradication.

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Radiofrequency ablation (RFA) is an effective and accepted method for the eradication of Barrett's esophagus (BE). Guidelines advise eradicating high-grade dysplasia (HGD) and/or residual Barrett's after complete endoscopic resection of an intramucosal cancer. After primary circumferential ablation using the HALO^{360} balloon catheter, a subsequent focal RFA session is advised at follow-up to eradicate residual Barrett's but also to routinely perform an additional ablation of the neo-Z-line, irrespective of its endoscopic appearance. The rationale behind this is that often there is insufficient contact between the balloon-based electrode and the mucosa at this level. The aim of this study is to evaluate whether taking biopsies of the neo-Z- to prove complete eradication of the intestinal metaplasia (CEIM) and/or dysplasia (CED) after the primary ablation, can reduce the number of subsequent ablations of the neo-Z-line. All Barrett's esophagus patients undergoing circumferential RFA (HALO^{360}) at a single tertiary center were prospectively registered. After 3 months, eradication of the Barrett's epithelium was evaluated endoscopically. 4-quadrant biopsies were taken just below the neo-Z- in all patients with complete endoscopic eradication (CEE) of the Barrett segment or when the neo-Z- was completely eradicated but residual Barrett's more proximal remained. Primary outcome measures were the number of patients with CEE, CEIM and CED, and subsequently how many additional ablation sessions were prevented. 24 patients underwent RFA (HALO^{360}) between January 2012 and December 2014. In 19 patients (79%) an endoscopic mucosal resection (EMR) was performed prior to RFA. 15 patients (62%) had CEE of the neo-Z- after a single RFA session and in 14 patients (58%) biopsies were taken just below the neo-Z-line. In 8 patients (33%) no subsequent RFA session of the neo-Z- was performed, and of those 6 (25%) had CEIM and all 8 had CED of the neo-Z- at the last follow-up endoscopy (mean 18mths, range 8-32). 4 patients underwent additional treatment of proximal residual Barrett's by EMR of RFA. In 2 patients with no CEE of the neo-Z-line, biopsies of the Barrett's segment demonstrated intestinal metaplasia without dysplasia during follow-up (mean 15mths, range 10-20).
Conclusion: This study demonstrates that it is clinically relevant to take biopsies of the neo-Z- after primary circumferential ablation (HALO^{360}) when complete endoscopic eradication of Barrett's esophagus is observed. In at least 25% of patients, additional ablation of the neo-Z- can be omitted, which has a significant impact on patient burden and treatment associated costs.

Improved prediction of neoplastic progression in patients with Barrett's esophagus using specific histological criteria for low grade dysplasia

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Barrett esophagus (BE) is a known precursor of esophageal adenocarcinoma (EAC) which incidence has increased dramatically in the Western world over the last decades. To detect EAC at an early stage BE patients undergo surveillance endoscopies. Histologic diagnosis of low grade dysplasia (LGD) is an important criterion to mark the probability for neoplastic progression to high grade dysplasia (HGD) or EAC. However, the clinical applicability of LGD diagnosis is limited by an overall low rate of neoplastic progression and a high interobserver variation amongst pathologists. Therefore we aim to identify histological criteria that strengthen the diagnosis of LGD and improve risk stratification of patients. Four experienced gastro-intestinal pathologists examined 152 histological samples with LGD, randomized into two sets. Both sets contained biopsies of patients who developed HGD or EAC on follow-up (progressors) and patients without progression on follow-up (non-progressors). The first set was evaluated using 12 standard criteria for LGD as described in the guidelines for BE of the British Society of Gastroenterology. A subsequent consensus meeting was organized and the criteria were jointly discussed and specified according to consensus opinion. The second set was evaluated using the 12 refined histological LGD criteria. The criteria with an improved interobserver agreement defined as a kappa value of >0.4 in the second set were correlated with clinical outcome. The first set included 52 samples, 23 of progressors and 29 of non-progressors; the second set consisted of 100 biopsies, 28 of progressors and 72 of non-progressors. Between the first and second set the interobserver agreement improved for all 12 criteria, four of which (loss of surface maturation, mucine depletion, nuclear enlargement and increase of mitosis) reached a kappa value of >0.4. Combination of these four specified criteria identified patients with a high risk for progression if 3-4 of these criteria were present (incidence of progression 20% (95% CI 11-33) per patient/year) in contrast to only low risk patients if 0-2 criteria were present (incidence of progression 3% (95% CI 1-6) per patient/year). In conclusion, selected histological criteria for LGD have moderate interobserver variation and can improve the prediction progression in BE patients. We propose that specific histological LGD criteria could be used to tailor surveillance intervals of BE patients and have potential to improve cost-effectiveness.

Stepwise development of a volumetric laser endomicroscopy prediction score and computer algorithm to detect Barrett's neoplasia using matched VLE-histology images of endoscopic resection specimens

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Background: Endoscopic detection of early neoplasia in Barrett's esophagus (BE) is difficult. Volumetric laser endomicroscopy (VLE) is an imaging system incorporating 2nd generation optical coherence tomography, providing 6-cm long circumferential scan of the esophageal wall up to 3 mm deep. Study aims were 1) to identify VLE features of BE neoplasia, based on VLE-histology correlation, and to develop and validate a clinical VLE prediction score for early BE neoplasia; 2) to investigate feasibility of a computer algorithm to identify early BE neoplasia on VLE. Methods: A unique database of VLE images from endoscopic resection specimens and corresponding histology from BE patients +/- neoplasia was used. We previously described one-to-one VLE-histology correlation methodology. In the orientation phase, 25 VLE-histology images were evaluated unblinded, identifying features potentially predictive for early BE neoplasia. In the learning phase, 20 VLE images ((high-grade dysplasia (HGD) or early adenocarcinoma (EAC); n=10) and non-dysplastic (ND)BE tissue (n=10)) were scored by 2 VLE experts – blinded to histology – for presence of neoplasia and previously identified VLE features. A prediction score was created based on multivariable logistic regression analysis and was validated by additional scoring of 40 VLE images (20 HGD/EAC; 20 NDBE) using area under receiver operating characteristic (ROC) curve (AUC). Significant VLE features were incorporated in a computer algorithm based on linear support vector machine, which was tested on the same 60 VLE images and validated using leave-one-out cross-validation. Results: After the learning phase 3 VLE features turned out to be significantly and independently associated with BE neoplasia: 1) lack of layering; 2) surface signal > subsurface signal; 3) presence of irregular, dilated glands/ducts. With these features the VLE neoplasia prediction score was developed. ROC curve of the prediction score showed an AUC of 0.83 in the learning and 0.81 in the validation phase. Sensitivity and specificity of 85% and 68% in the learning and 83% and 71% in the validation phase, respectively, was derived from the ROC curve. Features 1 and 2 were incorporated in the computer algorithm. The performance of the algorithm showed an AUC of 0.91 to detect BE neoplasia. Conclusion: This study, using precise ex vivo VLE-histology correlation, shows that the VLE features layering, surface signal, and irregular glands are significantly associated with early BE neoplasia. Using these features, we developed and validated a VLE prediction score and a computer algorithm to detect BE neoplasia, both with promising accuracy.

Efficacy and safety of the CryoBalloon Focal Ablation System for the eradication of dysplastic Barrett's oesophagus islands

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Radiofrequency ablation (RFA) is currently the preferred ablation technique for eradication of Barrett's oesophagus (BO). However, this technique has drawbacks, such as the need for large controller units and multiple deployment steps. Cryoablation using the CryoBalloon Focal Ablation System (CbFAS) may be an attractive alternative. The CbFAS is a balloon-based system, which uses nitrous oxide as a refrigerant. It is designed to overcome the drawbacks of RFA, and earlier studies show that the CbFAS is feasible and safe, and that 10 second ablations resulted in complete eradication of BO. However, efficacy of 10 second ablations in a larger group of patients has not been investigated, nor the potential of precise targeting of BE islands. The aim of our study was to assess the efficacy and performance (i.e. targeting of BO islands) of the CbFAS in patients with flat, dysplastic BO. In this ongoing prospective trial, patients with dysplastic BOE or residual BO after removal of early cancer will be enrolled. Up to two 10 second ablations will be performed on a BO island or group of BO islands with a maximum size of 1 cm^2. Follow-up (FU) endoscopy is performed 6-8 weeks post-ablation. The primary outcome parameter is the percentage of completely eradicated BO areas at FU. Secondary outcome parameters are the percentage of ablated areas with at least 50% eradication, device performance, and adverse events. As of December 2015, 26 patients were enrolled and treated (23 male, median BO C0M2). 11 patients (42%) underwent endoscopic resection (ER) of a visible lesion before ablation therapy. Worst pathology found, either in the ER-specimen or in biopsies, was LGD in 13 patients (50%), HGD in 5 (19%) and early adenocarcinoma in 8 (31%). Twenty patients (77%) had circumferential RFA-treatment prior to inclusion in this study. A total of 40 ablations were performed. Median cryoablation time was 4 (IQR 2-6) minutes, while the overall endoscopy duration was 13 (IQR 11-17) minutes. Device malfunction occurred in 5/26 (19%) procedures, but this did not hamper completion of the ablation. 93% (38/41) of the BO areas could be targeted adequately. No adverse events occurred during the procedure. As of December 2015, 25/26 patients underwent FU endoscopy. Complete eradication of BO areas, endoscopically and histologically, was observed in 38/38 (100%) completely ablated areas. No buried glands were found on biopsy. The 2 patients in whom the BO areas were incompletely ablated, residual BO was observed and confirmed by the presence of intestinal metaplasia in biopsies. Conclusion: Preliminary results suggest that cryo-ablation of BO islands using CbFAS is effective and safe.

What should be the target diameter of endoscopic dilation of benign esophageal anastomotic strictures?

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Whether the target diameter for endoscopic dilation of esophageal strictures should be 16mm or 18mm is unknown. Our aim was to compare the dysphagia-free period for patients who underwent endoscopic dilation up to 16 mm with patients who were dilated up to >16mm. Patients who underwent esophageal dilation therapy between January 2005 and June 2015 were retrospectively identified from our endoscopic database. In an attempt to select a large and homogeneous population, we included adult patients who received bougie/balloon dilation for a benign anastomotic stricture after esophagectomy. The main exclusion criteria were active esophageal malignancy or metastatic disease, stent placement, incision therapy and active postsurgical fistula. An anastomotic stricture was defined as dysphagia in combination with a luminal diameter of ≤13mm at endoscopy. The primary outcome was the dysphagia-free period. Follow-up ended at time of stricture recurrence, tumor recurrence or last contact. Stricture recurrence was defined as dysphagia requiring endoscopic dilation in the absence of locoregional tumor recurrence. A total of 179 patients (male 71%; mean age 63.8 years) were identified in our database. A maximum diameter of 16mm was reached in 88 patients and >16mm in 91 patients: 16.5mm(2), 17mm(45) and 18mm(44). Base characteristics between the two groups were comparable (p>0.1) for time to stricture diagnosis, stricture diameter at first dilation and method of dilation. Patients in the >16mm group had more end-to-end anastomoses (p=0.024), a higher incidence of postsurgical leakage (p=0.083), a higher rate of strictures in the proximal esophagus (p=0.013) and less Kenacort injected (p=0.001). The stricture recurrence rate was 79.5% in the 16mm group and 68.1% in the >16mm group (p=0.083). The median dysphagia-free period was 41.5 (range 8-3233) days and 92 (range 17-1745) days, respectively (p<0.001). For patients who developed a stricture recurrence, the median dysphagia-free period was 28 (range 8-487) days and 63 (range 17-1013) days, respectively (p=0.001). Cox regression analysis showed a crude hazard ratio for stricture recurrence over time of 0.57 (95% CI 0.41-0.81) for dilation up to >16mm compared with the 16mm group. Adjusted for the variables with p<0.1 in univariable analysis, the HR was 0.48 (95% CI 0.33-0.70) with p<0.001. Conclusions: Endoscopic dilation of benign esophageal anastomotic strictures up to >16mm is more effective than dilation up to 16mm regarding the dysphagia-free period.

Early experience of Duodenal Mucosal Resurfacing treatment for Type 2 Diabetes when expanding from single to multiple sites

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Introduction: Bariatric surgery elicits prompt improvement in glycemia in type 2 diabetes (T2D) through weight-independent mechanisms. Duodenal mucosal resurfacing (DMR) is an investigational endoscopic procedure involving novel balloon catheter-based thermal ablation of duodenal mucosa. A single-site, first-in-human (FIH) study showed robust improvements in glycemic control after DMR among patients with T2D. Objectives: We observed the early safety and feasibility of DMR at a small number of additional sites with an improved DMR procedure, and compared this with the experience in the FIH study. Methods: At all study sites, endoscopists received a day of both didactic and hands-on DMR training in a porcine model before treating patients with T2D sub-optimally controlled on oral glucose-lowering medication. DMR involved duodenal lumen measurement and subsequent mucosal lifting with a submucosal expansion catheter and final mucosal circumferential ablation (length ~9 cm) with a thermal ablation catheter. Thereafter, patients followed a graduated diet for 2 weeks and a proton pump inhibitor was prescribed for 5 weeks. Safety was compared between the single-site FIH study and the subsequent multi-site study. Results: During the FIH study, 39 patients (age 54±7 years, base HbA1c 9.5±1.3%) received DMR, with full cohort safety data capture up to 6 months. In the multi-site study, 27 patients (age 55±9 years, base HbA1c 8.7±1.0%) received DMR treatment with current follow-up of at least 4 weeks post-procedure. In both cohorts, the procedure was implemented according to protocol and well tolerated by patients. In the FIH study, a duodenal stenosis developed in 3 patients within 6 weeks post-DMR. Each stenosis resolved with endoscopic dilation without sequelae. Analyses determined that overlapping ablation or ablation of non-lifted mucosa were underlying causes and a modified DMR procedure was instituted to mitigate this risk. No subsequent study-related serious adverse events or duodenal stenoses have been reported since the introduction of the modified DMR procedure. Adverse events were generally mild. Conclusion: The DMR procedure is an innovative endoscopic approach for the management of T2D. Early experience suggests scalability of the procedure when expanding to multiple centers. No additional duodenal stenoses or other serious adverse events developed after modification and optimization of the DMR procedure. Full assessment of clinical applicability, efficacy and safety is required.

Cap-assisted endoscopy for a complete visualization of the ampulla of Vater and duodenal surveillance in patients with familial adenomatous polyposis

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PURPOSE. Patients with familial adenomatous polyposis (FAP) have an increased risk for duodenal carcinoma, especially located at the ampulla of Vater (AV). Therefore, guidelines recommend surveillance endoscopy with both forward- and side-viewing instruments to identify duodenal and ampullary adenomas and stratify risk according to Spigelman classification. Including a side-viewing endoscopy increases burden, time and costs of duodenal surveillance, and not all endoscopists routinely perform this procedure. We hypothesized that the AV can be completely visualized during a forward-viewing endoscopy when using a short transparent plastic cap attached to the tip of the endoscope. METHODS. From Jul-Nov 2015 we enrolled all patients with FAP who were planned for a surveillance upper endoscopy, excluding those who had undergone a previous duodenectomy. All procedures were performed by one of two gastroenterologists specialized in the management of FAP. All patients underwent a forward-viewing endoscopy with a short transparent plastic cap (D-201-11304/-11804, Olympus medical systems corp., Japan) attached to the tip of the endoscope, aiming to visualize the complete AV including the orifice. If not successful, the procedure was followed by a side-viewing endoscopy. Complete visualization was documented with still images of the entire AV. Complications were reported by verifying medical files and the national endoscopic complication registry. Other variables that were collected: endoscopic size and aspect of AV, Spigelman stage. The study was approved by the ethical committee; no additional patient approval was required. RESULTS. 29 Patients with FAP were enrolled; 6 had undergone a previous ampullectomy. The (neo-)AV was completely visualized using the cap in 27 patients (93%). Median size of the AV was 6 (range 0-20) mm, 8 had an ampullary adenoma and median Spigelman stage was III (range 0-IV). In the 2 patients in whom the AV could not be visualized using the cap, the AV was visible during the subsequent side-viewing endoscopy. In both cases the AV was not enlarged and hidden behind a duodenal fold. Spigelman stages in those patients were III and 0 resp., and 1 had undergone a previous ampullectomy. No complications occurred during endoscopy or at follow-up. CONCLUSION. In this study, we show that in most FAP patients the AV can be completely visualized with a cap assisted forward-viewing endoscopy. Initiating an upper endoscopy using a forward-viewing endoscope with a cap could avoid the need for an additional side-viewing endoscopy in patients with FAP. This could reduce burden, time and costs, whilst maintaining adequate duodenal surveillance.

Molecular-guided fluorescence endoscopy for colorectal polyp identification: a dose-escalation study with bevacizumab-800CW

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Optical molecular imaging holds great promise to change gastroenterology practice, as it might improve macroscopic distinction and identification of aberrant tissue during endoscopic procedures. Here we present the first-in-human results of a molecular-guided fluorescence endoscopy (MFE) approach to identify colorectal polyps in patients with familial adenomatous polyposis (FAP), following systemic administration of a near-infrared (NIR) fluorescent tracer targeting Vascular Endothelial Growth Factor A (VEGF-A) in a dose-escalation study. The monoclonal antibody bevacizumab (anti-VEGF-A) was labeled with the NIR fluorescent dye IRDye800CW and administered intravenously three days prior to surveillance colonoscopy. Patients received 4.5, 10 or 25 mg bevacizumab-800CW to evaluate the optimal dose for polyp visualization. MFE was performed using a novel fiber-based imaging platform, displaying simultaneous white-light, NIR fluorescence and overlay images in real-time. Ex vivo, quantitative measurements of the fluorescent signal were performed on the resected colorectal polyps and biopsies, with multi-diameter single fiber reflectance single fiber fluorescence (MDSFR-SFF) spectroscopy. After formalin fixation and paraffin embedding, 800nm flatbed scanning (Odyssey scanner) and fluorescence microscopy were performed. Fluorescence images were analyzed using ImageJ. No adverse events were reported in all 17 patients. All adenomas, independently of tracer dose or dysplastic grade, could be visualized during MFE, while normal tissue showed negligible fluorescence. Visualization of smaller colorectal adenomas (< 5 mm) improved by increasing the dose up to 25 mg. This dose dependency was confirmed with use of ex vivo analyses; the absolute mean fluorescence intensity (MFI) of adenomas increased with escalating bevacizumab-800CW dose, while the adenoma-to-healthy ratio remained constant. Our results demonstrate the feasibility of molecular-guided endoscopy using a systemically administered NIR fluorescent antibody. Bevacizumab-800CW accumulated in all colorectal adenomas. Uptake and fluorescence intensities were dose dependent. Our novel imaging platform provided the endoscopist with real-time images, enabling the examination of the colon for targeted polyps. Prospective studies should elucidate the role of MFE using bevacizumab-800CW for improved polyp identification in high-risk populations like patients with Lynch syndrome.

Comparison of colonoscopy, sigmoidoscopy and multiple rounds of FIT-based colorectal cancer screening: long-term follow-up

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Several methods for colorectal cancer (CRC) screening are available; the most often used include colonoscopy, sigmoidoscopy and fecal immunochemical testing (FIT). To date, comparison between these screenings methods was mainly focused on one-time endoscopic screening to one-time FIT screening. A fair comparison of diagnostic yield (DY) of FIT would comprise cumulative DY after multiple rounds of FIT screening. The aim of our study is to compare the DY of multiple rounds of FIT-screening to one-time screening by sigmoidoscopy and colonoscopy. Demographic data of 30,007 randomly chosen individuals aged 50-74 were obtained from municipal population registers (June 2006 - August 2010); of these 15,046 were invited for four rounds of FIT, 8,407 for one-time sigmoidoscopy, and 6,600 for one-time colonoscopy screening. We compared 2 rounds of FIT to one-time sigmoidoscopy and 4 rounds of FIT to one-time colonoscopy. Cumulative (cum.) participation rate, positivity rate, number of colonoscopies, and diagnostic yield were calculated for each method. The DY was calculated relative to eligible invitees and participants. Between-group differences for participation, number of colonoscopies and DY were evaluated using multivariable logistic regression analysis adjusted for age and gender. In total, 28.515 eligible persons (median age 60 years, IQR 55-66; 50% males) were invited. Cum. participation was significantly higher for FIT (77%) than for sigmoidoscopy (31%; p<0.001) and colonoscopy (24%; p<0.001). Number of colonoscopies performed relative to eligible invitees was highest for colonoscopy (24%) compared to FIT (13%; p<0.001) and sigmoidoscopy (3%; p<0.001). For invitees the DY for advanced neoplasia (AN) was significantly higher after two rounds of FIT compared to one-time sigmoidoscopy (3.1% vs 2.2%; OR 1.41, 95%CI 1.18-1.68), and after four rounds of FIT compared to one-time colonoscopy (4.5% vs 2.2%; OR 2.19, 95%CI 1.81-2.68). For participants, DY for AN was significantly higher for endoscopic screening, OR 0.64 (95%CI 0.53-0.76) for 2 rounds of FIT (4.7%) compared to sigmoidoscopy (7.3%), and OR 0.67 (95%CI 0.55-0.82) for 4 rounds of FIT compared to colonoscopy. Conclusion In this population-based CRC screening cohort, we demonstrated that multiple rounds of FIT screening detects significantly more advanced neoplasia per invitee compared to one-time sigmoidoscopy and colonoscopy screening, and with significantly fewer colonoscopies needed. Colonoscopy detected more advanced neoplasia per participant. However, due to low participation in colonoscopy screening, FIT seems most effective in population-based CRC screening.

The extent of unnecessary surgery for benign rectal polyps in the Netherlands

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Endoscopic techniques, such as (piecemeal) endoscopic mucosal resection, endoscopic submucosal dissection and transanal endoscopic microsurgery, have become standard treatments for large, benign colorectal polyps. The rectum is particularly accessible for these minimally invasive techniques, which should be preferred over radical surgery, known for its morbidity and mortality. Nevertheless, a subset of patients with benign rectal polyps is still referred for radical surgery. This study investigated the magnitude and reason of referrals in the last decade, and a retrospective assessment of endoscopic treatment options. Records of patients who underwent radical surgical treatment for a histologically confirmed benign rectal polyp in the Netherlands between the years 2005–2014 were selected from the nationwide database of the Dutch Pathology Registry (PALGA). Data included year of resection, age, gender and histology of prior biopsies and/or polypectomies. In a representative subset of 7 hospitals (1 academic hospital, 2 large teaching hospitals, 4 general hospitals) a detailed analysis of patient records was performed, including characteristics of patients and polyps, reasons for surgery, morbidity and mortality of surgery. Since surgery referral rates will depend on the incidence of polyps, data were corrected for the number of colonoscopies performed per year for nationwide data, and per hospital for detailed analysis. Endoscopic images and reports were independently evaluated for endoscopic treatment options by 2 endoscopy experts. 575 patients with a benign polyp were referred for rectal surgery in the Netherlands between 2005–2014, and 56 patients in the 7 hospitals. The number of radical resections declined over the years, but after 2010 numbers stabilized around 50-55 yearly. Main reasons for referral for surgery were polyp size (34%), suspicion of malignancy (34%) and TEM failure (20%). In general hospitals referrals for rectal surgery were more prevalent than in academic hospitals ($p<0.01$). 39% of patients suffered from perioperative complications and 1 patient died (1.8%). In 54% of patients a stoma was formed, of which 60% were permanent. The endoscopy experts were able to retrospectively assess 41 cases (73%) as 'probably feasible' for endoscopic therapy.
Conclusions: The rate of radical rectal surgery for benign polyps in the Netherlands declined over the last 10 years, but stabilized from 2010. Therefore, a significant number of patients with difficult or large rectal polyps are still referred for invasive surgery at the cost of high morbidity and mortality. Referral to an expert endoscopist may avoid unnecessary surgery in the majority of cases.

Endoscopic full-thickness resection of colorectal neoplasias: Report on the first Dutch experience.

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Due to the screening programs for colorectal cancer the number of colonic polyps and T1-carcinomas that are endoscopically identified and resected is increasing. Existing advanced techniques such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) are not always sufficient. For non-lifting adenomas, adenomas on difficult-to-reach locations – such as in a diverticulum – and unconfirmed radical resection in low risk T1-carcinomas was surgery until recently the only available option. In these indications endoscopic full-thickness resection (eFTR) offers a minimally invasive alternative to surgery. The aim of this study is to evaluate and present the first Dutch experiences with the novel one-step FTRD® (full thickness resection device) System from Ovesco Endoscopy AG. This device has recently been aproved in Europe (CE marked) for colonic eFTR. From July until November 2015 six cases were treated by 2 gastroenterologists. Both have extensive experience in advanced endoscopic techniques for polypectomy, and were trained in eFTR on a cadaveric porcine model. Indications were non-lifting adenomas (n=4), residual adenoma in a diverticulum (n=1) and resection of scar tissue after endoscopically treated low risk T1-carcinoma in order to confirm radicality and avoid the need for additional surgery (n=1). Technical success was reached in all cases. Radical resection was histologically confirmed in five cases. In one case (primary non-lifting adenoma) the resection margins were positive. Planned procedural time of 60 minutes sufficed in all cases. No significant complications occurred. A single dose of amoxicillin/clavulanic acid 1000/200 mg was administered 30 minutes before initiation of endoscopy, covering most enterobacteriaceae and anaerobes. However, the need for antibiotic prophylaxis in a technique without fecal spill has yet to be determined. We experienced that eFTR has a significantly shorter learning curve than ESD, but it should only be applied by skilled endoscopists after adequate training.
Conclusions. One-step endoscopic full-thickness resection of colorectal lesions is a promising new technique, allowing gastroenterologists to reduce the need for surgical therapy in both benign and malignant colorectal neoplasias. Especially in the case of unclear radicality after endoscopic resection of a low-risk T1-colorectal carcinoma, eFTR may become an important diagnostic and therapeutic tool. We presented a series of six cases, in which eFTR was effective and safe. Prospective data on efficacy and safety are mandatory.

Sytematic review on the Treatment of Isolated Local Recurrence of Pancreatic Cancer after Initial Curative Resection; Re-resection, Chemoradiotherapy and Stereotactic Body Radiation Therapy.

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The majority of patients undergoing pancreatic resection for malignancy develop disease recurrence within two years. In around 30% of these patients, isolated local recurrence is found. Local tumour control could offer these selected patients a chance of extended survival. On the other hand, routine treatment of recurrence might generate considerable morbidity in patients with an already poor clinical status and limited survival outlook. Recently, several treatment options have been explored for this subgroup. To evaluate the literature on this topic, we performed a systematic searchâ€¯in PubMed, Embase and the Cochrane Library for articles published up to 10 November 2015. Included were studies reporting on the treatment of isolated local recurrence after initial curative resection of primary malignant pancreatic cancer. Studies reporting on neuroendocrine tumours, emergency intervention, metastatic recurrence and locally advanced disease were excluded. Primary endpoints were morbidity, mortality and survival. After screening 1052 studies, 16 studies reporting on 279 patients undergoing treatment for isolated local recurrence were included. Treatment options for local recurrence included surgical re-resection (8 studies, 100 patients), chemoradiotherapy (7 studies, 153 patients) and stereotactic body radiation therapy (SBRT) (2 studies, 26 patients).â€¯Pancreatic ductal adenocarcinoma was the primary tumour in 97% (n=272) of patients, with periampullary carcinoma (n=4) and adenosquamous carcinoma (n=3) making up the other 3%.â€¯Morbidity and mortality were reported for re-resection (29% and 1% respectively), chemoradiotherapy (54% and 0%) and SBRT (4% and 1%). Median survival after treatment of isolated local recurrence of up to 32, 18 and 13 months was reported for re-resection, chemoradiotherapy and SBRT respectively. Most patients had a prolonged disease-free interval, with a weighted mean of 43 ± 36 months for the surgical re-resection group and 26 ± 20 months for the chemoradiotherapy and SBRT group combined. In conclusion, treatment of isolated locoregional recurrence following pancreatic resection for pancreatic cancer seems safe, feasible and associated with relatively good survival. Specifically, patients with a prolonged disease free interval seem to benefit most from treatment of isolated local recurrence. Further prospective studies should focus on optimal screening and selection procedures and the comparison of treatment options.

Locally advanced colon cancer; evaluation of current clinical practice and treatment outcome at a population level.

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Background: Despite its prevalence and impact on prognosis, locally advanced colon cancer (LACC) is still an underexposed area in literature. The aim of this study was to evaluate current clinical practice and treatment outcome regarding locally advanced colon cancer (LACC) at a population level. Methods: Data from the Dutch Surgical Colorectal Audit (DSCA) from 2009 to 2014 were used. A total of 32,573 patients underwent resection for non-LACC and 6918 for LACC, defined as cT4 and/or pT4 stage. LACC was divided into those with and without multivisceral resection, LACC-MV (n=2263) and LACC-noMV (n=4655), respectively. Guide adherence, treatment strategy, and short term outcome were evaluated. Results: Guide adherence for LACC was more than 90% regarding preoperative imaging and 80% for preoperative multidisciplinary team discussion. In the elective setting, neoadjuvant (chemo)radiotherapy or chemotherapy was applied for cT4M0 stage in 5.5% and 4.2%, respectively. R0 resection rates were 99%, 88% and 84% in non-LACC, LACC-noMV and LACC-MV patients, respectively ($p<0.001$). A postoperative complicated course occurred in 18.9%, 24.3% and 27.4% ($p<0.001$), and 30-day/in-hospital mortality was 3.8%, 6.8%, and 5.7% ($p<0.001$) in the non-LACC, LACC-noMV and LACC-MV groups, respectively. Conclusion: This population based study suggests that there is room for improvement in treatment of LACC.

Short-course radiotherapy and chemoradiation have similar effects on quality of life in routinely treated rectal cancer patients during the first year

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Most rectal cancer patients are treated with neoadjuvant short-course radiotherapy (SCRT) or chemoradiation (CRT). If a good clinical response is obtained after CRT, patients are increasingly offered organ-preserving strategies. It has been proposed to replace SCRT by CRT in early tumors to increase the percentage of complete responders. However, this intensified neo-adjuvant treatment may affect patients' quality of life (QoL). This study compares patient-reported QoL between routinely treated patients receiving CRT, SCRT with immediate surgery, or SCRT with delayed surgery before, during and after treatment. This prospective cohort study includes rectal cancer patients of all stages referred for radiotherapy between February 2013 and May 2015. QoL was assessed by EORTC-C30 and -CR29 questionnaires at base (before radiation), 3, 6 and 12 months. For each patient, a propensity score (PS) was calculated for receiving CRT. PS was used for restriction and adjustment. Changes in QoL were analyzed by mixed models. Additionally, scores were compared to a normative age-matched Dutch population. After PS based restriction, 191 of 208 eligible patients were included, of which 122 underwent CRT and 69 SCRT (44 immediate and 25 delayed surgery). CRT patients were younger (62.2 vs. 68.0 year) with more advanced tumors (mesorectal fascia invasion (66.6% vs. 27.9%), T4 (21% vs. 10%)). Questionnaire return rates were 84% at base and 63-80% during follow-up. At baseline, global health, physical, emotional, social and role function scores were similar for all groups. At 3 and 6 months, all groups showed similar decrease in functional scores, with significantly worse physical function in delayed SCRT patients. At 12 months, all scores recovered to base levels except for role function. No significant symptom differences were found between the groups. Compared to the Dutch reference population, patients had impaired role and social function at 12 months. During rectal cancer treatment similar QoL changes are observed between SCRT and CRT. Most functional QoL domains return to base levels after 1 year, comparable to the Dutch population.

Endoscopic surveillance in individuals at risk for familial diffuse gastric cancer.

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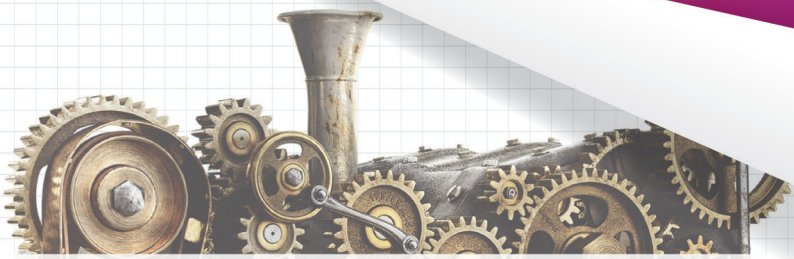
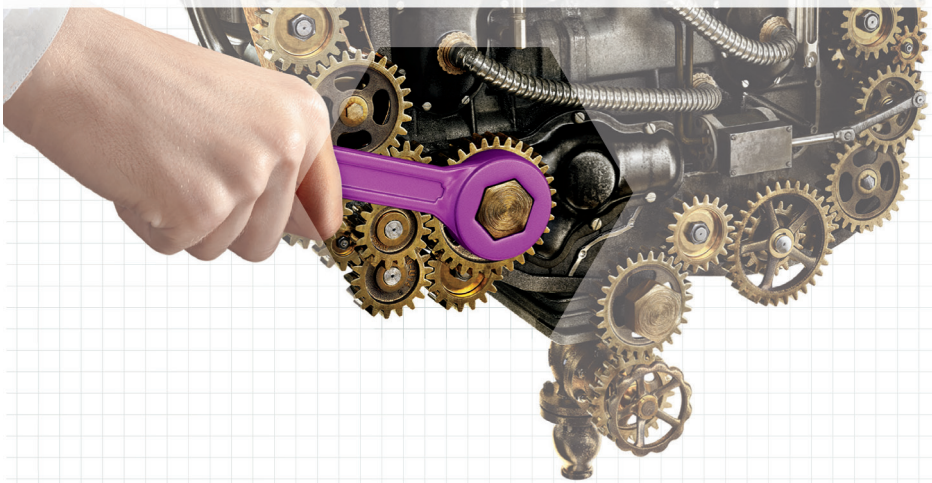
In more than 70% of families fulfilling criteria of hereditary diffuse gastric cancer (HDGC), no pathogenic CDH1 germ mutation can be identified. Clustering of CDH1-negative diffuse type gastric cancer (DCG) is seen within families, although sporadic DGC is more common. Little is known about the outcomes of endoscopic surveillance in relatives from CDH1-negative DGC patients. The aim of this study was to retrospectively analyze the outcomes of surveillance endoscopies in first-degree relatives of patients that fulfill the international HDGC criteria.A Retrospective cohort analysis was performed of first-degree relatives (FDR) from families fulfilling the international HDGC criteria and underwent surveillance endoscopies. Endoscopic surveillance was performed according to the international consensus guide for HDGC with a white light high definition endoscope, including an extensive inspection of the gastric mucosa and taking both targeted biopsies and 30 random biopsies of all regions of the stomach to identify (pre)malignant lesions, in particular signet ring cell carcinoma. Since 2004 73 individuals from 31 families fulfilling the HDGC criteria, were offered annual endoscopic surveillance. Between March 2004 and December 2015 these individuals underwent 233 surveillance endoscopies. The median number of endoscopies per individual was 3,2 (range 1-11). The median follow up was 52,9 months (range 2,3 – 143,4). Signet ring cell carcinoma foci were identified in 5 individuals (7%), which afterwards was attributed to a pathogenic CTNNA1 mutation. Eleven participants had active gastritis (15%), 46 had chronic atrophic gastritis (64%), and intestinal metaplasia (IM) was found in 29 participants (40%). Dysplasia was found in three participants (4%). Additionally, in 56 endoscopies, scar tissue due to earlier biopsies, was observed in the gastric mucosa, which hinders the detection of the small white lesions which are typical for HDGC.Conclusions: In FDR from HDGC families, the yield of annual endoscopic follow up with extensive biopsy collection seems limited. As this study represents a small group and a relative short follow up, no conclusion can be drawn about the lifetime gastric cancer development risk. Nevertheless, in this well defined group, prolonging the endoscopy interval, as well as a decrease of the amount of biopsies taken per endoscopy should be considered.

Entyvio is opgenomen** in de
Handleiding Behandeling IBD[1]



Patiënten met **colitis ulcerosa** of de **ziekte van Crohn** verdienen een **behandeling met precisie*.**



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** Raadpleeg de Handleiding Behandeling IBD voor meer informatie over de plek van Entyvio in de behandeling.

1. Handleiding Behandeling IBD 2014-2015, Moderniseren van de richtlijn IBD 2009, www.icc-ibd.com/richtlijn
2. Entyvio Samenvatting van de Productkenmerken. Takeda Pharma A/S. Augustus 2015

Is distinction of risk groups based on family history in the screening in familial colorectal carcinoma necessary?

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Objective: To determine yield of colorectal cancer (CRC) and advanced adenomas (AA) in individuals with familial colorectal carcinoma (FCRC) in groups with different relative risks (RR) based on family history. Should the surveillance of individuals with familial colorectal carcinoma (FCRC) be different depending their relative risk based on family history? Design: In this retrospective study we included individuals who met the criteria for FCRC (RR≥3, without any known hereditary colorectal cancer syndrome). We evaluated the timing and yield of all the endoscopic procedures per predicted RR. AA and/or CRC were registered as advanced neoplastic lesions. Results: In 373 individuals who met the criteria for FCRC, the yield of 1063 endoscopic procedures, during 3541 follow up years, could be evaluated. In total 38 advanced neoplastic lesions were found, of which 9 concerned CRC. There was no significant difference in incidence of advanced neoplastic lesions per RR group; CRC incidence seems higher in individuals with a RR ≥6. Mean age of developing an advanced neoplastic was not significant different per RR group, overall mean age is 57.8 years. CRC was only found in individuals who have a first degree relative (FDR) diagnosed at a young age with CRC (<50 years). Only in 8 cases an AA was found during follow up. Half of them already had an AA (n=3) or CRC (n=1) at the index endoscopy. Conclusions: These findings indicate that all individuals with FCRC, regardless of the height of the RR, should be screened similarly. Having more affected FDR's is associated with a higher risk, especially when FDR are diagnosed < 50 years. Previous adenoma removal seems to be a more important risk factor for the development of new colorectal neoplasia than the height of the RR.

Blockade of multiple co-inhibitory pathways can re-vitalize tumor-specific responsiveness of intra-tumoral T cells in liver cancer

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Targeting immune checkpoint co-inhibitory molecules has been shown a novel promising therapeutic approach for several types of cancer. To determine which co-inhibitory pathways contribute to intra-tumoral suppression of T-cell responses in liver cancer, we measured expressions of 4 co-inhibitory receptors using paired samples of leukocytes freshly isolated from liver tumor, tumor-free liver tissue (TFL) and peripheral blood of patients with hepatocellular carcinoma (HCC) or liver metastases from colorectal cancer (LM-CRC) by flow cytometry. We found that in both types of liver cancer, expressions of PD-1, TIM-3, LAG-3 and CTLA-4 on CD8+ and CD4+Foxp3- T cells in tumor were significantly higher than those in TFL and in blood. In HCC, PD-1, LAG-3 and TIM-3 were up-regulated on tumor associated-antigen (TAA)-specific CD8+ tumor-infiltrating lymphocytes (TIL). Moreover, their ligands PD-L1, Galectin-9, MHC-II, CD80 and CD86 were expressed on dendritic cells, monocytes and B cells in the tumor. Compared to the cells without expression, CD8+ and CD4+Foxp3- TIL expressing those co-inhibitory receptors displayed a more activated status but did not show enhanced cytotoxicity or cytokine production, suggesting that tumor-reactive T cells are suppressed by co-inhibitory pathways in the tumor microenvironment. Furthermore, blockade of PD-L1, LAG-3, TIM-3, and CTLA-4 increased ex vivo proliferation of CD4+ and CD8+ TIL to polyclonal stimuli and to HCC TAA presented by mRNA electroporated autologous antigen-presenting cells, and also increased effector cytokine production of CD8+ TIL in polyclonal and HCC TAA-specific peptide stimulation assays. Conclusion: These results demonstrate that co-inhibitory receptors PD-1, TIM-3, LAG-3 and CTLA-4 are up-regulated on intra-tumoral TAA-specific T cells in liver tumors, and that blockade of these co-inhibitory pathways re-vitalizes the functionality of tumor-derived T cells. Therefore, these co-inhibitory molecules may be attractive immunotherapeutic targets for the most prevalent types of liver cancer.

Prognosis and treatment after diagnosis of recurrent esophageal carcinoma following esophagectomy with curative intent.

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Background Strategies for treatment of recurrence after initial curative esophagectomy are increasingly being recognized. The aim of this study was to identify prognostic factors that affect survival in patients with recurrence and to evaluate treatment strategies. Methods A prospective database (2003-2013) was used to collect consecutive patients with esophageal carcinoma treated with initial curative esophagectomy. Locations, symptoms, and treatment of recurrence were registered. Post-recurrence survival was defined as time between the first recurrence and death or last follow-up. Results Of the 335 selected patients, 171 (51%) developed recurrence. Multivariable analysis identified distant recurrence as opposed to locoregional recurrence (hazard ratio [HR] 2.15, 95% confidence interval [CI] 1.27-3.65; p=0.005), >3 recurrent locations (HR 2.42, 95% CI 1.34-4.34; p=0.003) and treatment (HR 0.29, 95% CI 0.20-0.44; p<0.001) as independent prognostic factors associated with post-recurrence survival. Primary tumor characteristics including neoadjuvant therapy, histological type, pTN-stage, and radicality did not independently influence post-recurrence survival. Treatment was initiated in 62 patients (37%) and included chemotherapy, radiotherapy, and/or surgery. Median post-recurrence survival of all patients was 3.0 months (range 0-112). In total 6 patients (4%) are still disease free following treatment indicating cure. Conclusion In patients treated for esophageal cancer at curative intent, distant recurrence and >3 recurrent locations are independent prognostic factors associated with worse post-recurrence survival, irrespective of primary tumor characteristics. Although survival after recurrence is poor, treatment can prolong survival and in selected patients even lead to cure.

Palliative chemotherapy and targeted therapies for esophageal and gastro- esophageal junction cancer

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More than 50% of patients with esophageal or gastro-esophageal junction cancer (EC/GEJC) have metastatic disease at time of diagnosis. Chemotherapy and targeted therapies are increasingly being used for palliative treatment with the intention to control tumor growth, improve quality of life (QOL), and prolong survival. To date however, scientific proof is unclear. Therefore, the aim of this study is to compare the effectiveness of adding chemotherapy and targeted therapy to best supportive care (BSC) and, to compare the addition of a cytostatic or targeted therapeutic to a control arm in patients with EC/GEJC. The Cochrane Central Register of Controlled Trials, MED and EMBASE were searched. Randomized controlled trials on palliative chemotherapy, and/or targeted therapy, versus BSC or versus a control arm, in patients with EC/GEJC were included. Two authors independently extracted data. For the comparison of palliative chemotherapy or targeted therapy versus BSC, five trials with a total of 751 patients have been included in the meta-analysis of overall survival (OS). This analysis demonstrated a significant benefit in OS in favor of the group receiving palliative chemotherapy and/or targeted therapy, (hazard ratio (HR) 0.81, 95% CI 0.71 to 0.92). For the comparison of adding a cytostatic and/or targeted agent to a control arm, 10 trials, with 1288 patients were included for the meta-analysis of OS. This analysis demonstrated a significant benefit in OS, (HR 0.77, 95% CI 0.70 to 0.85). This was found for both cytostatic and targeted therapy compounds, when analyzed as separate groups. A separate analysis with only second therapies showed a similar benefit. Ramucirumab was the only agent, investigated more than once, that significantly improved both OS and PFS. However, the median absolute survival gain found was limited. Palliative chemotherapy and/or targeted therapy appeared to increase the frequency of treatment related toxicity of at least grade 3 in some studies. However, treatment related deaths did not appear to occur more frequently. QOL, for the studies that reported this outcome, appeared to improve in the arm with an additional agent. Conclusion - Palliative chemotherapy and/or targeted therapy significantly increases OS compared to BSC in patients with EC/GEJC. Additionally, patients who receive multiple agents have an increased OS and PFS. Although treatment-associated toxicities of at least grade 3 appeared to occur more frequent, there is no evidence of decreased QOL. Palliative chemotherapy and/or targeted therapy can thus be considered standard care for EC/GEJC.

Cost-effectiveness of Cetuximab for advanced esophageal squamous cell carcinoma

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Costly biologicals in palliative oncology are emerging at a rapid pace. For example, in patients with advanced esophageal squamous cell carcinoma, addition of cetuximab to a palliative chemotherapy regimen appears to improve survival. However, it simultaneously results in higher costs. We aimed to determine the incremental cost-effectiveness ratio of adding cetuximab to first- chemotherapeutic treatment of patients with advanced esophageal squamous cell carcinoma, based on data from a randomized controlled phase II trial. A cost effectiveness analysis model was applied based on individual patient data. It included only direct medical costs from the health-care perspective. Quality-adjusted life-years and incremental cost-effectiveness ratios were calculated. Sensitivity analysis was performed by a Monte Carlo analysis. The current Dutch maximum willingness to pay threshold of €40,000 per quality-adjusted life-year, which is representtative for the threshold used in developed countries, was used to determine whether the found cost of treatment would be considered effective. Adding cetuximab to a cisplatin-5-fluorouracil first- regimen for advanced esophageal squamous cell carcinoma resulted in an the incremental cost-effectiveness ratio of €176,836 per quality-adjusted life-year. Sensitivity analysis shows that there is a chance of less than 0.001 that the incremental cost-effectiveness ratio is below the maximum willingness to pay threshold of €40,000 per quality-adjusted life-year. Conclusion - Addition of cetuximab to a cisplatin-5-fluorouracil first- regimen for advanced esophageal squamous cell carcinoma is not cost-effective when appraised according to currently accepted criteria. Cost-effectiveness analyses using outcome data from early clinical trials (i.c. a phase II trial) enable pharmaceutical companies and policy makers to gain early insight into whether a new drug meets the current eligibility standards for reimbursement and thereby potential admittance for use in regular clinical practice.

Predictors and trends in fecal hemoglobin concentration: long term follow-up of population-based FIT-screenees

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Fecal immunochemical testing (FIT) is widely used in colorectal cancer (CRC) screening. Despite the fact that most FITs quantitatively measure fecal Hb ($_f$Hb) concentrations, they are invariably used in a qualitative manner using pre-specified cutoffs and fixed screening intervals. Many countries with FIT-based CRC screening programs are struggling with colonoscopy capacity. Hence, to increase screening efficiency, it makes sense to explore if participants with a negative result at first screen can be categorized according to their $_f$Hb concentration to predict their future risk of developing colorectal adenoma and cancer. From 2006 to 2014 average-risk subjects aged 50-74 years were invited for four rounds of population-based FIT screening using a $_f$Hb cut-off of 10 µg Hb/g feces. For this study all subjects with a negative FIT at their first participation in screening were included to assess their future risk of advanced neoplasia (AN). Base $_f$Hb was divided in 6 categories per 2 µg Hb/g ranging from 0 to <10 µg Hb (i.e. 0, >0-2, >2-4, >4-6, >6-8 and >8<10) to calculate cumulative incidence of AN using life tables. A Cox proportional hazard regression analysis was performed to calculate hazard ratios to identify factors associated with the development of AN. Factors that were considered included age, gender, base $_f$Hb, $_f$Hb concentrations in following rounds, and social economic status. In total 13.566 subjects were invited for screening of whom 9.561 (70%) eligible subjects participated at least once. Out of these participants 7.663 (92%) had a negative FIT at the first screening round and were included for analyses. Median follow-up was 4.7 years (IQR 2.0-6.1 years). Screenees with a base $_f$Hb between 8–10 µg Hb/g had a 28% higher cumulative incidence of AN than those with a base $_f$Hb of 0 µg Hb/g (5 vs. 33%; p<0.001). Hazard ratios increased from 1.34 to 7.97 for base $_f$Hb of respectively 0-2 up to 8-10 µg Hb/g compared to a $_f$Hb of 0 µg Hb/g (p<0.0001). For screenees with a $_f$Hb concentration of >5 µg in subsequent rounds hazard ratios were 2.20 (p<0.02) and 3.08 (p<0.02) for the second and third round respectively.
Conclusion Among screenees with a negative FIT, the base $_f$Hb concentration is an independent predictor for the risk of future AN with up to an 8-fold hazard increase. Furthermore, subsequent FIT results > 5µg Hb/g increase the risk of AN by two and three fold. These findings suggest a role for $_f$Hb in individual tailored screening, and may permit possible extension of screening interval for those with a base FIT result of 0 µg Hb/g to optimize use of limited colonoscopy resources.

Detection of advanced colorectal lesions in asymptomatic individuals; comparison of FIT, clinical risk factors and stool DNA.

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The fecal immunochemical test (FIT) is widely accepted as non-invasive triage test to select individuals for colonoscopy in the setting of colorectal cancer (CRC) population screening. However, additional methods might help to increase its diagnostic accuracy. We aimed to compare the performance of FIT combined with a panel of stool DNA (sDNA) markers and/or clinical risk factors as triage test in an asymptomatic CRC screening population. Data were collected from the colonoscopy arm of a randomized trial comparing colonoscopy with CT-colonography for population screening. FIT, whole stool samples and information on clinical risk factors were prospectively collected. Included risk factors were gender, age, familial history of CRC and smoking status. The sDNA panel included quantitative molecular assays for KRAS mutations and for aberrant NDRG4 and BMP3 methylation. Performance of FIT alone was compared to the risk factors plus FIT model, the sDNA plus FIT model, and a model of all factors combined, by use of Receiver Operator Characteristic (ROC) analyses. All FIT-plus models were designed by means of logistic regression modelling. Advanced colorectal lesions were defined as CRC, advanced adenomas (AA) and advanced (dysplastic and/or ≥10mm) serrated polyps (ASP). Analyses were performed in a complete-case only setting. 884 individuals (52% male) with a median age of 60 years (range 50-75) were included, of which 6 (0.7%) had CRC, 75 (8.5%) had AA and 25 (2.8%) had ASP as most advanced lesion. ROC analysis revealed an Area Under the Curve of 0.66 (95% CI 0.60-0.72) for FIT, compared to 0.74 (0.68-0.79) for the risk factors-FIT model ($p<0.01$), 0.74 (0.69-0.80) for the sDNA-FIT model ($p<0.01$) and 0.76 (0.71-0.81) for the combined model ($p<0.001$) (Figure 1). At a specificity of 95%, advanced lesions were detected with highest sensitivity by the combined model (34%), followed by the sDNA-FIT model (33%), the risk factors-FIT model (29%) and FIT alone (27%). At a specificity of 85%, advanced colorectal lesions were detected with highest sensitivity by the sDNA-FIT model (52%), followed by the combined model (50%), the risk factors-FIT model (44%) and FIT alone (42%). In an asymptomatic CRC screening cohort, both the addition of clinical risk factors as well as sDNA markers improved the detection of advanced colorectal lesions by FIT compared to FIT alone. A combined model based on clinical risk factors, sDNA as well as FIT did not show an additional improvement. Due to the marginal extent of the differences in sensitivity at a high specificity level (95%), the clinical value of these FIT-plus models seem largely depending on targeted specificity cut-off.

Incidence and endoscopic appearance of colorectal neuroendocrine tumors: a population-based study

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Although the neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC) account for a small fraction of all colorectal neoplasms, their endoscopic detection and diagnosis are essential for treatment (endotherapy versus surgery) and follow-up recommendation. According to the WHO classification, colorectal neuroendocrine tumors comprise NET grade 1, NET grade 2 and neuroendocrine carcinomas (grade 3). Little is known about the incidence of tumor subtypes in colonoscopy populations, their endoscopic features and relation with histopathology. We therefore examined the incidence, endoscopic appearance and histopathology of NET/NEC in a population-based study. We previously assembled a population-based cohort including all patients diagnosed with colorectal cancer (CRC) from January 2001 to December 2010, in a large gastroenterology practice. We retrieved all medical records of NET and NEC cases by cross-linking the national pathology database and hospital clinical data. Location, size and shape of the NET/ NEC were extracted from endoscopy reports. We applied the Paris classification for superficial neoplasms to categorize the shape of NETs and the Borrmann classification to categorize NECs. Experienced pathologists diagnosed NET/NEC cases based on immunohistochemical staining (synaptophysin and chromogranin A). In total, 5303 CRCs were diagnosed in a population of 623,728 inhabitants over a 10 year period. Of them, 1.0% (53 cases) were NETs/NECs (54.7% males, median age 65, range 41-88 yrs). Of the 53 cases, 35 were diagnosed with a colorectal NET and 18 with a NEC. From 2001 to 2010, incidence of colorectal NET/NEC in this population-based cohort was low, ranging from 0.3 to 1.6/100.000 inhabitants. With regard to endoscopic appearance, when comparing NET with NEC, NET are significantly smaller in size: (median, interquartile [IQR] range: 8 [4.75-16.25]mm) than NECs (median [IQR]: 50 [37.5-66.5]mm), $p<0.001$), more often located in the rectum (77.2% vs 50.0%, $p<0.001$) and had more often a polypoid shape (88.6% vs 7.7%, $p<0.001$). NETs were more likely to have a yellowish (lipoma-like) color (54.3% vs 0.0%), while NECs were often associated with ulceration and/or necrosis (72.2% vs 17.1%). Population-based data point to a stable, very low incidence of NETs/NECs in NL. Endoscopic features such as size, shape, color, presence of necrosis/ulceration are significantly different between colorectal NET and NEC. Standardized endoscopic characterization of NET and NEC should be implemented nationally and internationally to provide a basis for evidence-based treatment and surveillance recommendations.

CT-colonography versus colonoscopy for detection of high-risk sessile serrated polyps

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Sessile serrated polyps (SSPs) are the suggested precursors of 15-30% of all colorectal cancers (CRCs). Therefore, CRC screening modalities should also be designed to detect high-risk SSPs. Computed tomography colonography (CTC) can be used for CRC screening, however data on the performance of CTC in the detection of high-risk SSPs are lacking. We aimed to compare the performance of CTC and colonoscopy to detect high-risk SSPs (SSP with dysplasia and/or SSP ≥10mm in size) in a screening program for average-risk individuals. This study has a post-hoc design, using data from a randomized controlled trial that compared CTC with colonoscopy for population screening. Screening-naïve average-risk individuals, aged 50-75 years were eligible to be included. In total 8,844 individuals were invited to participate (1:2 allocation). All individuals diagnosed at CTC with at least one lesion ≥10mm in size were referred for colonoscopy. Individuals with only 6-9mm lesions were offered surveillance CTC after 3 years, followed by colonoscopy in case of any lesion ≥6mm. Yield of both was accumulated to mimic current CTC referral strategy (referral of individuals with any lesion ≥6mm), and compared with colonoscopy for the detection of high-risk SSP on a per participant level using multiple logistic regression analysis. In total 982 CTC and 1,276 colonoscopy invitees participated in the study (Figure 1). Mean age of CTC participants was 60.3 years (SD 6.4) and 507 were male (52%). Mean age of colonoscopy participants was 60.1 years (SD 6.2) and 652 were male (51%). In the colonoscopy arm, 4.3% of individuals were diagnosed with ≥1 high-risk SSP, compared to 0.8% in the CTC arm (OR 5.5; 95% CI 2.6-11.6; p<0.001) (Table 1). As most advanced lesion, 3.1% of individuals in the colonoscopy arm were diagnosed with high-risk SSPs, compared to 0.4% in the CTC arm (OR 7.7; 95% CI 2.7-21.6; p<0.001). As compared to findings in the colonoscopy arm, the current CTC strategy showed a marked lower detection for especially flat high-risk SSPs (17 vs 0), high-risk SSP located in the proximal colon (32 vs 1) and SSPs with dysplasia (30 vs 1). We demonstrated that the detection rate of high-risk SSPs is significantly lower for CTC based screening when compared to colonoscopy. This might have implications for the value of CTC as primary CRC screening tool in opportunistic screening. Results from other large screening cohorts are needed to elaborate our findings and to determine the performance of CTC in the detection of advanced neoplasia, including high-risk SSPs, compared to the performance of colonoscopy, both in an opportunistic as well as a population-based screening setting.

RNF43 in serrated polyposis and serrated polyps

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Nearly a third of all colorectal malignancies are expected to develop through the serrated pathway. Serrated polyps are the precursor lesions to colorectal cancer in the serrated pathway. Patients with multiple serrated polyps in their colorectum are classified as serrated polyposis syndrome (SPS) by criteria defined by the WHO. Unfortunately, there is no known germ mutation for patients with SPS and the serrated pathway to colorectal cancer is mostly not clarified yet. Recently, germ truncating mutations in the RNF43 gene have been associated with SPS. It has also been shown that 18-20% of the patients with sporadic colorectal carcinomas (CRC) have a somatic mutation in RNF43. Our first aim was to determine the presence of germ RNF43 mutations in a cohort of SPS patients. Twenty-five SPS patients were tested on having a mutation in one of the exones of the RNF43 gene in their germ DNA. The DNA was analyzed by method of PCR and Sanger Sequencing. No truncating RNF43 germ mutations were found in our cohort of SPS patients. Our second aim was to determine the presence of somatic RNF43 mutations in codon 117 and 659 in subtypes of serrated polyps (SP). We isolated DNA from 25 hyperplastic polyps, 35 sessile serrated lesions and 39 traditional serrated adenomas. Immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 was performed to determine the MSI status of the colorectal lesions. Somatic RNF43 mutations encoding p.Arg117fs and p.Gly659fs were found in 7.5% of TSA. These TSA also showed loss of expression of mismatch-repair (MMR) proteins MSH2 and/or MSH6. The other subtypes of polyps did not show any somatic RNF43 mutation in codon 117 or codon 659. In conclusion, RNF43 germ mutations are not frequently observed in Dutch SPS patients. Somatic mutations in RNF43 are not likely to be driver mutations in the formation of different subtypes of serrated polyps, but are likely to occur secondary to microsatellite instability.

Informatie over de expositie treft u op de volgende bladzijden aan.

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Background Patients with multiple colorectal adenomas may carry germ mutations in the APC or MUTYH gene. There are few studies on the prevalence of APC and MUTYH mutations in large populations with polyps. The aim of this study is to determine the prevalence of familial adenomatous polyposis (FAP, associated with a pathogenic APC mutation) and MUTYH associated polyposis (MAP) in a cohort of polyposis patients and to determine patient characteristics predictive of finding a pathogenic germ mutation. Methods We investigated a cohort of 2151 patients who had undergone sequencing of the APC gene and/or MUTYH gene ascertained from family cancer clinics in the Netherlands. DNA samples were sent in between 1992 and present. Predicting factors of a pathogenic germ mutation were analyzed using logistic regression analysis and included: cumulative polyp count, age of diagnosis, CRC diagnosis and family history. Mutation detection rate was also analyzed per year. Results Through evaluating the phenotypic differences between individuals with FAP and MAP, a pattern can be seen. The prevalence of APC mutations significantly increases with polyp count ('category in brackets): (0) 2% [95%CI 0.4-6], (1-9) 1% [0.2-3], (10-19) 1% [0.4-3], (20-49) 8% [6-11], (50-99) 12% [8-19], (100<)71% [66-76]) where, notably MAP has his peak prevalence in individuals with 50-99 adenomas: (0) 1% [0.1-5], (1-9) 3% [CI 1-6], (10-19) 2% [0.9-4], (20-49) 7 % [5-9], (50-99) 16% [11-24], (>100) 7% [5-11]) Polyp count and younger age at adenoma discovery were associated with a pathogenic mutation in the multivariable analyses. Interestingly, family history of CRC was not a predictive factor of identifying APC or MUTYH mutations when corrected for – amongst others - polyp count (APC: 1.02 [95%CI: 0.67-1.6]; MUTYH: 0.95 [95%CI: 0.6-1.5]). The detection rate of APC and MUTYH mutations steadily declines over the years from 54% before 2004 till 14% after 2004 on average. Conclusion FAP and MAP prevalence varies by polyp count, more specifically FAP predominated the classic polyposis phenotype (100 polyps or more) and biallelic MUTYH dominated the attenuated polyposis (20-99 polyps) type. Our results show that polyp count is more important in selecting patients for germ mutation screening than family history of CRC. The declining mutation detection rate needs attention and might impact referral policy by the gastroenterologist.

Diarrhea is a risk factor for liver injury and may lead to Intestinal Failure Associated Liver Disease in critical illness

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Liver injury is common in the ICU. Risk factors include toxicity of drugs and TPN, but etiology is often unknown. Currently, there is emerging interest in the relation between intestinal failure (IF) and liver injury (IF Associated Liver Disease, IFALD). The occurrence of IFALD is mostly attributed to the use of TPN in patients with IF, but recent data suggest that interruption of the enterohepatic cycle also may be an important cause. Diarrhea induces nutrient malabsorption in critical illness but may also impair intestinal reabsorption of bile acids, interrupting the gut-liver axis. Along this line of reasoning diarrhea may be an unidentified risk factor for liver injury in critical illness through the development of IFALD. We aimed to study whether diarrhea is an independent risk factor for the development of liver injury in critically illness. We retrospectively analyzed all patients that were admitted >48 hours to our ICU from 01-09-2014 until 28-02-2015. Markers of liver injury and other parameters were recorded on the day diarrhea (>250 ml/day) developed (median at the second day of ICU admission) and 2 days thereafter. In patients without diarrhea data were recorded at the day of ICU admission and 2 days later. Patients with liver injury (defined as an elevation of serum γ-GT or alkaline phosphatase levels above reference values) at inclusion were excluded. 79 patients remained for analysis of which 19 (24%) developed liver injury). Uni- and multivariate analyses were performed to identify risk factors for liver injury. At baseline there were no significant differences between both groups. In patients who developed liver injury, diarrhea was more frequent than in control patients (58% vs. 22%, p=0.003, X2-test). In a multivariate binary logistic regression analysis diarrhea was found to be an independent risk factor for the development of liver injury. (OR 4.1 (95% CI 1.2-14.5), p=0.028). pConclusions: Diarrhea is an independent risk factor for the development of liver injury in the ICU. This supports the hypothesis that disturbance of the gut-liver axis due to diarrhea and bile salt malabsorption in ICU patients should be regarded as a manifestation of intestinal failure, potentially leading to intestinal failure associated liver disease. Future research should be aimed at mechanisms of IFALD in ICU patients and at interventions limiting malabsorption or its consequences.

The effects of two weeks synbiotic supplementation on intestinal permeability: a randomized controlled trial

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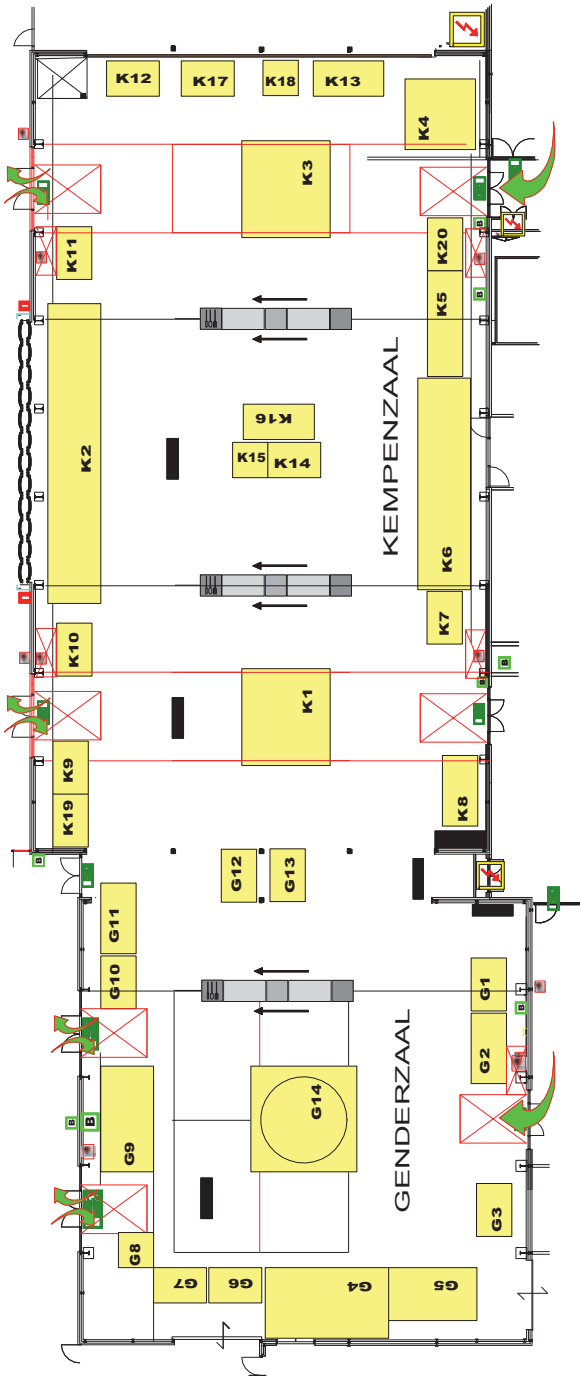
The intestinal barrier consists of an epithelial, mucus, and immunological barrier. Impaired intestinal barrier function may lead to the infiltration of noxious luminal substances into the intestinal mucosa. This may induce local immune activation or stimulate afferent nerve endings and, subsequently, cause symptoms such as abdominal pain. Pro-, pre- and especially synbiotics are suggested to exert beneficial effects on the intestinal barrier, thereby decreasing intestinal epithelial permeability. The objective of this study was to assess the influence of two weeks synbiotic supplementation on intestinal permeability *in vivo* in healthy adults. We hypothesized that two weeks synbiotic supplementation will reinforce intestinal barrier function, as reflected by a decrease in intestinal permeability *in vivo.* Twenty healthy adults completed a double-blind, placebo-controlled, randomized parallel design study. Groups either received synbiotic (10 g FOS P06 + 1.5 × 10^{10} CFU Ecologic® 825 per day) or placebo supplements for two weeks. Intestinal segment specific permeability was assessed non-invasively by oral administration of multiple sugar probes and, subsequently, assessing the excretion of these probes in urine. This test was conducted prior to and after intervention in the absence and, on separate test days, in the presence of an indomethacin challenge. The non-steroidal anti-inflammatory drug indomethacin has been shown to induce reversible damage to the upper gastrointestinal tract, and was applied as a model to study the effects of the supplementation on compromised intestinal barrier function. Gastroduodenal and small intestinal permeability were significantly increased in the indomethacin stressed condition, compared with the unstressed condition, as assessed by urinary sucrose recovery (0.248 [0.206-0.318] vs. 0.363 [0.291-0.637] $P<0.05$) and urinary lactulose/rhamnose excretion ratio (0.047 [0.039-0.069] vs. 0.118 [0.082-0.165] $P<0.001$). Indomethacin did not affect colonic permeability as determined by sucralose/erythritol excretion ratio. The synbiotic supplementation did not affect gastroduodenal, small intestinal, and colonic permeability as reflected by urinary sucrose recovery, lactulose/rhamnose excretion ratio and sucralose/erythritol excretion ratio, respectively. In conclusion, we confirmed that indomethacin causes damage to the stomach and small intestine. Further, we conclude that two weeks supplementation of FOS P06+Ecologic® 825 does not reinforce gastroduodenal, small intestinal or colonic permeability in a healthy gut, nor in a compromised gut.

Lijst van standhouders, voorjaarscongres NVGE, 17 en 18 maart 2016 te Veldhoven

G = Genderzaal, D = Diezezaal, K = Kempenhal	*Standnummer*
AbbVie B.V.	G13
Alexion Pharma Netherlands BV	G11
Allergan B.V.	K13
Alvleeskliervereniging	K16
Boston Scientific Nederland B.V.	G14
Bristol Myers Squibb	K1
Cook Nederland B.V.	K4
Covidien	K5
Dr. Falk Pharma Benelux B.V.	G1
Erbe Nederland B.V.	K8
Ferring B.V.	K7
FMH Medical B.V.	K6
Fresenius Kabi Nederland B.V.	K19
Gilead Sciences Netherlands B.V.	K10
Hitachi Medical Systems	G5
Ipsen Farmaceutica B.V.	G6
Janssen-Cilag B.V.	K9
Lamepro B.V.	G7
Maag Lever Darm Stichting	K14
Medix Publishers BV`	G8
Merck Sharp & Dohme B.V.	K3
Mermaid Medical	G3
Norgine B.V.	G9
Olympus Nederland B.V.	K2
Pentax Medical	G4
Prion Medical BV	K17
RMS Medical Devices	G10
Stichting Opsporing Erfelijke Tumoren	K15
Teva Nederland BV	K20
Tramedico B.V.	K11
Vifor Pharma Nederland B.V.	G2
W.L. Gore & Associates	K18
Wellform Medical BV	K12
Zambon Nederland B.V.	G12



Genderzaal

G 1	Dr. Falk Pharma Benelux BV
G 2	Vifor Pharma Nederland BV
G 3	Mermaid Medical
G 4	Pentax Nederland Medical
G 5	Hitachi Medical Systems BV
G 6	Ipsen Farmaceutica BV
G 7	Lamepro BV
G 8	Medix Publisher BV
G 9	Norgine BV
G 10	RMS Medical Devices
G 11	Alexion Pharmaceuticals
G 12	Zambon Nederland BV
G 13	Abbvie BV
G 14	Boston Scientific Nederland BV

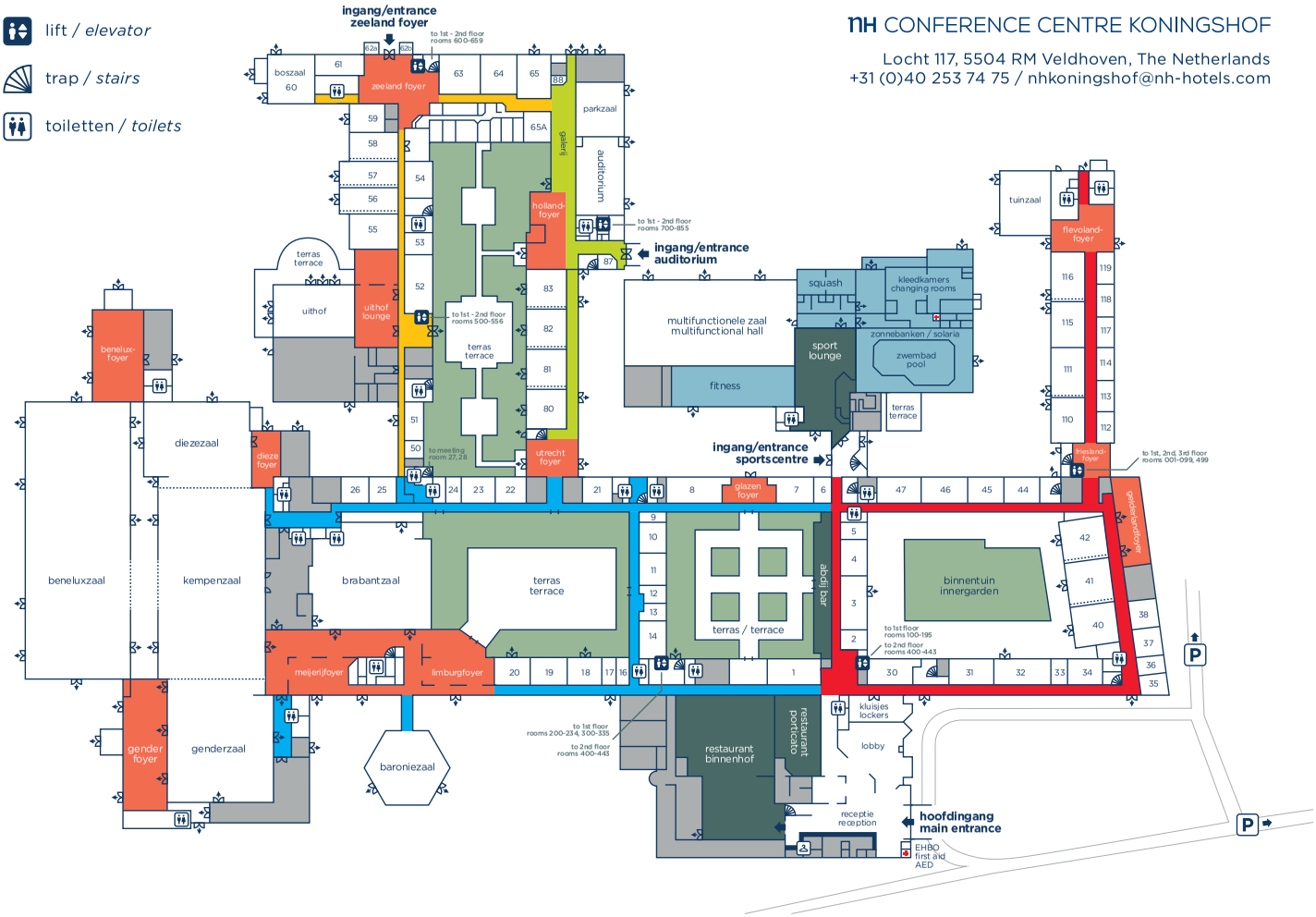
Kempenzaal

K 1	Bristol-Myers Squibb BV
K 2	Olympus Nederland BV
K 3	MSD BV
K 4	COOK Nederland BV
K 5	Medtronic
K 6	FMH Medical BV
K 7	Ferring BV
K 8	Erbe Nederland BV
K 9	Janssen BV
K 10	Gilead Sciences Nederland BV
K 11	Tramedico
K 12	Wellform Medical BV
K 13	Allergan
K 14	MLDS
K 15	Stichting Opsporing Erfelijke Tumoren
K 16	Alvleeskliervereniging
K 17	Prion Medical BV
K 18	W.L. Gore & Associates
K 19	Fresenius Kabi Nederland BV
K20	Teva Nederland BV

lift / *elevator*

trap / *stairs*

toiletten / *toilets*



NH CONFERENCE CENTRE KONINGSHOF

Locht 117, 5504 RM Veldhoven, The Netherlands
+31 (0)40 253 74 75 / nhkoningshof@nh-hotels.com

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
- □ Sectie Inflammatoire Darmziekten
- □ Sectie Gastrointestinale Oncologie

n.b. Aanvullende lidmaatschappen van 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.

IBAN:

BIC:

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 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.

IBAN:

BIC:

Datum en handtekening:

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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).

VERKORTE PRODUCTINFORMATIE PRADAXA®

Samenstelling: 75 mg, 110 mg of 150 mg dabigatran etexilaat (als mesilaat) per capsule. Farmacotherapeutische categorie: directe trombineremmers. **Farmaceutische vorm:** harde capsules. **Therapeutische indicaties: 1.** Preventie van cerebrovasculair accident (CVA) en systemische embolie bij volwassen patiënten met non-valvulair atriumfibrilleren met één of meer risico factoren zoals: CVA of TIA in de anamnese, symptomatische hartfalen (≥ NYHA 2), ≥75 jaar, diabetes mellitus, hypertensie. **2.** Behandeling van diep veneuze trombose (DVT) en longembolie (PE) en preventie van recidiverende DVT en PE bij volwassenen.**3.** Primaire preventie van veneuze trombo-embolische (VTE) aandoeningen bij volwassen patiënten die electief een totale heupvervangende operatie (THO) of een totale knievervangende operatie (TKO) hebben ondergaan. **Dosering en wijze van toediening:** Capsules niet openen, innemen met een glas water, met of zonder voedsel. Preventie van CVA of systemische embolie, behandeling van DVT/PE, preventie van recidiverende DVT/PE: 300 mg per dag, ingenomen als één capsule van 150 mg tweemaal daags. Patiënten van 80 jaar en ouder: 220 mg ingenomen als één capsule van 110 mg tweemaal daags. Preventie VTE na electieve TKO: éénmaal daags 220 mg, ingenomen als 2 capsules van 110 mg. Behandeling binnen 1 – 4 uur na de operatie starten, daarna 10 dagen voortzetten met 2 capsules éénmaal daags. Preventie VTE na electieve THO: éénmaal daags 220 mg, ingenomen als 2 capsules van 110 mg. Behandeling binnen 1-4 uur na de operatie starten met 1 capsule, daarna 28-35 dagen voortzetten met 2 capsules éénmaal daags. Na TKO of THO is bij patiënten met een matig verminderde nierfunctie (creatinineklaring 30 – 50 ml/min) en ouderen (> 75 jaar) de aanbevolen dosis 150 mg per dag, ingenomen als 2 capsules van 75 mg. Zolang geen hemostase is vastgesteld moet het begin van de behandeling bij TKO en THO worden uitgesteld. Begint de behandeling niet op de dag van de operatie, dan moet worden gestart met éénmaal daags 2 capsules. **Contra-indicaties:** Overgevoeligheid voor het werkzame bestanddeel of voor één van de hulpstoffen, ernstig verminderde nierfunctie (creatinineklaring < 30 ml/min), actieve, klinisch significante bloedingen, laesie of aandoening die als een significante risicofactor voor majeure bloedingen wordt beschouwd, gelijktijdige behandeling met andere anticoagulantia, verminderde werking van de lever of leveraandoeningen die naar verwachting invloed hebben op de overleving, gelijktijdige behandeling met systemische ketoconazol, ciclosporine, itraconazol, en dronedarone, kunsthartklep waarvoor antistollingsbehandeling vereist is. **Bijzondere waarschuwingen en voorzorgen voor gebruik:** Voor de start van de behandeling met dabigatran dient de nierfunctie bepaald te worden door berekening van de creatinineklaring (m.b.v. de Cockgroft-Gaultmethode). Tijdens de behandeling dient de nierfunctie bepaald te worden in klinische situaties waarbij verwacht wordt dat de nierfunctie zal afnemen of verslechteren en tenminste eens per jaar bij patiënten ≥75 jaar of met nierinsufficiëntie. Bij patiënten met een verhoogde kans op bloedingen dient een dosis van 220 mg dabigatran, ingenomen als één capsule van 110 mg tweemaal per dag, overwogen te worden voor de preventie van CVA of systemische embolie en bij de behandeling van DVT/PE en preventie van recidiverende DVT/PE. Een stollingstest (dTT, ECT of aPTT) kan worden gebruikt om patiënten met verhoogde dabigatran concentraties te identificeren. Een INR-test is onbetrouwbaar bij patiënten die dabigatran gebruiken. Patiënten die dabigatran gebruiken, hebben, wanneer zij een operatie of invasieve procedure ondergaan, een verhoogd risico op bloedingen. Bij patiënten met verhoogde leverenzymen > 2 maal ULN, wordt dabigatran niet aanbevolen. Er is geen ervaring bij kinderen en adolescenten. Anesthesie via een postoperatieve inwendige epidurale katheter wordt niet aanbevolen. Na het verwijderen van de katheter moet ten minste twee uur gewacht worden met de eerste toediening van dabigatran. Niet gebruiken tijdens zwangerschap of borstvoeding. **Interacties met andere geneesmiddelen:** Er is geen of weinig ervaring met de volgende behandelingen die de kans op bloedingen, in combinatie met het gebruik van dabigatran, kunnen verhogen: anticoagulantia zoals UFH, LMWH en heparinederivaten, trombolytische middelen, vitamine K-antagonisten, rivaroxaban of andere orale anticoagulantia en plaatjesaggregratieremmers zoals GPIIb/IIIa-receptorantagonisten, ticlopidine, prasugrel, ticagrelor, dextran en sulfinpyrazon. Zowel het gebruik van acetylsalicylzuur, clopidogrel, SSRI's, SNRI's, als chronisch gebruik van NSAID's verhoogden in de RE-LY-studie het risico op bloedingen bij zowel dabigatran als warfarine. Dabigatran wordt niet gemetaboliseerd door het cytochroom-P450-systeem en heeft geen effect *in vitro* op menselijke cytochroom-P450-enzymen. De pro-drug dabigatran etexilaat is een substraat voor de effluxtransporter Pglycoproteïne. Proteaseremmers beïnvloeden Pglycoproteïne en gelijktijdige behandeling met dabigatran en deze middelen wordt daarom niet aanbevolen. Gelijktijdige toediening van P-glycoproteïne-inductoren (zoals rifampicine, sint-janskruid (Hypericum Perforatum), carbamazepine of fenytoïne) dient vermeden te worden. Preventie van CVA en systemische embolie, behandeling van DVT/PE, preventie van recidiverende DVT/PE: Voorzichtigheid is geboden bij gelijktijdig gebruik van dabigatran en lichte tot matig sterke Pglycoproteïneremmers (bv. amiodaron, kinidine, verapamil en ticagrelor), in het bijzonder bij patiënten met een licht tot matig verminderde nierfunctie. Bij patiënten die tegelijk dabigatran en verapamil krijgen, dient de dosis dabigatran te worden verlaagd naar 220 mg ingenomen als één capsule van 110 mg tweemaal per dag. Gelijktijdige behandeling met tacrolimus wordt niet aanbevolen. Gelijktijdige behandeling met protonpompremmers (PPI) leek de werkzaamheid van dabigatran niet te verminderen. De toediening van ranitidine samen met dabigatran had geen klinisch relevant effect op de mate waarin dabigatran werd geabsorbeerd. Preventie van VTE: Bij patiënten die gelijktijdig dabigatran en amiodaron, kinidine of verapamil gebruiken dient de dosering verlaagd te worden tot 150 mg dabigatran eenmaal daags. Bij patiënten met matige nierinsufficiëntie die gelijktijdig dabigatran en verapamil gebruiken dient een dosis van 75 mg dabigatran overwogen te worden. Bij patiënten die gelijktijdig dabigatran en claritromycine gebruiken dient nauwgezet klinisch toezicht te worden gehouden, in het bijzonder wat betreft het optreden van bloedingen, speciaal bij patiënten met milde tot matige nierinsufficiëntie. **Bijwerkingen:** De meest gemelde bijwerkingen zijn bloedingen. Ernstige bloedingen kunnen, ongeacht waar ze in het lichaam optreden, leiden tot invaliditeit, levensbedreigend zijn of zelfs een dodelijke afloop tot gevolg hebben. Indien ernstige bloedingen optreden moet de behandeling worden gestopt en de bron van de bloeding worden onderzocht. Er is geen antidotum voor dabigatran. Andere vaak voorkomende klachten zijn buikpijn, diarree, dyspepsie, misselijkheid en abnormale leverfunctie / leverfunctietest (minder dan 10%). Preventie van CVA en systemische embolie: Bloedingen kwamen in totaal bij ongeveer 16,6% van de patiënten voor; ernstige bloedingen werden zelden gerapporteerd in het klinisch onderzoek (minder dan 3,5%). Dabigatran werd in de RELY studie gerelateerd aan een hogere incidentie van majeure gastro-intestinale bloedingen. De toediening van een protonpompremmer kan overwogen worden om een gastro-intestinale bloeding te voorkomen. Behandeling van DVT/PE, preventie van recidiverende DVT/PE: Bloedingen kwamen in totaal bij ongeveer 19,4% van de patiënten voor; ernstige bloedingen werden zelden gerapporteerd in het klinisch onderzoek (minder dan 1,0%). Preventie van VTE: Bloedingen kwamen in totaal bij ongeveer 14% van de patiënten voor; ernstige bloedingen (inclusief wondbloedingen) werden zelden gerapporteerd (minder dan 2%). **Verpakking:** Pradaxa 75 mg, 110 en 150 mg worden geleverd in aluminium blisterverpakkingen van 60 stuks. **Afleverstatus:** U.R. **Registratie:** EU/1/08/442/003, EU/1/08/442/007, EU/1/08/442/011. Registratiedatum 18 mrt 2008 (VTE preventie na THO/TKO), 04 aug 2011 (CVA), 03 juni 2014 (acute DVT/LE, preventie recidiverende DVT/LE). **Vergoeding en prijzen:** Pradaxa wordt volledig vergoed binnen het GVS, mits geïnitieerd door een specialist. Voor prijzen, zie KNMP taxe. Voor volledige productinformatie is de 1B tekst op aanvraag beschikbaar**.** Boehringer Ingelheim bv., Comeniusstraat 6, 1817 MS Alkmaar. Tel. 0800-2255889. **Datum herziening van de tekst:** 6 augustus 2015.

VERKORTE PRODUCTINFORMATIE PRAXBIND®

▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg worden verzocht alle vermoedelijke bijwerkingen te melden. **Samenstelling:** Elke injectieflacon bevat 2,5 g idarucizumab, 2 g sorbitol en 25 mg natrium in 50 ml. Farmacotherapeutische categorie: specifiek antidotum voor dabigatran. **Farmaceutische vorm:** Oplossing voor injectie/infusie. **Therapeutische indicaties:** Volwassen Pradaxa (dabigatran etexilaat) gebruikers wanneer het anticoagulerend effect van dit middel snel moet worden geneutraliseerd voor spoedoperaties/ dringende ingrepen of bij een levensbedreigende/ongecontroleerde bloeding. **Dosering en wijze van toediening:** Uitsluitend voor gebruik in het ziekenhuis. De aanbevolen dosis is 5 g (2 x 2,5 g/50 ml), intraveneus toegediend als twee achtereenvolgende infusies van elk 5 tot 10 minuten of als bolusinjectie. **Contra-indicaties:** Geen. **Bijzondere waarschuwingen en voorzorgen voor gebruik:** Idarucizumab heft alleen het anticoagulerend effect van dabigatran, niet van andere anticoagulantia. Idarucizumab kan worden gebruikt in combinatie met standaard ondersteunende maatregelen, die vanuit medisch oogpunt in aanmerking dienen te komen. Het risico van het gebruik van Praxbind bij patiënten met een bekende overgevoeligheid (bijv. anafylactoïde reactie) voor idarucizumab of voor een van de hulpstoffen (bijv bij erfelijke fructose intolerantie) moet zorgvuldig worden afgewogen tegen het mogelijke voordeel. Indien een anafylactische reactie of een andere ernstige allergische reactie optreedt, dient de toediening van Praxbind onmiddellijk te worden gestaakt en een passende behandeling te worden gestart. Door neutralisatie van de dabigatrantherapie worden patiënten blootgesteld aan het verhoogde trombotisch risico van hun onderliggende aandoening en moet worden overwogen om de anticoagulatiebehandeling te hervatten zodra dat medisch verantwoord is. Praxbind veroorzaakt een voorbijgaande proteïnurie die niet wijst op nierschade, waarmee bij urineonderzoek rekening dient te worden gehouden. Praxbind bevat 2,2 mmol (of 50 mg) natrium per dosis waarmee bij patiënten met een natriumbeperkt dieet rekening te worden gehouden. **Interacties met andere geneesmiddelen:** Klinisch relevante interacties met andere geneesmiddelen worden onwaarschijnlijk geacht. In preklinische onderzoeken zijn er geen interacties aangetoond met infusievloeistoffen voor volume expansie, concentraten van stollingsfactor (bijv. (geactiveerde) protrombinecomplex concentraten, recombinant factor VIIa) en andere anticoagulantia (bijv. andere trombineremmers dan dabigatran, factor Xa remmers, inclusief laagmoleculair-gewichtheparine, vitamine K antagonisten, heparine). **Bijwerkingen:** De veiligheid van Praxbind is onderzocht bij 224 gezonde deelnemers en in een lopend fase III onderzoek bij 123 patiënten. Er zijn daarbij geen bijwerkingen vastgesteld. **Verpakking:** Oplossing van 50 ml in glazen injectieflacon (type I glas), met butylrubber stop, aluminium kap en etiket met geïntegreerde ophanglus. **Afleverstatus:** U.R. **Registratie:** EU/1/15/1056/001. **Vergoeding en prijzen:** Voor prijzen, zie KNMP taxe. Voor volledige productinformatie is de 1B tekst op aanvraag beschikbaar. Boehringer Ingelheim bv., Comeniusstraat 6, 1817 MS Alkmaar. Tel. 0800-2255889.

Boehringer Ingelheim

Verkorte productinformatie *Daklinza*®
▼ **Dit geneesmiddel is onderworpen aan aanvullende monitoring. Samenstelling**: Daklinza filmomhulde tabletten bevatten daclatasvir dihydrochloride overeenkomend met 30 mg of 60 mg daclatasvir. **Farmacotherapeutische categorie**: direct werkend antiviraal middel, ATC-code: J05AX14. **Indicaties**: Daklinza is in combinatie met andere geneesmiddelen geïndiceerd voor de behandeling van chronische hepatitis C-virus (HCV) infectie bij volwassenen. Zie verder SPC voor compleet overzicht van de verschillende combinatietherapieën met Daklinza en behandelduur (rubriek 4.2, 4.4 en 5.1). **Dosering**: De aanbevolen dosis Daklinza is 60 mg eenmaal daags, oraal ingenomen, met of zonder maaltijd. Daklinza moet worden toegediend in combinatie met andere geneesmiddelen. *Speciale populaties:* Er is geen dosisaanpassing voor Daklinza nodig bij ouderen (patiënten ≥ 65 jaar), patiënten met nierfunctiestoornis en patiënten met lichte (Child-Pugh A, score 5-6), matige (Child-Pugh B, score 7-9) of ernstige (Child-Pugh C, score ≥ 10) leverfunctiestoornis. Daklinza is niet onderzocht bij patiënten met gedecompenseerde cirrose. *Pediatrische patiënten:* De veiligheid en werkzaamheid van Daklinza bij kinderen en jongeren in de leeftijd tot 18 jaar zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. **Contra-indicaties**: Overgevoeligheid voor de werkzame stof of voor (één van) de hulpstoffen. Gelijktijdig gebruik van geneesmiddelen die cytochroom P450 3A4 (CYP3A4) en P-glycoproteïnetransporter (p-gp) sterk induceren en daarom kunnen leiden tot een lagere blootstelling aan en verlies van werkzaamheid van Daklinza. Deze groep van geneesmiddelen omvat, maar is niet beperkt tot, fenytoïne, carbamazepine, oxcarbazepine, fenobarbital, rifampicine, rifabutine, rifapentine, systemisch dexamethason en het kruidenmiddel Sint-Janskruid *(Hypericum perforatum)*. **Waarschuwingen en voorzorgsmaatregelen**: Daklinza mag niet als monotherapie worden toegediend. Daklinza moet worden toegediend in combinatie met andere geneesmiddelen voor de behandeling van chronische HCV-infectie. De veiligheid en werkzaamheid van Daklinza is niet vastgesteld voor de behandeling van HCV-infectie bij pre-, peri- of post-levertransplantatiepatiënten of bij patiënten met een andere orgaantransplantatie, patiënten met gelijktijdige infectie met hiv of HBV en patiënten met gedecompenseerde cirrose. De werkzaamheid van Daklinza als onderdeel van een herbehandelschema bij patiënten met eerdere blootstelling aan een NS5A-remmer is niet vastgesteld. Ernstige bradycardie en hartblok: Er zijn gevallen van ernstige bradycardie en hartblok waargenomen bij gelijktijdig gebruik van Daklinza in combinatie met sofosbuvir en amiodaron, met of zonder andere geneesmiddelen die de hartslag vertragen. Het mechanisme hiervan is niet vastgesteld. Omdat de gevallen potentieel levensbedreigend zijn, mag amiodaron bij patiënten, die Daklinza en sofosbuvir gebruiken, uitsluitend worden gebruikt wanneer andere antiaritmische behandelingen niet worden verdragen of gecontra-indiceerd zijn en wordt nauwlettende controle aanbevolen. Vanwege de lange halfwaardetijd van amiodaron dient ook geschikte monitoring plaats te vinden bij patiënten die in de afgelopen maanden zijn gestopt met amiodaron en die gaan beginnen met Daklinza in combinatie met sofosbuvir. Genotype-specifieke activiteit: Vanwege beperkte ervaring in het gebruik van sofosbuvir in combinatie met Daklinza bij patiënten met genotype 1-infectie en gecompenseerde cirrose zijn er onzekerheden betreffende de meest geschikte manier om Daklinza te gebruiken (duur, rol van ribavirine) bij zulke patiënten. Gegevens die de behandeling van genotype 2-infectie met Daklinza en sofosbuvir ondersteunen zijn beperkt. De gegevens van het ALLY-3 (AI444218) onderzoek ondersteunen een behandelduur van 12 weken van Daklinza + sofosbuvir voor behandelnaïeve en al eerder behandelde patiënten met genotype 3-infectie zonder cirrose. De gegevens van nog lopende *Compassionate Use* programma's, inclusief patiënten met genotype 3-infectie en cirrose, ondersteunen het gebruik van Daklinza + sofosbuvir gedurende 24 weken bij deze patiënten. De relevantie van het toevoegen van ribavirine aan deze behandelcombinatie is onduidelijk. Hoewel het niet is onderzocht bij patiënten met genotype 4-infectie, is de verwachting dat de combinatie van Daklinza en sofosbuvir vergelijkbare activiteit vertoont bij genotype 4 als gezien bij genotype 1, gebaseerd op *in vitro* antivirale activiteit en beschikbare klinische gegevens met Daklinza in combinatie met peginterferon en ribavirine. Daklinza is niet onderzocht bij patiënten met HCV genotypes 5 en 6, en er kan geen behandelschema aanbevolen worden. Zwangerschap en anticonceptievereisten: Daklinza dient niet te worden gebruikt tijdens de zwangerschap en bij vrouwen die zwanger kunnen worden en geen anticonceptie gebruiken. Het gebruik van zeer effectieve anticonceptie dient gecontinueerd te worden gedurende 5 weken na voltooien van de Daklinza behandeling. Ouderen: Klinische gegevens bij patiënten ≥65 jaar zijn beperkt. In klinische studies met Daklinza i n combinatie met sofosbuvir of met peginterferon alfa en ribavirine zijn geen verschillen in respons waargenomen tussen ouderen en jongere patiënten. Interacties met geneesmiddelen: Gelijktijdig gebruik van Daklinza kan de concentratie van andere geneesmiddelen beïnvloeden en andere geneesmiddelen kunnen de concentratie van daclatasvir beïnvloeden. Zie rubriek 4.3 voor een overzicht van geneesmiddelen die gecontra-indiceerd zijn voor gebruik met Daklinza wegens mogelijk verlies van therapeutisch effect. Zie rubriek 4.5 voor bekende en andere mogelijk significante geneesmiddelinteracties. Pediatrische patiënten: Daklinza wordt niet aanbevolen voor gebruik bij kinderen en jongeren tot 18 jaar omdat de veiligheid en werkzaamheid niet zijn vastgesteld bij deze patiënten. Belangrijke informatie over bepaalde bestanddelen van Daklinza: Daklinza bevat lactose. Patiënten met zeldzame erfelijke aandoeningen als galactose-intolerantie, Lapp lactasedeficiëntie of glucose-galactose malabsorptie dienen dit geneesmiddel niet te gebruiken. **Bijwerkingen**: *Daklinza in combinatie met sofosbuvir ± ribavirine:* De meest gemelde bijwerkingen waren vermoeidheid, hoofdpijn en misselijkheid. Er werden geen bijwerkingen van graad 3 of 4 gemeld. Twee patiënten zijn gestopt wegens bijwerkingen, welke als niet-gerelateerd aan de onderzoeksbehandeling werden beschouwd. Bij de behandelcombinatie *Daklinza + sofosbuvir* werden de volgende bijwerkingen zeer vaak gemeld: hoofdpijn en vermoeidheid. Vaak werden gemeld: insomnia, duizeligheid, migraine, nausea, diarree, buikpijn, artralgie en myalgie. Bij de behandelcombinatie *Daklinza + sofosbuvir + ribavarine* werden de volgende bijwerkingen zeer vaak gemeld: anemie, hoofdpijn, hoesten, nausea, pruritus en vermoeidheid. Vaak werden gemeld: verminderde eetlust, insomnia slapeloosheid, prikkelbaarheid, duizeligheid, migraine, opvliegerr, dyspneu, inspanningskortademigheid, neusverstopping, diarree, braken, buikpijn, gastro-oesofageale refluxziekte, constipatie, droge mond, flatulentie, rash, alopecia, droge huid, artralgie en myalgie. Het veiligheidsprofiel van daclatasvir in combinatie met peginterferon alfa en ribavirine was vergelijkbaar met wat wordt gezien bij peginterferon alfa en ribavirine alleen, ook bij patiënten met cirrose. **Afleverstatus**: UR **Vergoeding en prijzen:** voor prijzen zie Z-index. Voor volledige productinformatie, zie Samenvatting van de Productkenmerken. Bristol-Myers Squibb B.V., Utrecht, SPC September 2015.

Referenties

1. SmPC Daklinza.
2. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014; 370: 211-21.

Daklinza® (daclatasvir)

Bristol-Myers Squibb

1392NL15PR10030

Verkorte geneesmiddeleninformatie: ▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden. **Entyvio 300 mg** poeder voor concentraat voor oplossing voor infusie. **Kwalitatieve en Kwantitatieve samenstelling:** Elke injectieflacon bevat 300 mg vedolizumab. Na reconstitutie bevat elke ml 60 mg vedolizumab. **Therapeutische indicaties:** Colitis ulcerosa: Entyvio is geïndiceerd voor de behandeling van volwassen patiënten met matige tot ernstige actieve colitis ulcerosa die ontoereikend reageerden op, niet meer reageerden op of intolerantie vertoonden voor conventionele therapie of een tumornecrosefactoralfaantagonist (TNFaantagonist). Ziekte van Crohn: Entyvio is geïndiceerd voor de behandeling van volwassen patiënten met matige tot ernstige actieve ziekte van Crohn die ontoereikend reageerden op, niet meer reageerden op of intolerantie vertoonden voor conventionele therapie of een tumornecrosefactoralfaantagonist (TNFaantagonist). **Dosering en wijze van toediening:** zie SmPC. Het aanbevolen dosisschema van Entyvio is 300 mg, toegediend via intraveneuze infusie, op week nul, twee en zes, en daarna om de acht weken. **Contraindicaties:** Overgevoeligheid voor de werkzame stof of voor één van hulpstoffen. Actieve ernstige infecties, zoals tuberculose, sepsis, cytomegalovirus, listeriosis en opportunistische infecties, zoals progressieve multifocale leukoencefalopathie (PML). **Bijzondere waarschuwingen en voorzorgen bij gebruik:** Vedolizumab moet toegediend worden in een zorgsetting die is uitgerust voor behandeling van acute overgevoeligheidsreacties, zoals anafylaxie, voor het geval die zich voordoen. Geschikte monitoring en medische ondersteuningsmaatregelen moeten beschikbaar zijn voor onmiddellijk gebruik wanneer vedolizumab wordt toegediend. Alle patiënten moeten tijdens elke infusie voortdurend onder toezicht blijven. Infusiegerelateerde reacties: In klinisch onderzoek zijn infusiegerelateerde reacties (IRR) en overgevoeligheidsreacties gemeld, waarbij de meerderheid licht tot matig van aard was. Als een ernstige IRR, anafylactische reactie of andere ernstige reactie voorkomt, moet toediening van Entyvio onmiddellijk worden stopgezet en een aangewezen behandeling worden ingesteld (bijvoorbeeld epinefrine en antihistaminica).Als een lichte tot matige IRR voorkomt, kan de infusiesnelheid worden vertraagd of onderbroken en een aangewezen behandeling worden ingesteld. Infecties: Vedolizumab is een darmselectieve integrineantagonist waarvan geen systemische immunosuppressieve werking is vastgesteld). Artsen moeten zich bewust zijn van het mogelijke verhoogde risico op opportunistische infecties of infecties waarvoor de darm een defensieve barrière is. Behandeling met Entyvio mag niet worden ingesteld bij patiënten met actieve, ernstige infecties totdat de infecties onder controle zijn, en artsen moeten overwegen om de behandeling niet toe te dienen bij patiënten die een ernstige infectie ontwikkelen tijdens chronische behandeling met Entyvio. Voorzichtigheid is geboden wanneer het gebruik van vedolizumab wordt overwogen bij patiënten met een chronische, ernstige infectie die onder controle is of met een voorgeschiedenis van recidiverende, ernstige infecties. Patiënten moeten voor, tijdens en na behandeling nauwlettend worden opgevolgd voor infecties. Entyvio is gecontraindiceerd bij patiënten met actieve tuberculose. Sommige integrineantagonisten en sommige systemische immunosuppressiva zijn geassocieerd met progressieve multifocale leukoencefalopathie (PML); dat is een zeldzame en vaak fatale opportunistische infectie die wordt veroorzaakt door het John Cunninghamvirus (JCvirus). Door te binden aan het α4β7integrine dat tot expressie komt op gut-homing lymfocyten oefent vedolizumab een immunosuppressief effect uit op de darm. Hoewel geen systemisch immunosuppressief effect werd waargenomen bij gezonde personen, zijn de effecten op de functie van het systemische immuunsysteem bij patiënten met een inflammatoire darmziekte niet bekend. In klinisch onderzoek met vedolizumab zijn geen gevallen van PML gemeld, maar beroepsbeoefenaren in de gezondheidszorg moeten met vedolizumab behandelde patiënten opvolgen voor nieuwe of verergerende neurologische klachten en symptomen, zoals vermeld in het educatief materiaal voor artsen, en moeten, als deze voorkomen, neurologische verwijzing overwegen. De patiënt moet een patiëntenwaarschuwingskaart krijgen. Als PML wordt vermoed, mag behandeling met vedolizumab niet worden toegediend; eens bevestigd, moet de behandeling definitief worden stopgezet. Maligniteiten: Het risico op maligniteit is groter bij patiënten met colitis ulcerosa of de ziekte van Crohn. Immunomodulerende geneesmiddelen kunnen het risico op maligniteit vergroten. Voorafgaand en gelijktijdig gebruik van biologicals: Er zijn geen gegevens beschikbaar van klinisch onderzoek met vedolizumab voor patiënten die eerder zijn behandeld met natalizumab of rituximab. Voorzichtigheid is geboden. Patiënten die eerder zijn blootgesteld aan natalizumab moeten normaal minstens 12 weken wachten voordat behandeling met Entyvio wordt ingesteld. Er zijn geen klinische onderzoeksgegevens beschikbaar over het gelijktijdige gebruik van vedolizumab met biologische immunosuppressiva. Daarom wordt het bij deze patiënten niet aanbevolen. Levende en orale vaccins: Het wordt aanbevolen dat alle patiënten alle nodige immunisaties krijgen in overeenstemming met de huidige immunisatierichtlijnen voordat behandeling met Entyvio wordt ingesteld. **Bijwerkingen:** De volgende lijst van bijwerkingen is gebaseerd op ervaring tijdens klinisch onderzoek; zeer vaak: nasofaryngitis, hoofdpijn, artralgie. Vaak: Bronchitis, gastroenteritis, bovenste luchtweg-infectie, griep, sinusitis, faryngitis, paresthesie, hypertensie, orofaryngeale pijn, neusverstopping, hoesten, anaal abces, anusfissuur, nausea, dyspepsie, constipatie, abdominale distensie, flatulentie, hemorroïden, rash, pruritus, eczeem, erytheem, nachtzweet, acne, spierspasmen, rugpijn, spierzwakte, vermoeidheid, pijn in de ledematen, pyrexie. Soms; Luchtweginfectie, vulvovaginale candidiasis, orale candidiasis, folliculitis, reactie op infuusplaats (waaronder: pijn op infuusplaats en irritatie op infuusplaats), infusie gerelateerde reactie, koude rillingen, het koud hebben. Voor meer informatie over specifieke bijwerkingen zie SmPC. Afleverstatus: UR. EU/1/14/923/001 **Registratiehouder:** Takeda Pharma A/S, Denemarken. Farmacotherapeutische categorie: Farmacotherapeutische categorie: immunosuppressiva, selectieve immunosuppressiva, ATCcode: L04AA33. Volledige productinformatie is verkrijgbaar via de lokale vertegenwoordiger in Nederland: Takeda Nederland bv, Jupiterstraat 250, 2132 HK Hoofddorp. Educatief materiaal voor artsen en de patiëntwaarschuwingskaart worden ter beschikking gesteld. (Augustus 2015)

Takeda

Entyvio® vedolizumab

VERKORTE PRODUCTINFORMATIE HARVONI®▼

SAMENSTELLING: 90 mg ledipasvir en 400 mg sofosbuvir. **FARMACEUTISCHE VORM:** filmomhulde tablet. **INDICATIES EN DOSERING:** Harvoni is geïndiceerd voor de behandeling van chronische hepatitis C (CHC) bij volwassenen. Voor specifieke activiteit tegen de verschillende genotypes van het hepatitis C-virus (HCV), zie SmPC. De therapie met Harvoni moet worden gestart en gecontroleerd door een arts die ervaren is in de behandeling van patiënten met CHC. De aanbevolen dosering van Harvoni is één tablet eenmaal daags met of zonder voedsel. **CONTRA-INDICATIES:** Overgevoeligheid voor de werkzame stoffen of voor één van de hulpstoffen. Gelijktijdige toediening met rosuvastatine of St. Janskruid (Hypericum perforatum). **BIJZONDERE WAARSCHUWINGEN EN VOORZORG-EN BIJ GEBRUIK:** Harvoni mag niet gelijktijdig worden toegediend met andere geneesmiddelen die sofosbuvir bevatten. ***Specifieke activiteit tegen verschillende genotypes:*** zie SmPC. De klinische gegevens die het gebruik van Harvoni bij patiënten geïnfecteerd met HCV-genotype 2, 3 en 6 ondersteunen zijn beperkt. ***Ernstige bradycardie en hartblok:*** Er zijn gevallen van ernstige bradycardie en hartblok waargenomen bij gelijktijdig gebruik van Harvoni met amiodaron, met of zonder andere geneesmiddelen die de hartslag vertragen. Omdat de gevallen potentieel levensbedreigend zijn, mag amiodaron bij patiënten die Harvoni gebruiken, uitsluitend worden gebruikt wanneer andere antiaritmische behandelingen niet worden verdragen of gecontra-indiceerd zijn. Patiënten die in de afgelopen maanden zijn gestopt met amiodaron en beginnen met Harvoni dienen aan geschikte monitoring te worden onderworpen. Zie voor meer informatie de SmPC. ***Behandeling van patiënten met eerdere blootstelling aan direct werkende antivirale middelen tegen HCV:*** Bij patiënten bij wie de behandeling met ledipasvir/sofosbuvir faalt, wordt in de meeste gevallen selectie van NS5A-resistentie-mutaties gezien die de gevoeligheid voor ledipasvir aanzienlijk verminderen. Er zijn op dit moment geen gegevens die de effectiviteit ondersteunen van herbehandeling van patiënten bij wie de behandeling met ledipasvir/sofosbuvir faalde met een daaropvolgend regime dat een NS5A-remmer bevat. Patiënten kunnen daarom afhankelijk zijn van andere geneesmiddelen- klassen voor klaring van HCV-infectie. ***Nierfunctiestoornis:*** De veiligheid van Harvoni is niet onderzocht bij patiënten met een ernstige nierfunctiestoornis (eGFR < 30 ml/min/1,73 m²) of ESRD die hemodialyse vereist. Raadpleeg de SmPC van ribavirine voor patiënten met een creatinineklaring (CrCl) < 50 ml/min. ***Gedecompenseerde cirrosse/levertransplantatie:*** zie SmPC. ***Gebruik met krachtige P gp inductoren:*** krachtige inductoren van P glycoproteïne (P gp) (bijv. rifampicine, St. Janskruid [Hypericum perforatum], carbamazepine en fenytoïne), kunnen leiden tot een significante daling van de plasmaconcentratie van ledipasvir en sofosbuvir, wat kan resulteren in een verminderd therapeutisch effect van Harvoni. Deze mogen niet samen met Harvoni te worden gebruikt. ***Gebruik met bepaalde antiretrovirale regimes tegen HIV:*** Het is gebleken dat Harvoni de blootstelling aan tenofovir verhoogt, met name bij gebruik in combinatie met een HIV-regime dat tenofovirdisoproxilfumaraat en een farmacokinetische booster (ritonavir of cobicistat) bevat. De veiligheid van tenofovirdisoproxilfumaraat in het kader van een behandeling met Harvoni en een farmacokinetische booster is niet vastgesteld. Er moet rekening worden gehouden met de mogelijke risico's en voordelen van gelijktijdige toediening van Harvoni met de tablet met de vaste-dosiscombinatie die elvitegravir/cobicistat/emtricitabine/tenofovirdisoproxilfumaraat bevat of tenofovirdisoproxilfumaraat in combinatie met een gebooste HIV-proteaseremmer (bijv. atazanavir of darunavir), vooral bij patiënten met verhoogd risico op een nierfunctie-stoornis. Patiënten die Harvoni gelijktijdig met elvitegravir/cobicistat/ emtricitabine/tenofovirdisoproxilfumaraat of met tenofovirdisoproxil fumaraat en een gebooste HIV-proteaseremmer krijgen, moeten worden gecontroleerd op tenofovir-gerelateerde bijwerkingen. Raadpleeg de SmPC van tenofovirdisoproxilfumaraat, emtricitabine/tenofovirdisoproxilfumaraat of elvitegravir/cobicistat/emtricitabine/tenofovirdisoproxilfumaraat voor aanbevelingen over niercontrole. ***Gebruik met HMG-CoA-reductaseremmers:*** Gelijktijdige toediening van Harvoni met HMG-CoA-reductaseremmers (statines) kan leiden tot een significante stijging van de concentratie van het statine, wat het risico op myopathie en rabdomyolyse verhoogt ***Hulpstoffen:*** Harvoni bevat de azokleurstof zonnegeel FCF aluminiumpigment (E110), die allergische reacties kan veroorzaken. Het bevat ook lactose. **INTERACTIES:** Voor een compleet overzicht en informatie over geneesmiddeleninteracties van Harvoni met potentieel gelijktijdig gebruikte geneesmiddelen, zie SmPC. **VRUCHTBAARHEID, ZWANGERSCHAP EN BORSTVOEDING:** Het heeft de voorkeur het gebruik van Harvoni te vermijden tijdens de zwangerschap en tijdens de periode dat borstvoeding wordt gegeven. Bij gebruik van Harvoni in combinatie met ribavirine moet uiterste voorzichtigheid worden betracht om een zwangerschap te vermijden bij vrouwelijke patiënten en bij vrouwelijke partners van mannelijke patiënten. Significante teratogene en/of embryocide effecten zijn aangetoond bij alle diersoorten die aan ribavirine werden blootgesteld. Vrouwen die zwanger kunnen worden of hun mannelijke partners moeten een effectieve vorm van anticonceptie toepassen tijdens de behandeling en gedurende een periode na beëindiging van de behandeling, zoals wordt aanbevolen in de SmPC van ribavirine. **BEÏNVLOEDING VAN DE RIJVAARDIGHEID EN VAN HET VERMOGEN OM MACHINES TE BEDIENEN:** Harvoni (alleen toegediend of in combinatie met ribavirine) heeft geen of een verwaarloosbare invloed op de rijvaardigheid en op het vermogen om machines te bedienen. Patiënten moet echter worden verteld dat vermoeidheid vaker voorkwam bij patiënten behandeld met ledipasvir/sofosbuvir in vergelijking met placebo. **BIJWERKINGEN:** Zeer vaak: vermoeidheid,hoofdpijn. ***Harvoni en ribavirine:*** zie SmPC van Harvoni en ribavirine. **FARMACOTHERAPEUTISCHE GROEP:** Direct werkend antiviraal middel, ATC code: J05AX65. **AFLEVERSTATUS:** U.R. **PRIJS:** Zie Z-index. **VERGOEDING:** Op verstrekking van dit geneesmiddel bestaat aanspraak krachtens en onder de voorwaarden van de Nederlandse Zorgverzekeringswet en begeleidende uitvoeringswetgeving. **VERGUNNING:** EU/1/14/958/001-002. **REGISTRATIEHOUDER:** Gilead Sciences International Ltd., Verenigd Koninkrijk. **LOKALE VERTEGENWOORDIGER:** Gilead Sciences Netherlands B.V., Claude Debussylaan 22, 1082 MD Amsterdam. **DATUM:** deze tekst is het laatst herzien in februari 2016. Voor de volledige productinformatie zie de geregisteerde Samenvatting van de Productkenmerken.

▼ *Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden bij Nederlands Bijwerkingen Centrum Lareb Website: www.lareb.nl of Gilead Sciences Netherlands B.V. Tel: 020-718-3698 e-mail: Bsafety@gilead.com*

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