DIGESTIVE DISEASE DAYS

2017

PROGRAMMA

23 - 24 maart

Congrescentrum NH Koningshof
Veldhoven

NVGE
NEDERLANDSE VERENIGING
VOOR GASTRO-ENTEROLOGIE

DIGESTIVE DISEASE DAYS - DDD

De hoofdsponsors van de NVGE in 2017:
Dr. Falk Pharma BV
Ferring BV
Olympus Nederland BV
Takeda
Norgine

Het programma werd samengesteld met inbreng van de volgende verenigingen en secties:
Nederlandse Vereniging voor Gastroenterologie
Nederlandse Vereniging voor Gastrointestinale Chirurgie
Nederlandse Vereniging voor Hepatologie
Nederlandse Vereniging van Maag-Darm-Leverartsen

Secties:
Dutch Experimental Gastroenterology and Hepatology Meeting
Netherlands Society of Parenteral and Enteral Nutrition
Sectie Gastrointestinale Endoscopie
Sectie Neurogastroenterologie en Motiliteit
Sectie Experimentele Gastroenterologie
Sectie Gastrointestinale Oncologie
Sectie Inflammatoire Darmziekten IBD
Sectie Kinder-MDL
Verpleegkundigen & Verzorgenden Nederland - MDL

NVGE
NEDERLANDSE VERENIGING VOOR GASTRO-ENTEROLOGIE

DIGESTIVE DISEASE DAYS - DDD

INHOUDSOPGAVE **pag**

Tijdstippen diverse ledenvergaderingen op donderdag:

Sectie Inflammatoire Darmziekten (IBD) (korte ledenvergadering)	23 maart	09.40 uur – Zaal 80
Nederlandse Vereniging voor Gastroenterologie	23 maart	11.30 uur – Brabantzaal
NVMDL i.o.	23 maart	12.00 uur – Boszaal
Nederlandse Vereniging voor Hepatologie	23 maart	15.00 uur – Baroniezaal

INHOUDSOPGAVE **pag**

Tijdstippen diverse ledenvergaderingen op vrijdag:

Nederlandse Vereniging van Maag-Darm-Leverartsen	24 maart	08.00 uur – Zaal 81-83
Sectie Kinder-MDL	24 maart	14.00 uur – Zaal 20

Belangrijke mededeling
over de aanwezigheid van farmaceutische industrieën

Aan alle deelnemers tijdens het Digestive Disease Days op 23 en 24 maart 2017

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 het congres 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 wederom 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 de Digestive Disease Days op 23 en 24 maart a.s. in NH Conference Center Koningshof te Veldhoven. Zoals gebruikelijk wordt ons congres vooraf gegaan door het cursorisch onderwijs op woensdag 22 maart, deze keer over hepatologie, waarvan u het programma aantreft op bladzijde 8, 9 en 10.

Traditioneel is er in het voorjaar veel aandacht voor basaal onderzoek. Dit wordt gepresenteerd door de DEGH, met op donderdag middag een symposium over microbiota onderzoek. Het programma georganiseerd door de NVGIC vindt op donderdag plaats en heeft een sterk multidisciplinair karakter. De onderwerpen die aan bod komen zijn onder meer IBD, bloedingen en behandeling van het rectum carcinoom. Op donderdag ook een symposium over alledaagse vragen binnen de hepatologie. Na de President Select met de prijsuitreikingen en de bekendmakingen van de verstrekte NVGE subsidies volgt de Presidential Lecture door ondergetekende over Fecale Microbiota Transplantatie en de Nederlandse Donor Feces bank.

Op vrijdag aansluitend aan de ledenvergadering van de NVMDL, vindt een door Marc Verhagen georganiseerde bijeenkomst over taakherschikking plaats in de Parkzaal. Tevens op vrijdag een oncologie symposium over orgaansparende behandeling, een kindergeneeskunde/NVGE symposium over kinderziektes op volwassen leeftijd en een symposium van de sectie Endoscopie over complicaties op vrijdagmiddag. Parallel hieraan het NESPEN programma in zaal 80 met een symposium over parenterale voeding en het programma van de V&VN MDL in de Brabantzaal.

Op donderdag zijn er meet the expert sessies over dysplasie in de bovenste tractus digestivus door Jacques Bergman en Arjun Koch, en over voeding door Geert Wanten en Ad van Bodegraven.

Tot ziens in Veldhoven!

Dr. J.J. Keller, secretaris NVGE

Programma donderdag 23 maart 2017

Donderdag	Brabantzaal	Auditorium	Baroniezaal	Parkzaal
08.30 - 10.00	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie
10.00 - 11.30	Symposium: Wie behandelt wanneer? Moderne behandeling is multidisciplinaire behandeling *pagina 11*	Symposium: Dagelijkse praktijk in de hepatologie *pagina 15*	DEGH Oral presentations *pagina 19*	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie *pagina 24*
11.30 - 12.00	Ledenvergadering NVGE	Geen programma i.v.m. Ledenvergadering NVGE	Geen programma i.v.m. Ledenvergadering NVGE	Geen programma i.v.m. Ledenvergadering
12.00 - 13.00	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal	Lunch in expositiehal
13.00 - 15.00	Symposium: De multimodaliteitsaanpak van het rectumcarcinoom *pagina 11*	Vrije voordrachten Inflammatoire Darmziekten *pagina 15*	DEGH Oral presentations *pagina 20*	Vrije voordrachten Nederlandse Vereniging voor Gastrointestinale Chirurgie *pagina 26*
15.00 - 15.30	Theepauze	Theepauze	Theepauze + ALV NVH	Theepauze
15.30 - 17.00	Symposium: Inflammatory Bowel Disease: to operate or not to operate? *pagina 12*	Symposium: The microbiota in GI diseases: what is new? *pagina 18*	Vrije voordrachten Gastrointestinale Oncologie *pagina 22*	Vrije voordrachten Neurogastroenterologie en Motiliteit *pagina 28*
17.00 - 17.30	Voordrachten President Select *pagina 13*			
17.30 - 17.40	NVGE Subsidies *pagina 14*			
17.40 - 18.00	NVGE Gastrointestinale Researchprijs 2017 *pagina 14*			
18.05 - 18.35	Presidential Lecture Josbert Keller *pagina 14*			
18.30 - 19.30	Borrel in expositiehal			
19.30 - 22.00	Diner Genderzaal			
22.00 - 01.00	Borrel / Muziek in foyer			

Donderdag	Zaal 80	Zaal 81 – Meet the expert	Zaal 82 – Meet the expert
10.00 -	Vrije voordrachten Inflammatoire Darmziekten *pagina 31*		
13.00 - 17.00		Dysplasie bovenste tractus digestivus *pagina 35*	Voeding gerelateerde problemen *pagina 35*
15.30 - 17.00	Vrije voordrachten Gastrointestinale endoscopie *pagina 33*		

Programma vrijdag 24 maart 2017

Vrijdag	Brabantzaal	Auditorium	Baroniezaal	Parkzaal
08.30 - 09.30	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie	Ontvangst en koffie
09.30 - 11.00	Programma V&VN *pagina 52*	Symposium Gastrointestinale Oncologie *pagina 36*	DEGH - Pitches + Oral presentations *pagina 39*	Programma NVMDL *pagina 43*
11.00 - 11.30	11.30 Koffiepauze expo	Koffiepauze expo	Koffiepauze expo	Koffiepauze expo
11.30 - 13.00	Programma V&VN *pagina 52*	Symposium Kindergeneeskunde *pagina 37*	DEGH - Oral presentations + Short pitches *pagina 40*	Vrije voordrachten Gastrointestinale Endoscopie *pagina 44*
13.00 - 14.00	Lunch expositiehal	Lunch expositiehal	Lunch expositiehal	Lunch expositiehal
14.00 - 15.40	Programma V&VN *pagina 53*	Symposium gastrointestinale Endoscopie *pagina 38*	DEGH - Battle *pagina 42*	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie *pagina 45*

Programma vrijdag 24 maart 2017
NESPEN en sectie Gastrointestinale Endoscopie

Vrijdag	Zaal 80
09.30 - 11.00	Vrije voordrachten NESPEN - *pagina 47*
11.00 - 11.15	Koffiepauze in de expositiehal
11.15 - 13.00	Symposium NESPEN: enterale voeding - *pagina 48*
13.00 - 14.00	Lunch in de expositiehal
14.00 - 15.30	Vrije voordrachten Nederlandse Vereniging voor Gastroenterologie - *pagina 50*

Woensdag 22 maart 2017

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
Dr. J. Heisterkamp, chirurg, St. Elisabeth Ziekenhuis, Tilburg
Dr. M.A.J.M. Jacobs, MDL-arts, VUmc, Amsterdam
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
Mevr. dr. K. Verweij, Erasmus MC, Rotterdam

Onderwerp: Hepatologie

Hepatologie I: Diagnostiek en het Virus-ABC

Voorzitters: *Prof. dr. U.H.W. Beuers (Amsterdam), Prof. dr. B. van Hoek (Leiden)*

14.30 – 14.35 Inleiding

14.35 – 14.55 Diagnostisch algoritme bij leverziekten e.c.i.
Dr. J.T. Brouwer, MDL-arts, Reinier de Graaf Ziekenhuis, Delft

15.00 – 15.20 Hepatitis B en D: Behandelopties en -indicaties 2017
Prof. dr. R.A. de Man, MDL-arts, Erasmus MC, Rotterdam

15.25 – 15.45 Hepatitis C: Iedereen behandelen en hoe behandelen in 2017?
Prof. dr. J.P.H Drenth, MDL-arts, Radboudumc, Nijmegen

15.50 – 16.10 Hepatitis A en E: Hoe voorkomen, hoe herkennen, wanneer behandelen?
Prof. dr. H.L. Zaaijer, medisch microbioloog, Sanquin, Amsterdam

16.15 – 16.40 Pauze

Hepatologie II: Levensbedreigende situaties

Voorzitters: *Dr. J. Heisterkamp (Tilburg), Prof. dr. R.A. de Man (Rotterdam)*

16.40 – 17.00 Acuut leverfalen
Prof. dr. H.J. Metselaar, MDL-arts, Erasmus MC, Rotterdam

17.05 – 17.25 Gedecompenseerde cirrose: diagnostiek en behandeling van ascites, SBP, HRS, HE
Dr. M.J. Coenraad, MDL-arts, LUMC, Leiden

17.30 – 17.50 Maligne levertumoren: diagnostiek en interventionele therapie
Dr. K.J. van Erpecum, MDL-arts, UMCU, Utrecht

17.55 – 18.15 Maligne lever-/galwegtumoren: extreme resecties en functionele restcapaciteit
Prof. dr. T.M. van Gulik, chirurg, AMC, Amsterdam

18.20 – 18.45 Pauze

Hepatologie III: 'Hot topics'

Voorzitters: *Prof. dr. J.P.H. Drenth (Nijmegen), Dr. K. Verweij (Rotterdam)*

18.45 – 19.05 Cholestatische leverziekten (PBC, PSC, IAC etc): Nieuwe ontwikkelingen
Prof. dr. U.H.W. Beuers, MDL-arts, AMC, Amsterdam

19.10 – 19.30 NASH: De bedreiging voor de toekomst?
Dr. S.W.C. van Mil, moleculaire bioloog, UMCU, Utrecht

19.35 – 19.55 Echo en fibroscan: onmisbaar voor de MDL-arts in 2017!
Dr. R.J. de Knegt, MDL-arts, Erasmus MC, Rotterdam

Woensdag 22 maart 2017

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

20.00 – 20.20	Levertransplantatie in Nederland 2017 *Prof. dr. R.J. Porte, chirurg, UMCG, Groningen*
20.30	Einde cursus, diner

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.

Symposium Nederlandse Vereniging voor Gastrointestinale Chirurgie Brabantzaal

NVGIC Themajaar 2017 'Treasure Island'

Themajaarcommissie:
J.F.M. Lange, J. Heisterkamp (voorzitters), J.A. Apers, J.D.W. van der Bilt, M.T. de Boer, S.S. Gisbertz, F.J.H. Hoogwater, B.R. Klarenbeek, I.T.A. Pereboom, Ch. Van Rossem, K. Talsma en M. Westerterp.

Voorzitters: I.T.A. Pereboom en M. Westerterp

Symposium: Wie behandelt wanneer?
Moderne behandeling is multidisciplinaire behandeling

10.00 Een gastro-intestinale bloeding! Wie (be)handelt eerst?
Drs. K.P. van Lienden, interventieradioloog AMC, Amsterdam
Dr. R.J. Verburg, MDL-arts Medisch Centrum Haaglanden, Den Haag

10.30 De etiologie, diagnostiek en gezamenlijke behandeling van een volvulus.
Drs. T.H. van Dijk, kinderchirurg, UMC Groningen
Dr. F. ter Borg, MDL-arts Deventer ziekenhuis

11.00 De samenwerking tussen chirurg en bekkenfysiotherapeut in de proctologie
Drs. C.B.H. Deen-Molenaar, chirurg, Proctos Kliniek Bilthoven
Mw. D. van Reijn, bekkenfysiotherapeute, Proctos Kliniek Bilthoven

11.30 Algemene ledenvergadering Nederlandse Vereniging Gastro-Enterologie

12.00 Lunch in expositiehal

Voorzitters: M. Meerdink en K. Talsma

Symposium: De multimodaliteitsaanpak van het rectumcarcinoom

13.00 De bevindingen van de radioloog; hoe beoordeel je een MRI van het kleine bekken?
Drs. J. Nederend, radioloog Catharina ziekenhuis Eindhoven

13.15 Volledige respons na neoadjuvante chemoradiotherapie:
wait and see en de rol van de endoscopist
Drs. C. Hoff, chirurg Medisch Centrum Leeuwarden

Donderdag 23 maart 2017

13.30 Chemo- en immunotherapie voor het colorectaal carcinoom, de laatste inzichten
Dr. J. Tol, oncoloog, Jeroen Bosch Ziekenhuis, Den Bosch

13.45 Behandeling bij lekkage van de lage naad met de endospons
Dr. P.J. Tanis, chirurg, AMC, Amsterdam

14.00 De behandeling van het locally advanced rectumcarcinoom en de rol van intra-operatieve radiotherapie
Prof. dr. H.J.T. Rutten, chirurg, Catharina Ziekenhuis Eindhoven

15.00 Theepauze

Symposium Nederlandse Vereniging voor Gastrointestinale Chirurgie Brabantzaal

Voorzitters: Y. Panis en J.D.W. van der Bilt

Symposium: Inflammatory Bowel Disease: to operate or not to operate?

15.30 Biologicals and IBD, a safe and golden combination?
Prof. dr. G. Dijkstra, MDL-arts, UMC Groningen

15.45 De role of the radiologist – the value of imaging in IBD
Dr. J.B.C.M. Puylaert, radioloog, Medisch Centrum Haaglanden

16.00 Terminal ileitis and the role of the surgeon
Dr. C.J. Buskens, chirurg, AMC, Amsterdam

16.15 De significance of the appendix in Ulcerating Colitis.
Drs. S. Sahami, arts-onderzoeker MDL, Leids UMC

16.30 Advanced Surgery for Inflammatory Bowel Disease
Prof. dr. Y. Panis, Head of the Department of Colorectal Surgery, Beaujon Hospital, Clichy, France

17.00 Einde symposium

Voordrachten President Select **Brabantzaal**

Voorzitters: P.D. Siersema en L.P.S. Stassen

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

17.00 Incidence of malignant progression in persistent nondysplastic Barrett's esophagus, a Dutch nationwide cohort study (p.55)

Y. Peters[1], J. Honing[1], W. Kievit[2], I.D. Nagtegaal[3], P.D. Siersema[1]. [1]Dept of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen. [2]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen. [3]Dept of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands

17.10 Laparoscopic ileocecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: The LIR!C trial (p.56)

R.M. van Amelsfoort, A. Cats, E.P.M. Jansen, N.C.T. van Grieken, N.K. Aaronson, H. Boot, P.A. Lind, E. Meershoek – Klein Kranenbarg, J.P.B.M. Braak, M. Nordsmark, H. Putter, A.K. Trip, J.W. van Sandick, K. Sikorska, I. Walraven, M.C. Hulshof, H.W. van Laarhoven, M.I. van Berge Henegouwen, H. van Tinteren, C.J.H. van de Velde, M. Verheij, on behalf of all CRITICS investigators. Cancer Institute/Antoni van Leeuwenhoek, Free University Medical Center, Leiden University Medical Center, Academic Medical Center, Karolinska University Hospital, Arhus University Hospital, The Netherlands

17.20 A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradio-therapy in resectable gastric cancer: the CRITICS study (p.57)

R.M. van Amelsfoort, A. Cats, E.P.M. Jansen, N.C.T. van Grieken, N.K. Aaronson, H. Boot, P.A. Lind, E. Meershoek – Klein Kranenbarg, J.P.B.M. Braak, M. Nordsmark, H. Putter, A.K. Trip, J.W. van Sandick, K. Sikorska, I. Walraven, M.C. Hulshof, H.W. van Laarhoven, M.I. van Berge Henegouwen, H. van Tinteren, C.J.H. van de Velde, M. Verheij, on behalf of all CRITICS investigators. Cancer Institute/Antoni van Leeuwenhoek, Free University Medical Center, Leiden University Medical Center, Academic Medical Center, Karolinska University Hospital, Arhus University Hospital, The Netherlands

NVGE subsidies **Brabantzaal**

17.30 **Bekendmaking toegekende NVGE-subsidies**:
- Subsidies Gastrostart
- Subsidies voor multidisciplinaire en instelling-overstijgende onderzoeks-initiatieven of werkgroepen

Prijsuitreiking **Brabantzaal**

17.40 **NVGE Gastrointestinale Researchprijs 2017**
De prijsuitreiking wordt gevolgd door een korte voordracht door de winnaar.

Lecture **Brabantzaal**

Voorzitters: P.D. Siersema en L.P.S. Stassen

17.50 **Presidential Lecture**
Fecale Microbiota Transplantatie
Dr. J.J. Keller, MDL-arts, Medisch Centrum Haaglanden, Den Haag

18.20 Einde programma, congresborrel in expositiehal

20.00 Diner in Genderzaal

Symposium Nederlandse Vereniging voor Hepatologie **Auditorium**

Voorzitters: U.H.W. Beuers, H.J. Metselaar

Symposium: Dagelijkse praktijk in de hepatologie

10.00-10.10 Hepatitis B: Wie, hoe en hoe lang behandelen?
Dr. L.C. Baak, OLVG, Amsterdam

10.15-10.25 Vena portae trombose: wanneer en hoe behandelen?
Dr. S. Darwish Murad, Erasmus MC, Rotterdam

10.30 -10.40 Voeding en leverziekten: koffie en andere ingrediënten.
Drs. L. Alferink, arts-onderzoeker MDL, Erasmus MC, Rotterdam

10.45-10.55 Chirurgie bij patiënten met leverziekten
Prof. dr. H.J. Metselaar, MDL-arts, Erasmus MC Rotterdam

11.00-11.10 Screening voor HCC: heeft het zin?
Dr. B. Takkenberg, MDL-arts, AMC, Amsterdam

11.15-11.25 Levertransplantatie voor polycystische leverziekte:
hoe voorkomen en wanneer overwegen?
Prof. dr. J.P.H. Drenth, MDL-arts, Radboudumc, Nijmegen

12.00 Lunchpauze in expositiehal

Abstractsessie – Sectie Inflammatoire Darmziekten **Auditorium**

Voorzitters: M.W. Mundt en C. Spooren

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

13.00 T-Cell activation and signalling in Crohn's disease: from risk genes to molecular networks (MLDS presentatie WO 11-72) (p.58)
R. Weersma, [1]Dept of Gastroenterology, UMC Groningen, The Netherlands

13.10 Unchanged Infliximab Serum Concentrations after Switching from the Reference Infliximab to the Biosimilar CT-P13 in Patients with Quiescent Crohn's Disease: a Prospective Study (p.59)

A.S. Strik[1], W. van de Vrie[2], Y.J.B. van Megen[3], J.P.J. Bloemsaat-Minekus[3], T. Rispens[4], G.R. D'Haens[1]. [1]Dept of Gastroenterology, Academic Medical Center Amsterdam. [2]Dept of Gastroenterology, Albert Schweitzer Hospital, Dordrecht. [3]Mundipharma Pharmaceuticals BV, Leusden. [4]Sanquin Research, Sanquin Laboratory, Amsterdam, the Netherlands

13.20 Optimal anti-TNF stop week during pregnancy depends on anti-TNF type (p.60)

S.L. Kanis, A. de Lima and C.J. van der Woude. Dept of Gastroenterology and Hepatology of the Erasmus University Medical Center, Rotterdam, The Netherlands

13.30 Switching from Remicade® to biosimilar CT-P13 in inflammatory bowel disease: One year follow-up of a prospective observational cohort study (p.61)

L.J.T. Smits[1], A. Grelack[1], J.P.H. Drenth[1], D.J. de Jong[1], R.S. Boshuizen[2], A.A.J. van Esch[1], L.A.A.P. Derikx[1], F. Hoentjen[1]. [1]Inflammatory Bowel Disease Center, Dept of Gastroenterology and Hepatology, Radboud university medical center, Nijmegen. [2]Biologics Laboratory, Sanquin Diagnostic Services, Amsterdam, The Netherlands

13.40 Relapse risk and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-tnf therapy (p.62)

S.J.A. Bots[1], S. Kuin[1], C. Ponsioen[1], G. van den Brink[1], M. Lowenberg[1], G. D'Haens[1]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

13.50 The therapeutic efficacy of anti-TNF requires Fc-gamma receptors and can be improved by antibody hypo-fucosylation (p.63)

F.M. Bloemendaal[1], A.D. Levin[1], M.E. Wildenberg[1], P.J. Koelink[1], J.W.C. Claassens[2], R. Visser[3], G.R.A.M. D'Haens[4], B.L. McRae[5], J.S. Verbeek[2], G. Vidarsson[3], G.R. van den Brink[1,4]. [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, The Netherlands. [2]Dept of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands. [3]Dept of Experimental Immunohematology, Sanquin Research, Amsterdam, The Netherlands. [4]Dept of Gastroenterology and Hepatology, Academic Medical Center, The Netherlands. [5]Abbvie Bioresearch Center, Worcester, MA, USA

14.00 Vedolizumab induces significantly higher endoscopic remission rates at week 16 in ulcerative colitis as compared to Crohn's disease (p.64)

R.W.M. Pauwels[1], A.C. de Vries[1,2], C.J. van der Woude[1,2]. [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam. On behalf of: [2]Initiative on Crohn and Colitis (ICC), The Netherlands

14.10 Serological biomarkers of tissue turnover can early identify responders to infliximab in Crohn's disease (p.65)

W.T. van Haaften[1,2], J.H. Mortensen[3], M.L. Olesen[3,4], M.A. Karsdal[3], P. Olinga[2], A.C. Bay-Jensen[3], G. Dijkstra[1]. [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. [2]Dept of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands. [3]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark. [4]Dept of Medical Gastroenterology, University of Southern Denmark and Odense University Hospital, Odense, Denmark

14.20 Telemedicine enables a safe shift from examination room based care to personalised care for inflammatory bowel disease: a pragmatic randomised multicenter trial with my IBD coach (p.66)

M.J. de Jong[1,2], R. Huibregtse[1], A.E. van der Meulen-de Jong[3], M.J. Romberg-Camps[4], M.C. Becx[5], M. Cillissen[1], J.P. Maljaars[3], A.A. van Bodegraven[4], N. Mahmmod[5], T. Markus[6], W.M. Hameeteman[1], G. Dijkstra[7], A.A. Masclee[1,2], A. Boonen[8,9], D.M. Jonkers[1,2], A. van Tubergen[8,9], M.J. Pierik[1,2]. [1]Dept of Internal Medicine, division of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht. [2]NUTRIM – School for Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht. [3]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden. [4]Dept of Gastroenterology, Geriatrics, Internal and Intensive Care Medicine (Co-MIK), Zuyderland Medical Center, Sittard-Geleen. [5]Dept of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein. [6]CCUVN, Woerden. [7]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen. [8]Dept of Internal Medicine, division of Rheumatology, Maastricht University Medical Center, Maastricht. [9]CAPHRI - School for Public Health and Primary Care, Maastricht University Medical Center, Maastricht, The Netherlands

14.30 Mucosal lymphocyte subsets in Ulcerative Colitis at diagnosis and during follow-up (p.67)

C Smids[1], C. Horjus Talabur Horje[1], M. Groenen[1], E. van Koolwijk[2], P. Wahab[1], E. van Lochem[2]. [1]Rijnstate Hospital, Gastroenterology and Hepatology, Arnhem. [2]Rijnstate Hospital, Microbiology and Immunology, Arnhem, The Netherlands

14.40 Therapeutic drug monitoring after thiopurine initiation improves drug efficacy (p.68)

W Heida[1], C. Smids[1], M. van Luin[2], C. Horjus[1], M. de Leest[1], G. Huisman-de Waal[3], P. Wahab[1], M. Groenen[1]. [1]Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem. [2]Dept of Clinical Pharmacy, Rijnstate Hospital, Arnhem. [3]IQ-health care, Radboud Institute for Health Sciences, Nijmegen, The Netherlands

14.50 MR Enterography in addition to ileocolonoscopy in newly diagnosed adults with Crohn's disease (p.69)

C.S. Horjus Talabur Horje[1], W. Geerts[1], L. Roovers[3], F.B.M. Joosten[2], M.J.M. Groenen[1], P.J. Wahab[1]. [1]Dept of Gastroenterology, Rijnstate Hospital, Arnhem. [2]Dept of Radiology, Rijnstate Hospital, Arnhem. 3Dept of Epidemiology and Statistics, Rijnstate Hospital, Arnhem, The Netherlands

15.00 Theepauze

DEGH – microbiota symposium **Auditorium**

Voorzitters: D.M.A.E. Jonkers en J.J. Keller

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

Symposium: The microbiota in GI diseases: what is new?

15.30 Introductory lecture: defining the microbiota from birth to adulthood
Dr. J. Penders, epidemioloog, Afd. Medische Microbiologie, MUMC

15.50 Microbiota in GI diseases: current insights
Prof. dr. R.K. Weersma, maag-darm-leverarts, UMC Groningen

16.10 Microbiota in liver diseases: current insights
Prof. dr. S. van der Merwe, hepatoloog, UZ Leuven, België

16.30 The microbiome of inflammatory bowel disease and irritable bowel syndrome – a case- control study of 1792 individuals (p.70)
A. Vich Vila[1,2], F. Imhann[1,2], V. Collij[1,2], S. Jankipersadsing[2], Z. Mujagic[3], T. Gurry[4], A. Kurilshikov[2], M.J. Bonder [5], X. Jiang [4], L. Franke[2], G. Dijkstra[1], E.A.M. Festen[1,2], J. Fu[2], R.J. Xavier[6], E. Alm[4], C. Wijmenga[2], D. Jonkers[3], A. Zhernakova[2], R.K. Weersma[1]. [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, Maastricht, The Netherlands. Division Gastroenterology-Hepatology, NUTRIM School for Nutrition, and Translational Research in Metabolism [4]Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA. [5]European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK. [6]Massachusetts General Hospital, Boston, USA

16.44 SLC39A8 missense variant is associated with Crohn's disease but not with the gut microbiota composition (p.71)
V. Collij[1,2], F. Imhann[1,2], A. Vich Vila[1,2], J. Fu[3], G. Dijkstra[1], E.A.M. Festen[1,2], R. Barbieri[1,2], M.J. Daly[4], R.J. Xavier[4,5], C. Wijmenga[2], A. Zhernakova[2], R.K. Weersma[1]. [1]Dept of Gastroenterology and Hepatology, Groningen, The Netherlands. [2]University of Groningen, University Medical Center Groningen, Dept of Genetics, Groningen, The Netherlands. [3]University of Groningen, University Medical Center Groningen, Dept of Pediatrics, Groningen, The Netherlands. [4]Broad Institute of Harvard and MIT, Boston, USA. [5]Massachusetts General Hospital, Boston, USA

17.00 Plenair programma in de Brabantzaal

18.30 Einde programma, congresborrel in expositiehal

20.00 Diner in Beneluxzaal

DEGH – oral presentations **Baroniezaal**

Voorzitters: R. Sverdlov en R. Weersma

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

10.00 Inhibition of canonical WNT signaling pathway by β-catenin/CBP inhibitor ICG001 ameliorates liver fibrosis in vivo through suppression of stromal CXCL12 (p.72)

R. Bansal[1], B.Ö. Akcora[1], G. Storm[1,2], J. Prakash[1]. [1]Targeted Therapeutics, Dept of Biomaterials Science and Technology, University of Twente, Enschede. [2]Dept of Pharmaceutics, Utrecht University, Utrecht, The Netherlands

10.12 Relaxin-coated iron-oxide nanoparticles as a novel theranostic approach for the diagnosis and treatment of liver fibrosis (p.73)

R. Bansal[1], B. Nagórniewicz[1], G. Storm[1,2], J. Prakash[1]. [1]Targeted Therapeutics, Dept of Biomaterials Science and Technology, University of Twente, Enschede. [2]Dept of Pharmaceutics, Utrecht University, Utrecht, The Netherlands

10.24 HBV synthetic long peptide can boost CD4 + and CD8 + T cell responses in chronic HBV patients ex vivo (p.74)

Y. Dou[1], N. van Montfoort[1,2], A. van den Bosch[1], K. Melief[3], S.I. Buschow[1] and A.M. Woltman[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center Rotterdam. [2]Current address: Cancer Immunotherapy, Leiden University Medical Center, Leiden. [3]ISA Pharmaceuticals BV, Leiden, The Netherlands

10.36 Multifaceted interaction and regulation of hepatitis E virus infection by mitochondria (p.75)

Y. Wang[1,2], W. Wang[1], E. Shokrollahi[2], W. Cao[1], L. Xu[1], Y. Yin[1], M. Li[1], X. Zhou[1], E.G. Mik[3], F. Huang[4], N. Kamar[5,6,7], N.J.H. Raat[3], M.P. Peppelenbosch[1], Q. Pan[1]. [1]Dept. of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands. [2]Dept. of pathology and Hepatology, Beijing 302 Hospital, Beijing. [3]Dept. of Anesthesiology, Laboratory of Experimental Anesthesiology, Erasmus University Medical Center, Rotterdam, The Netherlands. [4]Medical Faculty, Kunming University of Science and Technology, Kunming, China. [5]Dept. of Nephrology and Organ Transplantation, CHU Rangueil, France. [6]INSERM U1043, IFR-BMT, CHU Purpan, France. [7]University Toulouse III-Paul Sabatier, France

10.48 Cathepsin D regulates lipid metabolism in murine steatohepatitis (p.76)

T. Houben[1], S.M.A. Walenbergh[1], Y. Oligschläger[1], T. Hendrikx[1,2,3], A.V. Bitorina[1], P.J. van Gorp[1], M.J.J. Gijbels[1], S. Friedrichs[4], J. Plat[1], D. Lütjohann[4], M.H. Hofker[5], R. Shiri-Sverdlov[1]. [1]Depts of Molecular Genetics and Human Biology, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands. [2]Dept of Laboratory Medicine, Medical University of Vienna, Austria. [3]Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences, Vienna, Austria. [4]Institute of Clinical Chemistry and Clinical Pharmacology, University of Bonn, Bonn, Germany. [5]Molecular Genetics Section, Dept of Pediatrics, University Medical Center Groningen, Groningen, The Netherlands

11.00 2'-C-methylcytidine inhibits hepatitis E virus replication but antagonizing Ribavirin (p.77)
C. Qu, L. Xu, Y. Yuebang, M.P. Peppelenbosch and Q. Pan, W. Wang. Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

11.12 Mesenchymal stromal cells prevent progression of liver fibrosis in a zebrafish embryo model (p.78)
D. van der Helm[1], A. Groenewoud[2], E.S.M. de Jonge-Muller[1], M.C. Barnhoorn[1], L.J.A.C. Hawinkels[1], M.J. Coenraad[1], B. van Hoek[1], B.E. Snaar-Jagalska[2], H.W. Verspaget[1]. [1]Dept of Gastroentrology, Leiden University Medical Center, Leiden. [2]Dept of Biology, Leiden University, Leiden, The Netherlands

11.24 Einde programma *(voor leden NVGE: ledenvergadering in de Brabantzaal)*

12.00 Lunchpauze in expositiehal

DEGH – oral presentations **Baroniezaal**

Voorzitters: L. Hawinkels en F. Vidal-Vanaclocha

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

Expert Lecture

13.00 Liver metastasis-related genes at primary and metastatic sites from patients with colorectal cancer
Prof. F. Vidal-Vanaclocha, Professor and Chair of Molecular and Translational Medicine, Deputy Director, Valencia Institute of Pathology, Spain.

13.30 Fibroblast-specific endoglin knockout enhances polyp formation by affecting stromal interactions (p.79)
M.J.A. Schoonderwoerd[1,], M. Paauwe[1,2,*], L. Ottevanger[1], E.S.M. de Jonge-Muller[1], H.W. Verspaget[1], M.J.T.H. Goumans[2], M.F. Fransen[3], J.C.H. Hardwick[2], P. ten Dijke[1], L.J.A.C. Hawinkels[1,2]. [1]Dept of Gastroenterology-Hepatology, [2]Dept of Molecular Cell Biology, [3]Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands *Equal contribution*

13.42 Blockade of LAG-3 or PD-L1 enhances the functionality of tumor-infiltrating T cells in liver metastasis from mismatch-repair proficient colorectal cancer (p.80)
G. Zhou[1], L. Noordam[1], D. Sprengers[1], M. Doukas[2], R. Erkens[1], P. Drill[1], D. Grünhagen[3], P.J.W.A. Burger[3], A.G. Menon[4], C. Verhoef[3], J. Kwekkeboom[1], M. Bruno[1]. Depts of [1]Gastroenterology and Hepatology, [2]Pathology, and [3]Surgery, Erasmus University Medical Center, Rotterdam. [4]Dept of Surgery, Havenziekenhuis, Rotterdam, The Netherlands

13.54 Cripto an indicator of a more aggressive hepatocellular carcinoma phenotype (p.81)

D. van der Helm[1], S. Karkampouna[2], H.W. Verspaget[1], A. Farina Sarasqueta[3], L. Chen[4], S. Osanto[5], M.C. Burgmans[6], A.F.M. Schaapherder[7], B.E. Snaar-Jagalska[4], B. van Hoek[1], L. Terracciano[8], M. Kruithof-de Julio[2], M.J. Coenraad[1]. [1]Dept of gastroentrology, Leiden University Medical Center, Leiden, The Netherlands. [2]Dept of Clinical research, Bern University, Bern, Switzerland. Depts of [3]Pathology, [4]Biology, [5]Oncology, [6]Radiology, [7]Surgery, Leiden University Medical Center, Leiden, The Netherlands. [8]Pathology, University Hospital Basel, Basel, Switzerland

14.06 Identification of specific subpopulations of Tumor Associated Macrophages in Esophageal Adenocarcinoma is associated with poor survival (p.82)

S. Calpe[1], S. Hoefnagel[1], M. del Carmen Sancho-Serra[1], D. Straub[1], K.K. Krishnadath[1,2]. [1]Center for Experimental & Molecular Medicine (CEMM), AMC, Amsterdam. [2]Dept of Gastroenterology & Hepatology, AMC, Amsterdam, The Netherlands

14.18 Smooth muscle cell contractile phenotype and cachexia in pancreatic cancer patients: a pilot study (p.83)

R.D.W. Vaes[1], D.P.J. van Dijk[1], L. van den Berk[1], L. Rayen[1], D. Rennspiess[2], A. zur Hausen[2], S.W.M. Olde Damink[1], S.S. Rensen[1]. [1]Dept of Surgery and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht. [2]Dept of Pathology and GROW School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, The Netherland

14.30 Einde sessie, theepauze

15.00 Algemene ledenvergadering Nederlandse Vereniging voor Hepatologie

Vrije voordrachten – Sectie Gastrointestinale Oncologie **Baroniezaal**

Voorzitters: R.W.M. Schrauwen en V.M.C.W. Spaander

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

15.30 The impact of EUS in staging of locally advanced esophageal cancer patients following PET-CT (p.84)

M.H.P. Gorter, R. Bijlsma, C.E. de Groot, J. Westerhof, H.M. van Dullemen and W.B. Nagengast. Dept of Gastroenterology and Hepatology, University Medical Hospital Groningen, The Netherlands

15.40 Identification of three distinct biological subtypes in esophageal and junctional adenocarcinoma by RNA sequencing (p.85)

S.J.M. Hoefnagel[1], B.P. Scicluna[1], J. Koster[2], C.M. del Sancho-Serra[1], M.I. van Berge- Henegouwen[3], H.W.M. van Laarhoven[1], J.J.G.H.M. Bergman[4], S.L. Meijer[5], S. Calpe[1], K. Krishnadath[1,4]. [1]Center for Experimental & Molecular Medicine (CEMM), AMC, Amsterdam. [2]Dept of Oncogenomics, AMC, Amsterdam. [3]Dept of Surgery, AMC, Amsterdam. [4]Dept of Gastroenterology and Hepatology, AMC, Amsterdam. [5]Dept of Pathology, AMC, Amsterdam, The Netherlands

15.50 The expression of the MHC-I pathway correlates with poor patient's survival and it is regulated by microRNA in esophageal adenocarcinoma (p.86)

L.M. Mari[1], B. Scicluna[1], F. Milano[4], M. van de Meent[3], M.H.M. Heemskerk[3], J.P. Medema[1], K.K. Krishnadath[1,2]. [1]Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, The Netherlands. [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands. [3]Dept of Hematology, Leiden University Medical Center, Leiden, The Netherlands. Institute of Hematology, Centro di Ricerca Emato- Oncologico (CREO), University of Perugia, Perugia, Italy

16.00 High mRNA expression of splice variant SYK short correlates with hepatic disease progression in untreated lymph node negative colon cancer patients (p.87)

R.R.J. Coebergh van den Braak[1], A.M. Sieuwerts[2,3], Z. Lalmahomed[1], S. Bril[1,2], M. Timmermans[2], V. de Weerd[2], A. van Galen[2], M. Smid[2], K. Biermann[4], J.H. van Krieken[5], W. Kloosterman[6], J.A. Foekens[2], J.W.M. Martens[2,3], J.N.M. IJzermans[1]. [1]Dept of Surgery, Erasmus MC, Rotterdam. [2]Dept of Medical Oncology, Erasmus Cancer Institute, Erasmus University MC, Rotterdam. [3]Cancer Genomics Center Netherlands, Amsterdam. [4]Dept of Pathology, Erasmus MC, Rotterdam. [5]Dept of Pathology, Radboud UMC, Nijmegen. [6]Dept of Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

16.10 Pooled incidence of fecal occult blood test interval cancers in colorectal cancer screening; a systematic review and meta-analysis (p.88)

E. Wieten[1], E.H. Schreuders[1], E.J. Grobbee[1], D. Nieboer[2], M.J. Bruno[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, The Netherlands

16.20 Validation and pathway analysis of a metastasis-specific microRNA signature in primary colon cancer (p.89)

R.R.J. Coebergh van den Braak[1], A.M. Sieuwerts[2,3], Z. Lalmahomed[1], M. Smid[2], V. de Weerd[2], M. van der Vlugt-Daane[2], A. van Galen[2], S. Xiang[2], K. Biermann[4], J.A. Foekens[2], J.W.M. Martens[2,3], J.N.M. IJzermans[1]. [1]Dept of Surgery, Erasmus Medical Center, Rotterdam. [2]Dept of Medical Oncology, Erasmus Cancer Institute, Erasmus University Medical Center, Rotterdam. [3]Cancer Genomics Center Netherlands, Amsterdam. [4]Dept of Pathology, Erasmus Medical Center, Rotterdam. [5]Dept of Pathology, Radboud UMC, Nijmegen. [6]Dept of Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

16.30 Locally advanced colorectal cancer: true peritoneal penetration as a predictive factor for peritoneal metastases (p.90)

C.E.L. Klaver[1], N.C.M. van Huijgevoort[1], A. de Buck van Overstraeten[3], A.M. Wolthuis MD[3], P.J. Tanis[1], J.D.W. van der Bilt[1,3], X. Sagaert[2] and A. D'Hoore[3]. [1]Dept of surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. [2]Dept of pathology, UZ Leuven, Belgium. [3]Dept of abdominal surgery, UZ Leuven, Belgium. [4]Dept of surgery, Flevoziekenhuis, Almere, The Netherlands

16.40 Adherence to food guidelines of the World Cancer Research Fund & American Institute for Cancer Research and pancreatic cancer risk (p.91)

J. Fest[1], R. Ruiter[2], M.A. Ikram[2], C.H.J van Eijck[1], J.C. Kiefte-de Jong[2,3], B.H. Stricker[2]. [1]Dept of Surgery, Erasmus Medical Center, Rotterdam. [2]Dept of Epidemiology, Erasmus Medical Center, Rotterdam. [3]Dept of Global Public Health, Leiden University College, The Hague, The Netherlands

16.50 Einde programma

17.00 Vervolg plenair programma in de Brabantzaal.

18.30 Einde programma, congresborrel in expositiehal

20.00 Diner in Genderzaal

Abstractsessie – Nederlandse Vereniging voor Gastrointestinale Chirurgie Parkzaal

Voorzitters: R. Blom en J.A.B. van der Hoeven

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

10.00 The prognostic impact of radical resection margins on the Recurrence of Crohn's Disease (p.92)

J.E. van Amesfoort[1], L. Koens[2], W.A. Bemelman[1], C.J. Buskens[1]. [1]Dept of surgery, Academic Medical Center, Amsterdam. [2]Dept of pathology, Academic Medical Center, Amsterdam, The Netherlands

10.10 Smooth Seton® for perianal fistulas: a knot-less solution (p.93)

M.E. Stellingwerf[1], E.J. de Groof[1], C.J. Buskens[1], W. Nerkens[2], T. Horeman[2], W.A. Bemelman[1]. [1]Dept of Surgery, Academic Medical Center, Amsterdam. [2]MediShield B.V., Delft, The Netherlands

10.20 Perianal fistulas and the lift procedure: predictive factors for success (p.94)

R.J.F. Felt-Bersma[2], G.J.H. van der Mijnsbrugge[1], D.K.F. Ho[2], T. Jordanov[1], C.B.H. Deen- Molenaar[1]. [1]Proctos Kliniek, Bilthoven. [2]Dept of Gastroenterology and Hepatology, Vrije Universiteit medical Center Amsterdam, The Netherlands

10.30 Late anastomotic leakage and chronic presacral sinus following low anterior resection. Incidence and predisposing factors in a population based cohort (p.95)

W.A.A. Borstlap, P.J. Tanis and W. Bemelman. Academic Medical Center, Amsterdam, The Netherlands

10.40 Vacuum assisted early transanal closure of leaking low colorectal anastomoses, the CLEAN-study (p.96)

W.A.A. Borstlap[1] ,G.D. Musters[1], L.P.S. Stassen[3], H.L. van Westreenen[4], D. Hess[5], S. van Dieren, S. Festen[6], E.J. van der Zaag[7], P.J. Tanis[1], W.A. Bemelman[1]. [1]Dept of surgery, Academic Medical Center, University of Amsterdam, Amsterdam. [2]Dept of surgery, University Medical Center, Groningen. [3]Dept of surgery, Academic Hospital Maastricht , Maastricht. [4]Dept of surgery, Isala Klinieken, Zwolle. [5]Dept of surgery, Antonius Zorggroep, Sneek. [6]Dept of surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam. [7]Dept of surgery, Gelre Hospital, Apeldoorn, The Netherlands

10.50 Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis: a pooled analysis of individual data for 1980 patients (p.97)

H.C. van Santvoort[2,29], S. van Brunschot[1], R.A. Hollemans[2,3*], O.J. Bakker[4], M.G. Besselink[2], T.H. Baron[5], H.G. Beger[6], M.A. Boermeester[2], T.L. Bollen[7], M.J. Bruno[8], R. Carter[9], R.M. Charnley[10], D. Coelho[11], B. Dahl[12], M.G. Dijkgraaf[13], N. Doctor[14], P.J. Fagenholz[15], G. Farkas[16], C. Fernández-del Castillo[15], P. Fockens[1], M.L. Freeman[17], T.B. Gardner[18], H. van Goor[19], H.G. Gooszen[20], G. Hannink[21], R. Lochan[10], C.J. McKay[9], J.P. Neoptolemos[22], A. Oláh[23], R.W. Parks[24], M.P. Peev[15], M. Raraty[22], B. Rau[25], T. Rösch[26], M. Rovers[20], H. Seifert[12], A.K. Siriwardena[27] and K.D. Horvath[28] *Both authors contributed equally. Dept of [1]Gastroenterology, [2]Surgery, and [13]Clinical Research Unit, Academic Medical Center, Amsterdam, The Netherlands. Dept of Research and [3]Development, [29]Surgery, and [7]Radiology St Antonius Hospital, Nieuwegein, The Netherlands. [4]Dept of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands. [5]Dept of Gastroenterology and Hepatology, University of North Carolina, North Carolina, USA. [6]Dept of Surgery, University of Ulm, Ulm, Germany. [8]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands. [9]West of Scotland Pancreatic Unit, Glasgow Royal*

Infirmary, Glasgow, UK. [10]Dept of Surgery, Freeman Hospital, Newcastle upon Tyne, UK. [11]Dept of Surgery, Hospital Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. [12]Dept of Internal Medicine, Oldenburg Municipal Hospital, Oldenburg, Germany. [14]Dept of Gastrointestinal Surgery, Jaslok Hospital and Research Center, Mumbai, India. [15]Dept of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, USA. [16]Dept of Surgery, University of Szeged, Szeged, Hungary. [17]Dept of Gastroenterology, University of Minnesota, Minnesota, USA. [18]Dept of Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA. Dept of [19]Surgery, Operating Rooms - [20]Evidence Based Surgery, and Orthopaedic Research Lab, Radboud Institute for [21]Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. [22]Clinical Directorate of General Surgery, National Institutes of Health Research Liverpool Pancreas Biomedical Research Unit, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK. [23]Dept of Surgery, Petz-Aladár teaching hospital, Györ, Hungary. [24]Dept of Surgery, University of Edinburgh, Edinburgh, UK. [25]Dept of Surgery, University of Rostock, Rostock, Germany. [26]Dept of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, Hamburg, Germany. [27]Dept of Surgery, Manchester Royal Infirmary, Manchester, UK. [28]Dept of Surgery, University of Washington, Seattle, USA

11.00 High hospital mortality after pancreatoduodenectomy explained by failure to rescue rather than major complications in a nationwide audit (p.98)

LB van Rijssen[1], M.J. Zwart[1], S. van Dieren[2], T. de Rooij[1], B.A. Bonsing[3], K. Bosscha[4], R.M. van Dam[5], C.H. van Eijck[6], M.F. Gerhards[7], J.J. Gerritsen[8], E. van der Harst[8], I.H. de Hingh[9], K.P. de Jong[10], G. Kazemier[11], J. Klaase[21], C.J. van Laarhoven[13], M.D. Luyer[9], I.Q. Molenaar[14], G.A. Patijn[15], C.G. Rupert[16], J.J. Scheepers[17], G.P. van der Schelling[18], O.R. Busch[1,#], H.C. van Santvoort[19,#], B. Groot Koerkamp[6,#], M.G. Besselink[1,#]. [#]These authors share senior authorship. [1]Dept of Surgery, Academic Medical Center, Amsterdam. [2]Clinical Research Unit, Academic Medical Center, Amsterdam. [3]Dept of Surgery, Leiden University Medical Center, Leiden. [4]Dept of Surgery, Jeroen Bosch Hospital, 's-Hertogenbosch. [5]Dept of Surgery, Maastricht University Medical Center, Maastricht. [6]Dept of Surgery, Erasmus Medical Center, Rotterdam. [7]Dept of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam. [8]Dept of Surgery, Medisch Spectrum Twente, Enschede. Dept of Surgery, Maasstad Hospital, Rotterdam. [9]Dept of Surgery, Catharina Hospital, Eindhoven. [10]Dept of Surgery, University Medical Center Groningen, Groningen. [11]Dept of Surgery, VU University Medical Center, Amsterdam. [12]Dept of Surgery, Medisch Spectrum Twente, Enschede. [13]Dept of Surgery, Radboud University Medical Center. [14]Dept of Surgery, University Medical Center Utrecht, Utrecht. [15]Dept of Surgery, Isala Clinics, Zwolle. [16]Dept of Surgery, Tjongerschans Hospital, Heerenveen. [17]Dept of Surgery, Reinier de Graaf Gasthuis, Delft. [18]Dept of Surgery, Amphia Hospital, Breda. [19]Dept of Surgery, St Antonius Hospital, Nieuwegein, The Netherlands

11.10 Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (DIPLOMA): a pan-European propensity score matched observational study (p.99)

J. van Hilst[1], T. de Rooij[1], S. Klompmaker[1], M. Rawashdeh[2], F. Aleotti[3], A. Alseidi[4], Z. Ateeb[5], G. Balzano[3], F. Berrevoet[6], B. Björnsson[7], U. Boggi[8], O. Busch[1], G. Butturini[9], R. Casadei[10], M. del Chiaro[5], F. Cipriani[2], R. van Dam[11], I. Damoli[12], S. Dokmak[13], B. Edwin[14], C. van Eijck[15], J. Fabre[16], M. Falconi[3], O. Farges[13], L. Fernández-Cruz[17], A. Forgione[18], I. Frigerio[9], D. Fuks[19], F. Gavazzi[20], B. Gayet[19], A. Giardino[9], B. Groot Koerkamp[15], T. Hackert[21], M. Hassenpflug[21], I. Kabir[22], T. Keck[23], I. Khatkov[24], A. Klock[25], M. Kusar[26], C. Lombardo[8], G. Marchegiani[12], R. Marshall[4], M. Montorsi[20], M. Orville[13], A. Pietrabissa[27], I. Poves[28], J. Primrose[2], R. Pugliese[18], C. Ricci[10], K. Roberts[29], B. Røsok[14], M. Sahakyan[14], S. Sánchez-Cabús[17], P. Sandström[7], L. Scovel[4], L. Solaini[30], Z. Soonawalla[22], R. Souche[16], R. Sutcliffe[29], G. Tiberio[30], A. Tomazic[26], R. Troisi[6], U. Wellner[23], S. White[31], U. Wittel[25], A. Zerbi[20], C. Bassi[12], M. Besselink[1], M. Abu Hilal[2]* for the DIPLOMA study group. [1]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands. [2]Dept of Surgery, Southampton University Hospital NHS Foundation Trust, Southampton, United Kingdom. [3]Dept of Surgery, San Raffaele Hospital, Milan, Italy. [4]Dept of Surgery, Virginia Mason Medical Center, Seattle, United States of America. [5]Dept of Surgery, Karolinska Institute, Stockholm, Sweden. [6]Dept of General and HPB Surgery and Liver Transplantation, Ghent University Hospital, Ghent, Belgium. [7]Dept of Surgery and Dept of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden. [8]Dept of Surgery, Università di Pisa, Pisa, Italy. [9]Dept of Surgery, Pederzoli Clinic, Peschiera, Italy. [10]Dept of Surgery, S. Orsola-Malpighi Hospital, Bologna, Italy. [11]Dept of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands. [12]Dept of Surgery, Verona University Hospital, Verona, Italy. [13]Dept of Surgery, Hospital of Beaujon, Clichy, France. [14]The Intervention Center*

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11.20 Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer (p.100)

L.G.M. van der Geest[1], V.E.P.P. Lemmens[1,2], I.H.J.T. de Hingh[3], C.J.H.M. van Laarhoven[4], T.L. Bollen[5], C. Yung Nio[6], C.H.J. van Eijck[7], O.R.C. Busch[8], M.G.H. Besselink[8] for the Netherlands Comprehensive Cancer Organisation and the Dutch Pancreatic Cancer Group. [1]Dept of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht. [2]Dept of Public Health, Erasmus MC University Medical Center, Rotterdam, The Netherlands. [3]Dept of Surgery, Catharina Hospital, Eindhoven. [4]Dept of Surgery, Radboud University Medical Center, Nijmegen. [5]Dept of Radiology, St. Antonius Hospital, Nieuwegein. [6]Dept of Radiology, Academic Medical Center, Amsterdam. [7]Dept of Surgery, Erasmus Medical Center, Rotterdam. [8]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

11.30 Algemene ledenvergadering Nederlandse Vereniging Gastro-Enterologie

12.00 Lunchpauze in expositiehal

Abstractsessie – Nederlandse Vereniging voor Gastrointestinale Chirurgie Parkzaal

Voorzitters: W. Eshuis en W.O. de Steur

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

13.00 Diagnostic laparoscopy, a safe and useful tool in the preoperative screening of patients considered for cytoreductive surgery + HIPEC (p.101)

E.C.E. Wassenaar[1], A. Lans Valera[1], H.J.W. Braam[1], D. Boerma[1], B. van Ramshorst[1], F.J.H. Hoogwater[1], M.J. Wiezer[1]. [1]Surgery Department, St. Antonius Hospital, Nieuwegein, The Netherlands

13.10 The influence of partial hepatectomy on the post-operative course of bile salts and FGF19: a cohort study on novelregulators of liver regrowth (p.102)

K.M.C. van Mierlo[1], K.V. Koelfat[1], M. Schmeding[2], T. Cramer[2], I. Sauer[2], C.H. Dejong[1,2,3], F.G. Schaap[1], U.P. Neumann[2,4], S.W. Olde Damink[1,2,5]. [1]Dept of surgery, Maastricht University Medical Center & NUTRIM School of nutrition and translational research inmetabolism, Maastricht University, Maastricht, The Netherlands. [2]Dept of general-, visceral- and transplant surgery, Uniklinikum RWTH Aachen, Aachen, Germany. [3]GROW School for oncology and developmental biology, Maastricht University, Maastricht, The Netherlands. [4]Dept of surgery, Maastricht University Medical Center, Maastricht, The Netherlands. [5]Dept of HPB surgery & liver transplantation, Institute for liver and digestive health, Royal Free Hospitals, University College London, London, United Kingdom

13.20 Seventeen-Year Outcome of a Randomized Clinical Trial Comparing Laparoscopic and Conventional Nissen Fundoplication: A Plea for Patient Counselling and Clarification (p.103)

J.E. Oor[1], D.J. Roks[1,2], J.A. Broeders[1], E.J. Hazebroek[1], H.G. Gooszen[3]. [1]Dept of Surgery, St. Antonius Hospital Nieuwegein. [2]Dept of Surgery, University Medical Center Utrecht, Utrecht. [3]Dept of Operation Rooms/Evidence Based Surger, Radboud University Medical Center, Nijmegen, The Netherlands

13.30 Long term quality of life in patients after total gastrectomy versus Ivor Lewis esophagectomy (p.104)

E. Jezerskyte, L. Saadeh, A.E. Slaman, M.I. van Berge Henegouwen, S.S. Gisbertz. Academic Medical Center Amsterdam, The Netherlands

13.40 Factors Influencing Quality Of Life After Curative Gastrectomy For Cancer (p.105)

H.J.F. Brenkman[1], J.J.W. Tegels[2], J.P. Ruurda[1], M.D.P. Luyer[3], E.A. Kouwenhoven[4], W.A. Draaisma[5], D.L. van der Peet[6], B.P.L. Wijnhoven[7], J.H.M.B. Stoot[2], R. van Hillegersberg[1], LOGICA study group. [1]Dept of Surgery, University Medical Center Utrecht, Utrecht. [2]Dept of Surgery, Zuyderland Medical Center, Sittard. [3]Dept of Surgery, Catharina Hospital, Eindhoven. [4]Dept of Surgery, Ziekenhuisgroep Twente, Almelo. [5]Dept of Surgery, Meander Medical Center, Amersfoort. [6]Dept of Surgery, VU Medical Center, Amsterdam. [7]Dept of Surgery, Erasmus Medical Center, Rotterdam, The Netherlands

13.50 Impact of the number of resected nodes on survival in patients treated with neoadjuvant chemoradiotherapy and esophagectomy – a population-based cohort study in The Netherlands (p.106)

E. Visser[1], P.S.N. van Rossum[1,2], J.P. Ruurda[1], R. van Hillegersberg[1]. [1]Dept of Surgery, University Medical Center Utrecht. [2]Dept of Radiation Oncology, University Medical Center Utrecht, The Netherlands

14.00 A single blinded randomized controlled trial comparing semi mechanical with hand sewn cervical anastomosis after esophagectomy for cancer (SHARE-study) (p.107)

N. Nederlof, H.W. Tilanus, T. de Vringer, J.J.B. van Lanschot, S.P. Willemsen, W.C.J. Hop, B.P.L. Wijnhoven. Erasmus Medical Center, Rotterdam, The Netherlands

14.10 Postoperative outcomes of minimally invasive gastrectomy during the early introduction in The Netherlands: a population-based cohort study (p.108)

H.J.F. Brenkman[1], S.S. Gisbertz[2], A.E. Slaman[2], L. Goense[1,3], J.P. Ruurda[1], M.I. van Berge Henegouwen[2], R. van Hillegersberg[1], on behalf of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. [1]Dept of Surgery, University Medical Center Utrecht, Utrecht. [2]Dept of Surgery, Amsterdam Medical Center, Amsterdam. [3]Dept of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

14.20 Targeted Next-Generation Sequencing of Commonly Mutated Genes in Esophageal Adenocarcinoma patients with Long-term Survival (p.109)

E. Visser[1], I.A. Franken[1], L.A.A. Brosens[2], W.W.J. de Leng[2], E. Strengman[2], J.A. Offerhaus[2], J.P. Ruurda[1], R. van Hillegersberg[1]. [1]Dept of Surgery, University Medical Center Utrecht. [2]Dept of Pathology, University Medical Center Utrecht, The Netherlands

14.30 Association between waiting time from diagnosis to treatment and survival in patients with curable gastric cancer - a population-based study in The Netherlands (p.110)

H.J.F. Brenkman[1], E. Visser[1], P.S.N. van Rossum[1,2], S. Siesling[3,4], R. van Hillegersberg[1], J.P. Ruurda[1]. [1]Dept of Surgery, University Medical Center Utrecht, Utrecht. [2]Dept of Radiation Oncology, University Medical Center Utrecht, Utrecht. [3]Dept of Research, Netherlands Comprehensive Cancer Organization, Utrecht. [4]Dept of Health Technology and Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands

14.40 A high lymph node yield is associated with prolonged survival in elderly patients undergoing curative gastrectomy for cancer – a Dutch population-based cohort study (p.111)

H.J.F. Brenkman[1], L. Goense[1,2], L.A. Brosens[3], N. Haj Mohammad[4], F.P. Vleggaar[5], J.P. Ruurda[1], R. van Hillegersberg[1]. [1]Dept of Surgery, University Medical Center Utrecht, Utrecht. [2]Dept of Radiation Oncology, University Medical Center Utrecht, Utrecht. [3]Dept of Pathology, University Medical Center Utrecht, Utrecht. [4]Dept of Medical Oncology, University Medical Center Utrecht, Utrecht. [5]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands

14.50 A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in The Netherlands (p.112)

M.F.J. Seesing[1], S.S. Gisbertz[2], L. Goense[1], R. van Hillegersberg[1], H.M. Kroon[3], S. Lagarde[3], J.P. Ruurda[1], A.E. Slaman[2], M.I. van Berge Henegouwen[2], B.P.L. Wijnhoven[3]. [1]University Medical Center, Utrecht. [2]Academic Medical Center, Amsterdam. [3]Erasmus University Medical Center, Rotterdam, The Netherlands

15.00 Theepauze

Abstractsessie – Sectie Neurogastroenterologie en Motiliteit — Parkzaal

Voorzitters: D. Hirsch en D. Keszthelyi

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

15.30 Impaired postprandial colonic response in the presence of coordinated propagating colonic contractions suggests an extrinsic neuropathy in children with intractable functional constipation (p.113)

I.J.N. Koppen[1,2], L. Wiklendt[3], D. Yacob[2], C. Di Lorenzo[2], M.A. Benninga[1], P.G. Dinning[3,4]. [1]Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands. [2]Division of Pediatric Gastroenterology and Nutrition, Dept of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio, United States of America. [3]Dept of Human Physiology, Flinders University, Adelaide, South Australia, Australia. [4]Depts of Gastroenterology and Surgery, Flinders Medical Center, Adelaide, South Australia, Australia

15.40 Esophageal stasis on barium esophagogram in achalasia patients without symptoms after treatment does not predict symptom recurrence (p.114)

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

15.50 Development of a new diagnostic test for esophageal food sensitization in EoE patients: the Esophageal Prick Test (EPT) (p.115)

M.J. Warners[1,2], I.Terreehorst[3], R.M.J.G.J. van den Wijngaard[2], J. Akkerdaas[4], B.C.A.M. van Esch[5], R. van Ree[4,3], S.A. Versteeg[4], 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 Otorhinolaryngology, Academic Medical Center, Amsterdam. [4]Dept of Experimental Immunology, Academic Medical Center, Amsterdam. [5]Dept of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

16.00 Acid and non-acid reflux as a cause of chronic unexplained cough (p.116)

T.V.K. Herregods[1], A. Pauwels[2], D. Sifrim[3], J. Tack[2], A.J.P.M. Smout[1] & A.J. Bredenoord[1]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands. [2]Translational Research Center for Gastrointestinal Disorders, University Hospital Gasthuisberg, University of Leuven, Belgium. [3]Barts and the London School of Medicine, Queen Mary University of London, UK

16.10 Age-related changes in abdominal pain in healthy individuals and IBS patients (p.117)

E Wilms[1], D.M.A.E. Jonkers[1], D. Keszthelyi[1], Z. Mujagic[1], L. Vork[1], Z.Z.R.M. Weerts[1], J.W. Kruimel[1], F.J. Troost[1], A.A.M. Masclee[1]. [1]Division Gastroenterology-Hepatology, Dept of Internal Medicine; NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center+, Maastricht, The Netherlands

16.20 The predictive value of colonic transit time for colonic motor abnormalities on colonic manometry in patients with chronic constipation (p.118)

L. Vork[1], M. van Avesaat[1], E.A. van Hoboken[2], D. Keszthelyi[1], N.F. Rinsma[1], A.A.M. Masclee[1]. [1]Division of Gastroenterology-Hepatology, Dept of Internal Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht. [2]Dept of Gastro-enterology-Hepatology, Leiden University Medical Center, Leiden, The Netherlands

16.30 Development, Content Validity and Cross-Cultural Adaptation of a Patient-Reported Outcome Measure for Real-time Symptom Assessment in Irritable Bowel Syndrome: MEASuRE (p.119)

L. Vork[1], D. Keszthelyi[1], J.W. Kruimel[1], C. Leue[2], Z. Mujagic[1], D.M.A.E. Jonkers[1], J. van Os[2], H. Törnblom[4], M. Simrén[4,7], A. Albu-Soda[3], Q. Aziz[3], M. Corsetti[5], J. Tack[5], D.A. Drossman[7], S.S. Rao[6], E.G. Quetglas[8], A.A.M. Masclee[1]. [1]Division of Gastroenterology-Hepatology, Dept of Internal Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism Maastricht University Medical Center, Maastricht, The Netherlands. [2]Dept of Psychiatry and Medical Psychology, Maastricht University Medical Center+, Maastricht, The Netherlands. [3]Wingate Institute of Neurogastroenterology, Center for Neuroscience and Trauma, Bizard Institute, Barts and the London School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom. [4]Dept of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [5]Translational Research Center for Gastrointestinal Disorders (TARGID), Dept of Clinical and Experimental Medicine, University of Leuven, Leuven, Belgium. [6]Digestive Health Center, Medical College of Georgia, Georgia Regents University, Augusta, Georgia. [7]Center for Functional Gastrointestinal and Motility Disorders, University of North Carolina at Chapel Hill, North Carolina, USA. [8]Medical Intelligence, Early Clinical Development, Grünenthal GmBH, Aachen, Germany

16.40 Large Increase in Incidence of Eosinophilc Esophagitis over the Last 20 Years in the Netherlands: Results from a Nationwide Pathology Database (p.120)

W.E. de Rooij[1], M.J. Warners[1], B.D. van Rhijn[2], J. Verheij[3], A.J.P.M. Smout[1], A.J. Bredenoord[1]. [1]Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam. [2]Dept of Dermatology and Allergology, University Medical Center, Utrecht. [3]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands

16.50 PEG-J for gastroparesis; the ultimate solution? (p.121)

D. Strijbos[1,2], D. Keszthelyi[1], J. Kruimel[1], L.P.L. Gilissen[2], R. de Ridder[1], J. Conchillo[1] and A.A.M Masclee[1]. [1]Division of Gastroenterology and Hepatology, Dept of Internal Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht. [2]Dept of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands

17.00 Einde programma, vervolg plenaire sessie in de Brabantzaal.

18.30 Congresborrel in expositiehal

20.00 Diner in Beneluxzaal

Abstractsessie – Sectie Inflammatoire Darmziekten **Zaal 80**

Voorzitters: I. Gisbertz en M.J. Pierik

09.40 **Ledenvergadering Sectie Inflammatoire Darmziekten**

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

10.00 Impact of anorectal complaints on quality of life in patients with inflammatory bowel disease: a survey of the Dutch National Crohn's and Colitis organization (p.122)

P.F. Vollebregt[1], A.A. van Bodegraven[1,2], T.M.L. Markus-de Kwaadsteniet[3], D. van der Horst[3], R.J.F. Felt-Bersma[1]. [1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam. [2]Dept of Gastroenterology, Geriatrics, Internal Medicine and Intensive Care Medicine (Co-MIK), Zuyderland Medical Center, Heerlen-Geleen-Sittard. [3]Dutch Crohn's and Colitis organisation (CCUVN), Woerden, The Netherlands

10.10 Risk of malignant and non-malignant complications of the rectal stump in patients with Inflammatory Bowel Disease (p.123)

J.M.K. Bogaerts[1], J.R. Ten Hove[1], M.M. Laclé[2], V. Meij[3], B. Oldenburg[1]. [1]Dept of Gastroenterology and Hepatology, [2]Dept of Pathology, [3]Dept of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

10.20 Long-term outcomes after restorative proctocolectomy and ileal pouch-anal anastomosis in children compared to adults (p.124)

K. Diederen[1], S.S. Sahami[2], M.M. Tabbers[1], M.A. Benninga[1], A. Kindermann[1], P.J. Tanis[2], M.W. Oomen[3], W.A. Bemelman[2], J.R. de Jong[3]. [1]Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital, Academic Medical Center, Amsterdam. [2]Dept of Surgery, Academic Medical Center, Amsterdam. [3]Dept of Pediatric Surgery, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands

10.30 Pregnancy in IBD: direct effect of sex-hormones on epithelial barrier function (p.125)

J. van der Giessen[1], C.J. van der Woude[1], M.P. Peppelenbosch[1], G.M. Fuhler[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center Rotterdam, The Netherlands

10.40 Fecal calprotectin accurately predicts symptomatic relapse in children and adolescents with inflammatory bowel disease in clinical remission (p.126)

K. Diederen[1], D.R. Hoekman[1], A. Leek[1], V.M. Wolters[2], T.Z. Hummel[3], T.G. de Meij[4], B.G.P. Koot[1], M.M. Tabbers[1], M.A. Benninga[1], A. Kindermann[1]. [1]Dept of Pediatric Gastroenterology and Nutrition, Academic Medical Center / Emma Children's Hospital, Amsterdam. [2]Dept of Pediatric Gastroenterology, University Medical Center Utrecht / Wilhelmina children's hospital, Utrecht. [3]Dept of Pediatrics, Medisch Spectrum Twente, Enschede. [4]Dept of Pediatric Gastroenterology, VU University medical center, Amsterdam, The Netherlands

10.50 Fecal Loss of Infliximab is Underestimated due to Proteolysis (p.127)

A.S. Strik[1], J.F. Brandse[1], P.J. Koelink[2], M.E. Wildenberg[2], A. de Vries[3], R. Boshuizen[3], G.R. van den Brink[1], G.R. D'Haens[1]. [1]Dept of Gastroenterology, Academic Medical Center Amsterdam. [2]Tytgat Institute for Liver and Intestinal Research, Amsterdam. [3]Sanquin Research, Sanquin Laboratory, Amsterdam, The Netherlands

11.00 Thiopurine dose adjustment during pregnancy in inflammatory bowel disease: a case series (p.128)

J. van der Giessen[1], S.L. Kanis[1], G.M. Fuhler[1], C.J. van der Woude[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center Rotterdam, The Netherlands

11.10 High rate of advanced neoplasia after detection of low-grade dysplasia in Inflammatory Bowel Disease patients with primary sclerosing cholangitis (p.129)

J.R. ten Hove[1], J. Torres[2], D. Castaneda[2], C. Palmela[2], E. Mooiweer[1], S.C. Shah[2], J.-F. Colombel[2], T. Ullman[2], S.H. Itzkowitz[2], B. Oldenburg[1]. [1]University Medical Center Utrecht, Dept of Gastroenterology and Hepatology, Utrecht, The Netherlands. [2]Icahn School of Medicine at Mount Sinai, The Henry D. Janowitz Division of Gastroenterology, New York, USA

11.20 Postoperative surgical recurrence in Crohn's Disease decreases significantly in the biologic era (p.130)

E.M.J. Beelen[1], W.R. Schouten[2], B. Oldenburg[3], A.E. van der Meulen-de Jong[4], C.I.J. Ponsioen[5], G. Dijkstra[6], M.J. Pierik[7], D.J. de Jong[8], N.K.H. de Boer[9], C.J. van der Woude[1], A.C. de Vries[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam. [2]Dept of General Surgery, Erasmus Medical Center, Rotterdam. [3]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht. [4]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden. [5]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam. [6]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen. [7]Dept of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht. [8]Dept of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen. [9]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

11.30 Einde programma, algemene ledenvergadering van de NVGE in de Brabantzaal.

12.00 Lunchpauze in expositiehal

Abstractsessie – Sectie Gastrointestinale Endoscopie **Zaal 80**

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

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

15.30 Inter-observer agreement of the Paris classification in pT1b esophageal adenocarcinoma (p.131)

A.W. Gotink[1], F.J.C. ten Kate[2], M. Doukas[2], B.P.L. Wijnhoven[3], M.J. Bruno[1], L.H.J. Looijenga[2], A.D. Koch[1], K. Biermann[2]. [1]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam. [2]Dept of Pathology, Erasmus Medical Center, University Medical Center Rotterdam. [3]Dept of Surgery, Erasmus Medical Center, University Medical Center Rotterdam, The Netherlands

15.40 Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma (p.132)

H.T. Künzli[1,2], K. Belghazi[1], R.E. Pouw[1], S.L. Meijer[3], C.A. Seldenrijk[4], B.L.A.M. Weusten[1,2], J.J.G.H.M. Bergman[1]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center Amsterdam. [2]Dept of Gastroenterology and Hepatology, St. Antonius Hospital Nieuwegein. [3]Dept of Pathology, Academic Medical Center Amsterdam. [4]Dept of Pathology, St. Antonius Hospital Nieuwegein, The Netherlands

15.50 Safety and efficacy of endoscopic Focal CryoBalloon Ablation for the treatment of esophageal squamous cell intraepithelial neoplasia (p.133)

S.N. van Munster[1], Y. Ke[2]*, J. Chen[3], F. Liu[4], H.T. Künzli[1], D. Zhao[3], W. Li[2], S. He[2], Y. Zhang[2], L. Dou[2], Y. Liu[2], X. Liu[2], L. Xue[5], N. Lv[5], S.M. Dawsey[6], B.L.A.M. Weusten[1,7], J.J.G.H.M. Bergman[1], G. Wang[2]. *These two authors contributed equally to this paper. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands. [2]Dept of endoscopy, Cancer Institute and hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, People's Republic of China. [3]Dept of endoscopy, Feicheng's People's hospital, Feicheng, People's Republic of China. [4]Dept of endoscopy, Donping's People's hospital, Donping, People's Republic of China. [5]Dept of pathology, Cancer Institute and hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, People's Republic of China. [6]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. [7]Dept of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, The Netherlands*

16.00 A novel fully covered double-bump stent for anastomotic leaks after bariatric surgery: a retrospective analysis (p.134)

T.C.C. Boerlage[1,2], G.M.P. Houben[1], M.J.M. Groenen[3], K. van der Linde[4], A.W.J.M. van de Laar[1], M. Emous[4], P. Fockens[2], R.P. Voermans[1,2]. [1]Slotervaart Medical Center, Amsterdam. [2]Academic Medical Center, Amsterdam. [3]Rijnstate Hospital, Arnhem. [4]Leeuwarden Medical Center, Leeuwarden, Netherlands

16.10 Esophageal stent placement for upper gastrointestinal leaks: a prediction model for successful leakage control (p.135)

E.E. van Halsema[1], W.F.W. Kappelle[2], B.L.A.M. Weusten[3], R. Lindeboom[4], M.I. van Berge Henegouwen[5], P. Fockens[1], F.P. Vleggaar[2], M.C.W. Spaander[6] and J.E. van Hooft[1]. [1]Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam. [2]Dept of Gastroenterology & Hepatology, University Medical Center Utrecht, Utrecht. [3]Dept of Gastroenterology & Hepatology, St. Antonius Hospital, Nieuwegein. [4]Dept of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam. [5]Dept of Surgery, Academic Medical Center, Amsterdam. [6]Dept of Gastroenterology & Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

16.20 Esophageal self-dilation for therapy-resistant benign strictures: towards a structured and standardized approach (p.136)

E.E. van Halsema, C.A.C. 't Hoen, P.S. de Koning, W.D. Rosmolen, J.E. van Hooft and J.J.G.H.M. Bergman. Dept of Gastroenterology & Hepatology, Academic Medical Center, Amsterdam, The Netherlands

16.30 Surveillance of premalignant gastric lesions – a multi-center prospective cohort study from low incidence regions (p.137)

W.J. den Hollander[1], I.L. Holster[1], C.M. den Hoed[1], L.G. Capelle[1], T. Tang[2], M-P. Anten[3], I. Prytz-Berset[4], E. Witteman[5], F. ter Borg[6], B. den Hartog[7], M.J. Bruno[1], M.P. Peppelenbosch[1], W. Lesterhuis[1,8], M. Doukas[9], E.J. Kuipers[1,10], M.C. Spaander[1]. Depts of [1]Gastroenterology and Hepatology, [9]Pathology, [10]Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands. [2]Dept of Gastroenterology and Hepatology, IJsselland Hospital, Capelle aan den IJssel, The Netherlands. [3]Dept of Gastroenterology and Hepatology, Sint Franciscus Hospital, Rotterdam, The Netherlands. [4]Dept of Gastroenterology, More and Romsdal Trust Ålesund, Ålesund, Norway. [5]Deparment of Gastroenterology and Hepatology, Canisius- Wilhelmina Hospital, Nijmegen, The Netherlands. [6]Dept of Gastroenterology and Hepatology, Deventer Hospital, Deventer, The Netherlands. [7]Dept of Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem, The Netherlands. [8]Dept of Gastroenterology and Hepatology, Albert Schweitzer Hospital, Dordrecht, The Netherlands

16.40 Safety and effectiveness of colorectal endoscopic full-thickness resection using a new, flat-based over-the-scope clip: a prospective study (p.138)

Y Backes[1], W.F.W. Kappelle[1], L. Berk[2], A.D. Koch[3], J.N. Groen[4], W.H. de Vos tot Nederveen Cappel[5], M.P. Schwartz[6], M. Kerkhof[7], R. Schröder[8], T.G. Tan[9], M.M. Lacle[10], F.P. Vleggaar[1], L.M.G. Moons[1] (on behalf of the T1 CRC working group). [1]Dept of Gastroenterology & Hepatology, University Medical Center Utrecht, Utrecht. [2]Dept of Gastroenterology & Hepatology, St. Fransciscus Hospital, Rotterdam. [3]Dept of Gastroenterology & Hepatology, Erasmus hospital, Rotterdam. [4]Dept of Gastroenterology & Hepatology, St. Jansdal, Harderwijk. [5]Dept of Gastroenterology & Hepatology, Isala, Zwolle. [6]Dept of Gastroenterology & Hepatology, Meander Medical Center, Amersfoort. [7]Dept of Gastroenterology & Hepatology, Groene Hart Hospital, Gouda. [8]Dept of Gastroenterology & Hepatology, Gelre Hospital, Apeldoorn. [9]Dept of Gastroenterology & Hepatology, Medical Center de Veluwe, Apeldoorn [10]Dept of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

16.50 Endoscopic full-thickness resection: a prospective case series from a large clinical teaching hospital in The Netherlands (p.139)

K.J.C. Haasnoot, B.W. van der Spek, G.D.N. Heine. Dept of Gastroenterology & Hepatology, Noordwest Ziekenhuisgroep, Alkmaar, Noord-Holland, The Netherlands

17.00 Einde programma in deze zaal, vervolg plenaire sessie in de Brabantzaal.

18.30 Congresborrel in expositiehal

20.00 Diner in Beneluxzaal

Meet the expert **Zaal 81**

Meet the expert sessie Dysplasie bovenste tractus digestivus

De sessie wordt verzorgd door:

Prof. dr. J.J.G.H.M. Bergman, MDL-arts, Academisch Medisch Centrum, Amsterdam
Dr. A.D. Koch, MDL-arts, Erasmus MC, Rotterdam

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

Groep 1: 13.00 tot 14.00 uur
Groep 2: 14.00 tot 15.00 uur

Meet the expert **Zaal 82**

Meet the expert sessie Voedinggerelateerde problemen

De sessie wordt verzorgd door:

Dr. A.A. van Bodegraven, MDL-arts, Zuyderland, Heerlen
Dr. G.J. Wanten, MDL-arts, Radboudumc, Nijmegen

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

Groep 1: 13.00 tot 14.00 uur
Groep 2: 14.00 tot 15.00 uur

Symposium Sectie Gastrointestinale Oncologie **Auditorium**

Voorzitters: J. van Dieren en N. van Lelyveld

Thema: Orgaanbesparende behandeling

Rectum

09.30 Casus rectum - aios

09.35 'Wait- and- see' bij het rectum
Dr. J.B. Tuynman, chirurg VUmc, Amsterdam

09.50 Discussie

Slokdarm

09.55 Casus Slokdarm

10.00 'Surgery as needed' voor de slokdarm
Prof. dr. J.J.B. van Lanschot, chirurg Erasmus MC, Rotterdam

10.15 Discussie

Lever

10.20 Casus CRC levermetastase

10.25 Meer of minder leversparende behandeling bij CRC metastasen?
Dr. K.F.D. Kuhlmann, chirurg Antoni van Leeuwenhoek, Amsterdam

10.40 Radiotherapie bij colorectale levermetastasen
Dr. M.P.W. Intven, radiotherapeut-oncoloog, UMC Utrecht

10.55 Discussie

11.00 Koffiepauze

Symposium Sectie Kinder-MDL **Auditorium**

Voorzitters: J.C. Escher en V.M.C.W. Spaander

Symposium: MDL op alle leeftijden

11.30	Opening door voorzitter(s)
11.40	Oesofagusatresie, problemen op de kinderleeftijd *Dr. H. IJsselstijn, kinderarts, Erasmus MC-Sophia, Rotterdam*
11.50	Late complicaties na oesofagusatresie *Dr. V.M.C.W. Spaander, MDL-arts, Erasmus MC, Rotterdam*
12.00	discussie
12.05	Eosinofiele oesofagitis, problemen op de kinderleeftijd *Dr. J.H. Oudshoorn, kinderarts-MDL, Gelre Ziekenhuis, Apeldoorn*
12.15	Late complicaties na eosinofiele oesofagitis *Drs. E. Kouw, MDL-arts, Gelre Ziekenhuis, Apeldoorn*
12.25	Discussie
12.30	NAFLD, een nieuwe kinderziekte *Dr. A.C.E. Vreugdenhil, kinderarts-MDL, Maastricht UMC*
12.40	Latere complicaties van NAFLD *Dr. G.H. Koek, MDL-arts, Maastricht UMC*
12.50	Discussie
13.00	Lunchpauze in expositiehal

Symposium Sectie Gastrointestinale Endoscopie **Auditorium**

Voorzitters: T. Römkens en B.L.A.M. Weusten

When shit hits the fan....

14.00 Wat als het bloedt na poliepectomie
Dr. L.M.G. Moons, MDL-arts, UMC Utrecht

14.20 Wat als ik perforeer
Prof. J.J.G.H.M. Bergman, MDL-arts, Academisch Medisch Centrum, Amsterdam

14.40 Dubbele pech: complicaties na PEG-plaatsing
Dr. M.A.J.M. Jacobs, MDL-arts, VU medisch centrum, Amsterdam

15.00 Wanneer help ik de chirurg uit de brand
Dr. M.J.M. Groenen, MDL-arts, Ziekenhuis Rijnstate, Arnhem

15.20 Wat als ik word aangeklaagd?
Mr. drs. J.A.G. Drapers, MDL-arts n.p., Academisch Medisch Centrum, Amsterdam

15.40 Einde symposium

DEGH – Pitches — Baroniezaal

Voorzitters: C.J. Buskens en D.M.A.E. Jonkers

Voordrachten in het Engels, spreektijd 4 minuten, discussietijd 2 minuten

09.00 Inhibition of the BMP pathway prevents development of Barrett's associated adenocarcinoma in a surgical rat model (p.140)
S. Calpe[1], W.M. Westra[1,2], D. Straub[1], K.K. Krishnadath[1]. [1]Center for Experimental and Molecular Medicine (CEMM), Academic Medical Center, Amsterdam. [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

09.06 BMP signalling leads to stem cell loss and epithelial differentiation in the mouse intestine: a next generation sequencing-based approach (p.141)
L.R.A. van der Burg[1], P.W. Voorneveld[1], I. Al Azzawi[1], E.S.M. de Jonge-Muller[1], J.J. van der Reijden[1], H. Mei[2], S.M. Kielbasa[3], H.W. Verspaget[1], L.J.A.C. Hawinkels[1], J.C.H. Hardwick[1]*. *equal contribution. [1]Dept of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden. [2]Sequence Analysis Support Core, Leiden University Medical Center, Leiden. [3]Dept of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands*

09.12 Einde sessie pitches

DEGH – Oral presentations — Baroniezaal

Voorzitters: C.J. Buskens en D.M.A.E. Jonkers

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

Expert Lecture

09.15 *Appendectomy in Ulcerative Colitis, surgery meets basis science*
Dr. C.J. Buskens, Academisch Medisch Centrum Amsterdam

09.45 Fibrostenotic phenotype of fibroblasts in Crohn's disease is dependent on tissue stiffness and reversed by LOX inhibition (p.142)
J.R. de Bruyn[1,2], G.R. van den Brink[1,2], J. Steenkamer[2], C.J. Buskens[3], W.A. Bemelman[3], S. Meisner[2], V. Muncan[2], A.A. te Velde[1,2], G.R. D'Haens[1] and M.E. Wildenberg[1,2]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam. [2]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam. [3]Dept of Surgery, Academic Medical Center, Amsterdam, The Netherlands

09.42 Oral Tyrosine Kinase 2 inhibitor ameliorates T cell transfer colitis (p.143)
L.C.S. de Vries[1,2], M.E. Wildenberg[1,2], H.P. van Hamersveld[1], O. Welting[1], C. Verseijden[1], G.R.A.M. D'Haens[2], W.J. de Jonge[1]. [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, Amsterdam. [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

09.54 Disrupting IL-10 receptor signaling on CD11c+ myeloid cells causes a gluten-dependent small intestinal inflammation (p.144)

L.M.M. Costes[1], D.J. Lindenbergh-Kortleve[1], L.A. van Berkel[1], S. Veenbergen[1], Y. Simons- Oosterhuis[1], J.J. Karrich[2], B.E. Clausen[3], T. Cupedo[2], J.N. Samsom[1]. [1]Laboratory of Pediatrics, Division Gastroenterology and Nutrition, Erasmus Medical Center, Rotterdam, the Netherlands, [2]Laboratory of Hematology, Erasmus Medical Center, Rotterdam, the Netherlands, [3]Institute for Molecular Medicine, University Medical Center of the Johannes Gutenberg- University, Mainz, Germany

10.06 Reduced frequencies of regulatory TIGIT-expressing mucosal T cells in the circulation are characteristic for ongoing intestinal disease (p.145)

M.E. Joosse[1], C.L. Menckeberg[1], L.F. de Ruiter[1], H.C. Raatgeep[1], L.A. van Berkel[1], Y. Simons-Oosterhuis[1], F. Muskens[2], R. Hendriks[2], R. Hoogenboezem[3], T. Cupedo[3], L. de Ridder[4], J.C. Escher,[4] S. Veenbergen[1], J.N. Samsom[1]. [1]Laboratory of Pediatrics, division Gastroenterology and Nutrition, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam. [2]Dept of Pulmonology, Erasmus University Medical Center, Rotterdam. [3]Dept of Hematology, Erasmus University Medical Center, Rotterdam. [4]Dept of Pediatric Gastroenterology, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands

10.18 Anti-TNF immune complexes inhibit mucosal IL-12 and IL-23 production via Fc engagement on pro-inflammatory macrophages (p.146)

F.M. Bloemendaal[1], C.P. Peters[2], H. Korf[3], P.J. Koelink[1], T. Rispens[4], K.A. van Schie[4], G.R.A.M. D'Haens[2], C.Y. Ponsioen[2], A.A. te Velde, S. Vermeire[3], G.R. van den Brink[1,2], M.E. Wildenberg[1]. [1]Tytgat Institute for Liver and Intestinal Research, Academic Medical Center, the Netherlands. [2]Dept of Gastroenterology and Hepatology, Academic Medical Center, The Netherlands. [3]Translational Research Center for Gastrointestinal Disorders [TARGID], Dept of Clinical and Experimental Medicine, KU Leuven, Leuven, Belgium. [4]Sanquin Research, Dept of Immunopathology, Amsterdam, The Netherlands, and Landsteiner Laboratory, Academic Medical Center, University of Amsterdam, The Netherlands

10.30 Local Administration of Mesenchymal Stromal Cells alleviates Experimental Colitis (p.147)

M.C. Barnhoorn, E.S.M. de Jonge-Muller, M.A.C. Mieremet-Ooms, D. van der Helm, M.L. van Gulijk, J.D. Hoogenboom, I. Molendijk, P.W.J. Maljaars, A.E. van der Meulen-de Jong, L.J.A.C. Hawinkels, H.W. Verspaget. Dept Gastroenterology and Hepatology, Leiden University Medical Center, The Netherlands

11.00 Koffiepauze

DEGH – Oral presentations — Baroniezaal

Voorzitters: K.F.J. van de Graaf en M.E. Wildenberg

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

11.30 The role of recipient epithelial cells in regeneration after liver transplantation: Different kinetics of chimerism for hepatocytes and bile duct epithelial cells (p.148)

F.J.M. Roos[1], J.W. Selten[1], W.G. Polak[1], M.M. Verstegen[1], H.F.B.M. Sleddens[2], M. Doukas[2], H.J. Metselaar[3], J.N.M. IJzermans[1], L.J.W. van der Laan[1]. [1]Dept of Surgery, Erasmus Medical Center Rotterdam, Rotterdam. [2]Dept of Pathology, Erasmus Medical Center Rotterdam, Rotterdam. [3]Dept of Gastroenterology and Hepatology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

11.42 Hepatic LGR5 stem cells contribute to liver carcinogenesis (p.149)

W. Cao[1], M. Li[1], P. Liu[1], J. Liu[1], M. Bolkestein[2] , K. Chen[1, 3], L.J.W. van der Laan[4], D. Sprengers[1], H.J. Metselaar[1], J. Kwekkeboom[1], R. Smits[1], M.P. Peppelenbosch[1] and Q. Pan[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands. [2]Dept of Experimental Surgical Oncology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands. [3]College of Life Sciences, Zhejiang Sci-Tech University, Hangzhou, China. [4]Dept of Surgery, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

11.54 Einde sessie oral presentations

DEGH – Short pitches **Baroniezaal**

Voordrachten in het Engels, spreektijd 4 minuten, discussietijd 2 minuten

11.54 *Niet aanwezig*

Pegylated interferon alpha treatment rapidly clears Hepatitis E Virus infections in humanized mice (p.150)

M.D.B. van de Garde[1], S.D. Pas[2], G.W. van Oord[1], L. Gama[4], Y. Choi[5], R.A. de Man[1], A. Boonstra[1], T. Vanwolleghem[1,3]. [1]Dept of Gastroenterology and Hepatology, [2]Dept of Viroscience, Erasmus University Medical Center, Rotterdam, The Netherlands. [3]Laboratory of Experimental Medicine and Pediatrics, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium. Dept of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium. [4]Dept of Molecular and Comparative Pathobiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [5]The Center for Disease Control and Prevention, Atlanta, Georgia, USA

12.00 Establishment of malignant organoid model from primary mouse liver tumors (p.151)

W. Cao[1], M. Li[1], P. Liu[1], Y. Yin[1], M.M.A. Verstegen[2], J. Liu[1], K. Chen[1,3], L.J.W. van der Laan[2], J. Kwekkeboom[1], R. Smits[1], M.P. Peppelenbosch[1] and Q. Pan[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands. [2]Dept of Surgery, Erasmus MC-University Medical Center, Rotterdam, The Netherlands. [3]College of Life Sciences, Zhejiang Sci-Tech University, Hangzhou, China

12.06 Analysis of HLA I peptides presented on human hepatocytes using ultra-sensitive mass spectrometry (p.152)

M.T.A. de Beijer[1], J.A. Demmers[2], K. Bezstarosti[2], P.J. Biesta[1], R.A. de Man[1], A.M. Woltman[1], S.I Buschow[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam. [2]Proteomics Center, Erasmus MC-University Medical Center, Rotterdam, The Netherlands

12.12 Pancreas and pancreatic tumor protein synthesis rates *in vivo* in cancer patients (p.153)

D.P.J. van Dijk[1,2], J.S.J. Smeets[2,3], A.M.H. Horstman[2,3], S.S. Rensen[1,2], C.H.C. Dejong[1,2,4], S.W.M. Olde Damink[1,2,5], L.J.C. van Loon[2,3]. [1]Dept of Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands. [2]NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands. [3]Dept of Human Biology and Movement Sciences, Maastricht University, Maastricht, The Netherlands. [4]GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands. [5]Institute for Liver and Digestive Health, University College London, London, United Kingdom

12.18 Autophagy regulates Rac1 and RhoA activity in dendritic cells (p.154)
M.M.C. Prins[1], P.J Koelink[1], G.R. van den Brink[1], M.E. Wildenberg[1]. [1]Tytgat Institute for Liver and Intestinal Research and Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

12.24 Immune responses in acute hepatitis B: chronicity versus resolved infection (p.155)
F. Stelma[1,2], A. de Niet[1,2], S.B. Willemse[1,2], M.J. Sinnige[2], H.L. Zaaijer[3], E.M.M. van Leeuwen[2], N.A. Kootstra[2], H.W. Reesink[1,2]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam. [2]Dept of Experimental Immunology, Academic Medical Center, Amsterdam. [3]Dept of Clinical Virology, Academic Medical Center, Amsterdam, The Netherlands

12.30 Hepatitis E virus activates signal transducer and activator of transcription 3 to facilitate virus replication (p.156)
W. Wang[1], C. Qu[1], L. Xu[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

12.36 6-thioguanine potently inhibits rotavirus infection through suppression of Rac1 activation (p.157)
Y. Yuebang[1], W. Wang[1], L. Xu[1], W. Dang[1], S. Chen[1], C. Qu[1], G. Fuhler[1], M.P. Peppelenbosch[1] and Q. Pan[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam

12.42 PI3K-Akt-mTOR-4E-BP1 axis sustains rotavirus infection and Represents an antiviral target (p.158)
Y. Yin[1], W. Dang[1], X. Zhou[1], L. Xu[1], W. Wang[1], W. Cao[1], M.P. Peppelenbosch[1] and Q. Pan[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

12.48 Splanchnic release contributes to the elevated pool of FGF19 in the circulation of patients with obstructive cholestasis (p.159)
K.V.K. Koelfat[1], E.P. Neis[1], S. Rensen[1], P.L.M. Jansen[1], C.H.C. Dejong[1,2], F.G. Schaap[1], S.W.M. Olde Damink[1,3]. [1]Dept of Surgery, Maastricht University Medical Center and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands. [2]GROW School for oncology and developmental biology, Maastricht University, Maastricht, The Netherlands. [3]Institute for Liver and Digestive Health, University College London, London, United Kingdom

12.54 Einde programma

13.00 Lunchpauze in expositiehal

DEGH – Battle **Baroniezaal**

Voorzitters: Bestuur DEGH

14.00 "The Battle": zes getalenteerde jonge onderzoekers zullen elk in 5 minuten een begrijpelijk overzicht geven van hun gepubliceerde topartikel. Een jury kiest op basis van deze korte presentaties de winnaars van de "Young Hepatologist Award" (een NVH prijs) en de "Basale Junior Onderzoekers Prijs" van de SEG.

Programma NVMDL **Parkzaal**

Voorzitter: M.A.M.T. Verhagen

Thema: taakherschikking binnen de MDL

09.30	Inleiding *Dr. M.A.M.T. Verhagen, MDL-arts, Diakonessenhuis, Utrecht* *Voorzitter Beroepsbelangencommissie NVMDL en Commissie Taakherschikking*
09.35	PA, VS en VE: wat zijn de verschillen? *Mw. T.A. Korpershoek (VS), Mw. E. Brons, (PA) en Mw. W. Kok (VE)*
09.45	Juridisch Kader en nieuwe ontwikkelingen in regelgeving *Mw. mr. B. van de Lagemaat, senior adviseur Federatie Medisch Specialisten*
10.05	PA als zaalarts? *Mw. M.J.C. Timmermans, MSc.*
10.25	Kiezen voor PA, VS of VE? *Dr. P. Honkoop, MDL-arts, Albert Schweitzer ziekenhuis* *Lid Commissie Taakherschikking*
10.40	Taakherschikking binnen MDL in Nederland. Werkdocumenten. *Mw. T.A. Korpershoek, voorzitter V&VN*
10.45	Discussie en vragen
11.00	Einde programma

Abstractsessie Sectie Gastrointestinale Endoscopie **Parkzaal**

Voorzitters: J.J.G.H.M. Bergman en J.W. Poley

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

11.30 High percentage of visible lesions in patients with Barrett's oesophagus referred with dysplasia in random biopsies (p.160)

I.C. Noordzij[1], W.L. Curvers[1], G. van Lijnschoten[2], C.J. Huysentruyt[2], E.J. Schoon[1]. [1]Dept of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven. [2]Laboratory of Pathology and Medical Microbiology, Eindhoven, The Netherlands

11.40 Salvage endoscopic resection in patients with oesophageal adenocarcinoma after chemoradiotherapy (p.161)

I.C. Noordzij[1], W.L. Curvers[1], C.J. Huysentruyt[2], G.A.P. Nieuwenhuijzen[3], G.J. Creemers[4], M.J.C. van der Sangen[5], E.J. Schoon[1]. [1]Dept of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven. [2]Laboratory of Pathology and Medical Microbiology, Eindhoven. [3]Dept of Surgery, Catharina Hospital, Eindhoven. [4]Dept of Oncology, Catharina Hospital, Eindhoven. [5]Dept of Radiation Oncology, Catharina Hospital, Eindhoven, The Netherlands

11.50 A randomized, controlled trial comparing a simplified and standard regimen for focal radiofrequency ablation treatment of dysplastic Barrett's esophagus (p.162)

H.T. Künzli[1,2], R.E. Pouw[1]*, R. Bisschops[3], C.M. Sondermeijer[1], A.D. Koch[4], P. Didden[4], A.W. Gotink[4], E.J. Schoon[5], W.L. Curvers[5], J.J.G.H.M. Bergman[1], B.L.A.M. Weusten[1,2]*. *These authors share first authorship. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, The Netherlands. [2]Dept of Gastroenterology and Hepatology, St. Antonius Hospital Nieuwegein, The Netherlands. [3]Dept of Gastroenterology and Hepatology, University Hospital Gasthuisberg, Leuven, Belgium. [4]Dept of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands. [5]Dept of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands*

12.00 Seven-year prospective follow-up results of radiofrequency ablation for Barrett's esophagus with high-grade dysplasia and early cancer (p.163)

K Belghazi[1], B.L.A.M. Weusten[1], S.L. Meijer[2], J.J.G.H.M. Bergman[1], R.E. Pouw[1]. [1]Dept of Gastroenterology, Academic Medical Center, Amsterdam. [2]Dept of Pathology, Academic Medical Center, Amsterdam, The Netherlands

12.10 Routine use of endoscopic ultrasound in patients with suspected common bile duct stones prevents unnecessary ERCP's (p.164)

A.C. Poen, M.S.E. Eenkhoorn, S. Mutsaers, R. Mousset, L.R.H. de Wijkerslooth. Dept of Gastroenterology, Isala, Zwolle, The Netherlands

12.20 Expert and construct validity of a novel mechanical ERCP simulator (p.165)

S.E. van der Wiel[1], A.D. Koch[1], M.J. Bruno[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, The Netherlands

12.30 Differences in colonoscopy associated costs between primary colonoscopy and colonoscopy after positive FIT in colorectal cancer screening (p.166)

E. Wieten[1], E.J. Kuipers[1], E.M. Stoop[1], E. Dekker[2], I. Lansdorp-Vogelaar[3] P.C.J. ter Borg[4], R.J.T. Ouwendijk[4], M.J. Bruno[1], M.C.W. Spaander[1]. [1]Dept of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Rotterdam. [2]Dept of Gastroenterology & Hepatology, Academic Medical Center Amsterdam, Amsterdam. [3]Dept of Public Health, Erasmus MC University Medical Center, Rotterdam. [4]Dept of Gastroenterology & Hepatology, Ikazia Hospital, Rotterdam, The Netherlands

12.40 Feasibility, safety and accuracy of the Extra Wide Angle View (EWAVE) Colonoscope for the detection of colorectal lesions (p.167)

M.E.S. Bronzwaer[1], E. Dekker[1], V. Weingart[2], M. Pioche[3], J. Rivory[3], T. Beyna[4], H. Neuhaus[4], T. Ponchon[3], H. Allescher[2], P. Fockens[1], T. Rösch[5]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. [2]Dept of Gastroenterology and Hepatology, Klinikum Garmisch-Partenkirchen, Ludwig-Maximilians University, Garmisch-Partenkirchen, Germany. [3]Dept of Endoscopy and Gastroenterology, Hospital Edouard Herriot, University of Lyon, Lyon, France. [4]Dept of Gastroenterology and Hepatology, Evangelischen Krankenhaus Düsseldorf, Düsseldorf, Germany. [5]Dept of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, University of Hamburg, Hamburg, Germany

12.50 Feasibility of the use of virtual reality glasses to relieve pain and discomfort in patients during colonoscopy (p.168)

G. Veldhuijzen[2], N. Klaassen[1], Y.K.P. Stiemer[2], J.P.H. Drenth[2], R.J.A. van Wezel[3], A.A. van Esch[2]. [1]Technical Medicine, University of Twente, Enschede. [2]Dept of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen. [3]Dept of Biomedical Signals And Systems, University of Twente, Enschede, The Netherlands

13.00 Lunch in expositiehal

Abstractsessie Nederlandse Vereniging Gastroenterologie **Parkzaal**

Voorzitters: K. Sebib Korkmaz en H.W. Verspaget

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

14.00 Visualizing hepatocellular amino acid kinetics through mass spectrometry imaging of stable isotopes (p.169)

Z. Soons[1], M. Arts[1,2], S.R. Ellis[2], L.J. Dubois[3], K.A. Pierzchalski[2], B. Balluff[2], G.B. Eijkel[2], T. Cramer[4], N. Lieuwes[3], S.M. Agten[5], T.M. Hackeng[5], L.J.C. van Loon[6], R.M.A. Heeren[2], S.W.M. Olde Damink[1]. [1]Dept of General Surgery, NUTRIM, Maastricht University. [2]Maastricht Multimodal Molecular Imaging Institute (M4I), Maastricht University. [3]Dept of Radiation Oncology (MAASTRO), GROW, Maastricht University. [4]Dept of General, Visceral and Transplantation Surgery, University Hospital RWTH Aachen. [5]Dept of Biochemistry, CARIM, Maastricht University. [6]Dept of Human Biology and Movement Sciences, NUTRIM, Maastricht University, The Netherlands

14.10 Reducing PPI and H2RA prescriptions in pediatrics (p.170)

N.F. Steutel[1,2], M.E.P. Jansen[3], M.W. Langendam[2], M.A. Benninga[1], M.M. Tabbers[1]. [1]Dept of Pediatric Gastroenterology and Nutrition, Emma Children's Hospital/ Academic Medical Center. [2]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center. [3]Dept of Pharmacology, Academic Medical Center, The Netherlands

14.20 The effect of specific refluxate components on bile receptor signaling and development of metaplastic Barrett-like glands in mice (p.171)

D. Straub[1,2], L. Mari[1,2], K.F.J. van de Graaf[3], K.K. Krishnadath[1]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam. [2]Center for Experimental and Molecular Medicine (CEMM), Amsterdam. [3]Tytgat Institute for Liver and Intestinal Research, Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

14.30 Increased frequency of Barrett's esophagus in patients with MUTYH associated polyposis (p.172)

C.G. Daans[1], M.E. Velthuizen[2], H.F.A. Vasen[3], G.J.A. Offerhaus[4], M.M. Laclee[4], P.S. Siersema[5], M.G.E.M. Ausems[2], J.J. Boonstra[3]. [1]Dept of Internal Medicine, HAGA Hospital, Den Haag. [2]Dept of Medical Genetics, University Medical Center Utrecht, Utrecht. [3]Dept of Gastroenterology, Leiden University Medical Center, Leiden. [4]Dept of Pathology, University Medical Center Utrecht, Utrecht. [5]Dept of Gastroenterology, Radboud UMC, Nijmegen, The Netherlands

14.40 Detection of sepsis in preterm infants by fecal volatile organic compounds analysis: a proof of principle study (p.173)

D.J.C. Berkhout[1,2], H.J. Niemarkt[3], M. Buijck[1], M.M. van Weissenbruch[4], P. Brinkman[5], M.A. Benninga[2], A.H. van Kaam[6], B.W. Kramer[7], P. Andriessen[3,7], K.H.N. de Boer[8], T.G.J. de Meij[1]. [1]Dept of Pediatric Gastroenterology, VU University Medical Center, Amsterdam. [2]Dept of Pediatric Gastroenterology, Emma Children's Hospital / Academic Medical Center, Amsterdam. [3]Neonatal Intensive Care Unit, Máxima Medical Center, Veldhoven. [4]Neonatal Intensive Care Unit, VU University Medical Center, Amsterdam. [5]Dept of Respiratory Medicine, Academic Medical Center, Amsterdam. [6]Neonatal Intensive Care Unit, Emma Children's Hospital / Academic Medical Center, Amsterdam. [7]Dept of Pediatrics, Maastricht University Medical Center, Maastricht. [8]Dept of Gastroenterology and Hepatology VU University Medical Center, Amsterdam, The Netherlands

14.50 Filgotinib, a selective JAK1 inhibitor, induces clinical remission in patients with moderate-to-severe Crohn's disease: results from the Phase II FITZROY study (p.174)

M. Löwenberg[1], G. D'Haens[1], S. Vermeire[2], L. Meuleners[3], C. Tasset[3], A. van der Aa[3], P. Harrison[3]. [1]Dept of gastroenterology, Academic Medical Center, Amsterdam, The Netherlands. [2]Dept of gastroenterology, University Hospital Leuven, Leuven, Belgium. [3]Galapagos NV, Mechelen, Belgium

15.00 Long-term follow-up in Dutch autoimmune hepatitis patients (p.175)

F.F. van den Brand, K. van der Veen, N. van Gerven, Y.S. de Boer, C.M.J. van Nieuwkerk, G. Bouma. Dept of Gastroenterology, VU Medical Center, Amsterdam, The Netherlands

15.10 Diagnostic yield of upper gastrointestinal endoscopy in young adults (18 - 40 years); the referral guide ("NHG maagklachten") tested in daily practice (p.176)

E.J. van Soest, T. Bakker. Dept of Gastroenterology, Spaarne Gasthuis, Haarlem, The Netherlands

15.20 Einde programma

Abstractsessie – NESPEN **Zaal 80**

Voorzitters: C.F. Jonkers en G. Wanten

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

09.30 Cholestatic liver injury during critical illness: disturbed enterohepatic bile salt signaling in patients with diarrhea (p.177)

R.J.J. van Gassel[1,2,3], F.G. Schaap[1,3], K.V. Koelfat[1,3], M. Baggerman[2], M. Bol[2], G. Nicolaes[4,5], D. Beurskens[4,5], M.C.G. van de Poll[1,2,3], S.W.M. Olde Damink[1,3]. [1]Dept of general surgery, Maastricht University Medical Center, Maastricht. [2]Dept of intensive care medicine, Maastricht University Medical Center, Maastricht. [3]NUTRIM, School of nutrition and translational research in metabolism, Maastricht. [4]Dept of biochemistry, Maastricht University, Maastricht. [5]CARIM Cardiovascular research institute Maastricht, Maastricht, The Netherlands

09.40 The effect of low FODMAP diet on long term global health outcomes in IBS patients (p.178)

T.L. Kortlever[1,2], S. Ten Bokkel Huinink[1,2], M. Offereins[1,2], C.R. Hebblethwaite[3], J.A. Leeper[3], L.A. O'Brien[3], J.S. Barrett[5], C.J.J. Mulder[2,6], R.B. Gearry[1,4]. [1]Dept of Medicine, University of Otago, Christchurch, New Zealand. [2]Dept of Medicine, VU Medical Center, Amsterdam, The Netherlands. [3]Digestive Health Service, Christchurch, New Zealand. [4]Dept of Gastroenterology, Christchurch Hospital, Christchurch, New Zealand. [5]Dept of Gastroenterology, The Alfred Hospital, Melbourne, Victoria, Australia. [6]Dept of Gastroenterology and Hepatology, VU Medical Center, Amsterdam, The Netherlands

09.50 Comparison of taste and texture of Metamucil®, Volcolon® and psyllium orange generic: a randomized double-blinded study (p.179)

P.F. Vollebregt[1], T.J. Lam[1], M.S. Vlietstra[1], R.J.F. Felt-Bersma[1]. Dept of Gastroenterology, VU University Medical Center, Amsterdam, The Netherlands

10.00 Prevalence and effects of paediatric home tube feeding in the Netherlands (p.180)

H. Krom[1], S.M.C. van Zundert[2], M.A.G.M. Otten[3], L. van der Sluijs Veer[4], M.A. Benninga[1], A. Kindermann[1]. [1]Dept of Paediatric Gastroenterology and Nutrition, Emma Children's Hospital/Academic Medical Center, Amsterdam. [2]Dept of Dietetics, Emma Children's Hospital/Academic Medical Center, Amsterdam. [3]Dept of Rehabilitation, Emma Children's Hospital/Academic Medical Center, Amsterdam. [4]Dept of Gastroenterology, Emma Children's Hospital/Academic Medical Center, Amsterdam, The Netherlands

10.10 Men are more prone to present with an atypical clinical subtype of celiac disease than women (p.181)

I.L. Tan[1,2], R.K. Weersma[1,2], M. Spijkerman[3], S. Withoff[2], C. Wijmenga[2], J.J. Kolkman[4], M.C. Visschedijk[1,2]. [1]Dept of Gastroenterology and Hepatology, University of Groningen and University Medical Center Groningen. [2]Dept of Genetics, University of Groningen and University Medical Center Groningen. [3]Gemeenschappelijke GezondheidsDienst Twente, Enschede. [4]Dept of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, The Netherlands

10.20 The effects of four weeks pectin intake on intestinal permeability in young adults and elderly (p.182)
E. Wilms[1,2], F. Troost[1,2], D. Jonkers[1], M. Elizalde[1], L. Tischmann[1], P. de Vos[2,3], A.A.M. Masclee[1]. [1]Div. Gastroenterology-Hepatology, Dept of Internal Medicine; NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center+, Maastricht. [2]Top Institute Food and Nutrition, Wageningen. [3]Immunoendocrinology, Dept of Pathology and Medical Biology, University Medical Center Groningen, Groningen, The Netherlands

10.30 The role of phase angle by bioelectrical impedance analysis in the assessment of nutritional status and disease severity in adult patients with mitochondrial disorders caused by the m.3243A>G mutation (p.183)
H.E.E. Zweers, J. Thijssen, E. Weerts, S. Leij, P. de Laat, G. Wanten en M.C.H. Janssen. Dept of Gastroenterology of Radboud UMC, Nijmegen, The Netherlands

10.40 Risk estimation for lymphoma and gastrointestinal carcinoma after diagnosis of celiac disease based on a nationwide population-based case-control study (p.184)
T van Gils[1], P. Nijeboer[1], L.I.H. Overbeek[2], D.A.R. Castelijn[1], G. Bouma[1], C.J.J. Mulder[1], F.E. van Leeuwen[3], D. de Jong[4]. [1]Celiac Center Amsterdam, Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam. [2]Foundation PALGA (The Nationwide Network and Registry of Histo- and Cytopathology in The Netherlands), Houten. [3]Dept of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam. [4]Dept of Pathology, VU University Medical Center, Amsterdam, The Netherlands

11.00 Koffiepauze

Symposium NESPEN — Zaal 80

Voorzitters: C.F. Jonkers-Schuitema en G.J. Wanten

Symposium: enterale voeding

11.15 Toegangswegen voor enterale voeding
Dhr. K. Boeykens, verpleegkundig specialist voedingsteam AZ Nikolaas, België

11.45 Discussie

12.00 Reduction of tube feeding and oral nutritional supplements while maintaining nutritional status in patients with head and neck cancer
Dr. M. van den Berg, diëtist-onderzoeker, Radboudumc, Nijmegen

12.10 Cortrak duodenal tube placements: a solution for all patients? A retrospective survey to evaluate the introduction of electromagnetic-guided placement of nasoenteral feeding tubes
Mw. W. Arjaans, verpleegkundige voedingsteam VUmc, Amsterdam

12.20 Impact van FoodforCare op voedingstoestand klinisch opgenomen patiënten
Drs. D. Dijxhoorn, arts-onderzoeker, Radboudumc, Nijmegen

12.30 Hongerprovocatie in de praktijk
Drs. Hilde Krom, arts-onderzoeker kinder-MDL, AMC

12.40 Inventarisatie voedingsbeleid na LTX
M. van Kemenade, diëtist Erasmus MC, Rotterdam

12.50 Proefschriftprijs presentatie

13.00 Uitreiking proefschriftprijs door voorzitter NESPEN

Lunch in expositiehal

Abstractsessie Nederlandse Vereniging Gastroenterologie **Zaal 80**

Voorzitters: J.C.H. Hardwick en W.H. de Vos tot Nederveen Cappel

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

14.00 Development and first experiences of the Netherlands Donor Feces Bank (p.185)

Y.H. van Beurden[2,3], E.M. Terveer[1], A. Goorhuis[4], J.F.M.L. Seegers[5], M.P. Bauer[6], E. van Nood[7], M.G.W. Dijkgraaf[8], C.J.J. Mulder[3], C.M.J.E. Vandenbroucke-Grauls[2], H.W. Verspaget[9], J.J. Keller[10,11], E.J. Kuijper[1]. [1]Dept of Medical Microbiology, Leiden University Medical Center, Leiden. [2]Dept of Medical Microbiology & Infection Control, VU University Medical Center, Amsterdam. [3]Dept of Gastroenterology, VU University Medical Center, Amsterdam. [4]Dept of Internal Medicine, Academic Medical Center, Amsterdam. [5]Unaffiliated. [6]Dept of Internal Medicine, Leiden University Medical Center, Leiden. [7]Dept of Internal Medicine, Havenziekenhuis, Rotterdam. [8]Clinical Research Unit, Academic Medical Center, Amsterdam. [9]Dept of Biobanking and Gastroenterology, Leiden University Medical Center, Leiden. [10]Dept of Gastroenterology, Medical Center Haaglanden, The Hague. [11]Dept of Gastroenterology, Leiden University Medical Center, Leiden, The Netherlands

14.10 Helicobacter pylori colonization is not associated with Non-Alcoholic Fatty Liver Disease (NAFLD) in the general population (p.186)

P. Honkoop[1], L.J.M. Alferink[1], C.M. den Hoed[1], P. Taimr[1], M.A. Ikram[2], E.J. Kuipers[1], B.H. Stricker[2], H.J. Metselaar[1], S. Darwish Murad[1]. [1]Dept of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam. [2]Dept of Epidemiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

14.20 Validation of a Score Chart to Predict the Risk of Chronic Mesenteric Ischemia: a Discriminative and Useful Tool in Clinical Decision-Making (p.187)

L.J.D. van Dijk[1,2], D. van Noord[1,3], R.H. Geelkerken[4], S.A. Berendsen[1], A.C. de Vries[1], A. Moelker[2], H.J.M. Verhagen[5], J.J. Kolkman[6,7], M.J. Bruno[1] – on behalf of the Dutch Mesenteric Study group (DMIS). [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam. [2] Dept of Radiology, Erasmus University Medical Center, Rotterdam. [3]Dept of Gastroenterology and Hepatology, Franciscus Gasthuis & Vlietland, Rotterdam. [4]Dept of Surgery, Medical Spectrum Twente and Experimental Center of Technical Medicine, Faculty Science and Technology, University Twente, Enschede. [5]Dept of Vascular Surgery, Erasmus University Medical Center, Rotterdam. [6]Dept of Gastroenterology and Hepatology, Medical Spectrum Twente, Enschede. [7]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands

14.30 Sustained Symptom Relief after Revascularization of Single Mesenteric Artery Stenosis in Patients with Chronic Mesenteric Ischemia (p.188)

L.J.D. van Dijk[1,2], L.M.G. Moons[3], D. van Noord[1,4], A. Moelker[2], H.J.M. Verhagen[5], M.J. Bruno[1], E.V. Rouwet[5]. [1]Dept of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam. [2]Dept of Radiology, Erasmus University Medical Center, Rotterdam. [3]Dept of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht. [4]Dept of Gastroenterology and Hepatology, Franciscus Gasthuis & Vlietland, Rotterdam. [5]Dept of Vascular Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands

14.40 Capsule endoscopy over the years in a large tertiary center cohort: the diagnostic yield in patients with obscure gastrointestinal bleeding (p.189)

M.L. Zuidhof[1], H. Beaumont[1], S.T. van Turenhout[1], M.A.J.M. Jacobs[1], C.J.J. Mulder[1]. [1]Dept of Gastroenterology and Hepatology, VU University Medical Center, Amsterdam, The Netherlands

14.50 Work ability in rectal cancer patients during the first year of treatment (p.190)

A.M. Couwenberg[1], M.P.W. Intven[1], J.P.M. Burbach[2], L. Hupkens[3], W.M.U. van Grevenstein[4], H.M. Verkooijen[5]. [1]Dept of Radiation-Oncology, University Medical Center Utrecht, Utrecht. [2]Dept of Surgery, Meander Medical Center, Amersfoort. [3]Blik op werk, Quality and research institute on workability, Utrecht. [4]Dept of Surgery, University Medical Center Utrecht, Utrecht. [5]Imaging Division, University Medical Center Utrecht, Utrecht, The Netherlands

15.00 Association of Chromosomal Instability, Microsatellite Instability and CpG Island Methylator Phenotype with Postcolonoscopy Colorectal Cancer in a retrospective cohort study (p.191)

R.M.M. Bogie[1], C.M.C. le Clercq[1], Q.J.M. Voorham[3], M. Cordes[2], D. Si[2], E. van den Broek[3], S.D.J. de Vries[2], N.C.T. van Grieken[2], R.G. Riedl[4], M. van Engeland[4], B. Ylstra[2], G.A. Meijer[3], A.A.M. Masclee[1], B. Carvalho[3], S. Sanduleanu[1]. [1]Division of Gastroenterology and Hepatology, Dept of Internal Medicine, Maastricht University Medical Center, GROW-School for Oncology and Developmental Biology. [2]Dept of Pathology, VU Medical Center Amsterdam. [3]Dept of Pathology The Netherlands Cancer Institute, Amsterdam. [4]Dept of Pathology, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, The Netherlands

15.10 Symptomatic patients participating in colorectal cancer screening: cancer risk and tumor location (p.192)

C.M. de Klerk[1], M. van der Vlugt[1], P.M. Bossuyt[2], E. Dekker[1]. [1]Dept of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam. [2]Dept of Clinical Epidemiology, Academic Medical Center, Amsterdam, The Netherlands

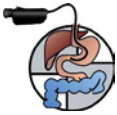
15.20 Vedolizumab prevents T-cell re-entry to intestinal and skin graft and ameliorates rejection: a case report (p.193)

G. Trentadue[1], T. Blokzijl[2], G. Kats-Ugurlu[3], G. Diercks[3], K.N. Faber[1], G. Dijkstra[1]. [1]Dept of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen. [2]Dept of Laboratory Medicine, Rijksuniversiteit Groningen, University Medical Center Groningen, Groningen. [3]Dept of Pathology, University Medical Center Groningen, Groningen, The Netherlands

15.30 Einde abstractsessie

Programma V&VN MDL **Brabantzaal**

Maag Darm Lever



Voorzitters: M.S.A. van Hout

09.30 Welkom

09.35 Diverse darmoperaties op een rij
Drs. W. van der Meij, chirurg fellow gastro-intestinale chirurgie Jeroen Bosch ziekenhuis, 's-Hertogenbosch

10.05 Herziende richtlijn: neus-maagsonde
Mw. M.E. Klos, voedingsverpleegkundige Gelre ziekenhuis, Apeldoorn

10.30 Interventionele Endoscopie
Mw. S.E. Smulders, verpleegkundig specialist i.o. interventionele endoscopie / MDL LUMC, Leiden

10.55 Koffiepauze

Programma V&VN MDL **Brabantzaal**

Voorzitters: T.A. Korpershoek

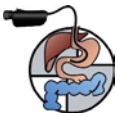
11.25 Bekkenfysiotherapie bij PDS en obstipatie
Mw. F.M.J. Voets – van de Koevering, fysiotherapeut Jeroen Bosch ziekenhuis, 's-Hertogenbosch

11.50 PDS: Diagnose, (nieuwe) behandelopties en de rol van de verpleegkundige
Mw. S. Luijten, verpleegkundig specialist MDL Amphia ziekenhuis, Breda

12.10 Algemene ledenvergadering V&VN MDL
Mw. T.A. Korpershoek, voorzitter V&VN MDL

12.50 Lunchpauze in expositiehal

Programma V&VN MDL **Brabantzaal**



Voorzitters: R.C. van Rhee-Martha en M.S.A. van Hout

14.00 Welkom

14.05 Endoscopische full thickness resectie
Drs. B.A. Bastiaansen, MDL-arts AMC, Amsterdam

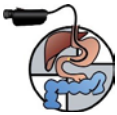
14.30 Zenker divertikel
Dr. W.R. ten Hove, MDL-arts Alrijne Ziekenhuis, Leiden

14.55 Endoscopische behandeling van overgewicht en Diabetes Mellitus type 2
Drs. P. Koehestanie, aios MDL Jeroen Bosch ziekenhuis, 's-Hertogenbosch

15.20 Propofol op de endoscopie kamer
Prof. dr. B. Preckel, anesthesioloog AMC, Amsterdam

15.40 Afronding

Programma verpleegkundig endoscopisten **Zaal 52**



Voorzitters: J. Oosterling

14.00 Welkom

14.05 Microscopische colitis
Dr. M.E. Tushuizen, MDL-arts ziekenhuis Amstelland, Amstelveen

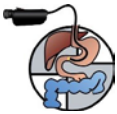
14.30 Familiare belasting
Dr. B.W.M. Spanier, MDL-arts Rijnstate ziekenhuis, Arnhem

Vrijdag 24 maart 2017

15.00 Het colocare proces van begin tot eind
Mw. M. van Berkom, casemanager Coloncare Elkerliek ziekenhuis, Helmond

15.25 Afronding

Programma IBD en leververpleegkundigen **Zaal 83**



Voorzitters: M. Bijmolen en P.C.W.M. Hurkmans

14.00 Welkom

14.05 NAFLD (non-alcoholic fatty liver disease), een toenemend probleem
Dr. G.H. Koek, MDL-arts MUMC, Maastricht

14.30 NAFLD: noodzaak tot leefstijlaanpassingen
Mw. I.L. Saro, verpleegkundig consulent levertransplantatie en leefstijlcoach UMCG, Groningen

14.50 Ustekinumab: nieuwe medicatie bij M. Crohn
Dr. M.J.L. Romberg-Camps, MDL-arts Zuyderland MC, Sittard-Geleen
Mw. L. Duijsens, verpleegkundig specialist Zuyderland MC, Sittard-Geleen

15.20 Klinische trials, wat levert het op voor de patiëntenzorg
Mw. A.F. Engelsman, research verpleegkundige UMCG, Groningen

15.40 Afronding

Incidence of malignant progression in persistent nondysplastic Barrett's esophagus, a Dutch nationwide cohort study

Y. Peters[1], J. Honing[1], W. Kievit[2], I.D. Nagtegaal[3], P.D. Siersema[1]. [1]Dept of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen. [2]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen. [3]Dept of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands

The risk of esophageal adenocarcinoma (EAC) in patients with non-dysplastic Barrett's esophagus (NDBE) may have been overestimated in some studies. Lower progression rates could lead to alteration of the current surveillance strategy, reducing its associated risks and costs. The aim of this study was to evaluate whether persistence of NDBE over consecutive surveillance endoscopies identifies patients at a very low risk for malignant progression. In this population-based retrospective study, patients with a first diagnosis of NDBE between 2003 and 2012 were selected using PALGA, a nationwide registry of histopathology diagnoses in the Netherlands. Patients were followed until the development of EAC or high-grade dysplasia (HGD), or until the last endoscopy contact with biopsy sampling (through May 2016). Persistent NDBE was defined as NDBE at the index and the first follow-up endoscopy with at least one year of follow-up after the first surveillance endoscopy. In this study 12,731 patients with NDBE were included, with a total follow-up of 64,898 (median 4.4 (IQR 3.0 – 6.8)) years. Median duration until first follow-up endoscopy was 2.2 years (IQR 1.5 – 3.2). During the study period, malignant progression was seen in 437 patients (3.4%), after a median follow-up of 5.1 years (IQR 3.2 – 7.3). This resulted in a progression rate to EAC of 0.47 (95% CI: 0.42 – 0.53) per 100 person-years and a progression rate to HGD/EAC combined of 0.68 (95% CI: 0.62 – 0.74) per 100 person-years. In the total study cohort, 11,854 patients (93%) were not found to have developed dysplasia at first follow-up endoscopy, whereas 675 (5.3%) and 202 (1.6%) patients showed progression to low-grade dysplasia and HGD/EAC, respectively. In patients with two consecutive endoscopies showing NDBE progression rates to EAC alone and HGD/EAC combined were 0.26 (95% CI: 0.22 – 0.32) and 0.40 (95% CI: 0.35 – 0.47) per 100 person-years, respectively. Patients with five or more consecutive non-progressive endoscopies had a 75% relative risk reduction for development of EAC (progression rate: 0.13 (95% CI: 0.11- 0.41) per 100 person-years).
Conclusions: persistent NDBE at two consecutive surveillance endoscopies reduces the risk of malignant progression towards EAC by almost twofold (0.47 to 0.26 per 100 person-years), which suggests that prolonging the surveillance intervals in patients with persistent NDBE could be considered. As progression risk reduces even further after more consecutive negative follow-up endoscopies, future studies should aim to establish the group of patients in whom surveillance could safely be discontinued.

Laparoscopic ileocecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: THe LIR!C trial

E.J. de Groof[1,2], W.A. Bemelman[2], E.J. Eshuis[1], T.J. Gardenbroek[2], P.M.M. Bossuyt[3], B.A. van Wagensveld[5], M.A. Brink[6], E.C.J. Consten[7], C.J. Buskens[2], G.R.A.M. D'Haens[1], P.C.F. Stokkers[4], C.Y. Ponsioen[1] on behalf of the LIR!C study group. [1]Dept of Gastroenterology & Hepatology, [2]Surgery, and [3]Epidemiology, Academic Medical Center, Amsterdam. [4]Dept of Gastroenterology & Hepatology and [5]Surgery, OLVG West, Amsterdam. [6]Dept of Gastroenterology & Hepatology and [7]Surgery, Meander Medical Center, Amersfoort, The Netherlands

Objective: The optimal therapeutic approach to ileocecal Crohn's disease (CD) is unclear. Aim of this study was to compare infliximab with laparoscopic ileocecal resection in patients with thiopurine/steroid refractory recurrent terminal ileitis, with respect to quality of life (QoL) and costs. Methods: A multiCenter randomized controlled trial was performed in 28 Centers in The Netherlands and the UK. Adult patients with CD of the terminal ileum who failed >3 months of thiopurine or steroids without signs of critical stricture were randomized to infliximab or laparoscopic ileocolic resection. Patients with a prior ileocecal resection, diseased length >40 cm, abdominal abscesses or fluid collections or an American Society of Anaesthesiologists (ASA) score of III/IV were excluded. Primary endpoint was QoL measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) at 1 year. Actual resource use per individual was prospectively documented and analysed according to intention-to-treat until 1 year. Dutch Trial Registry NTR1150. Results: Between May 2008 and October 2015, 143 patients were randomized (32.9% male) with a median age of 27 years (interquartile range (IQR) 22-40). Eventually, 65 patients started with infliximab and 70 patients were operated. At baseline, mean difference (MD) in IBDQ score was 4.9 in favour of the resection group. The MD at 1 year was 5.8 points in favour of resection (95% confidence interval (CI) -4.7 to 16.3, p=0.28). Mean direct total costs per patient at 1 year were €19,655 in the infliximab and €10,318 in the resection group (MD €-8,931; 95%CI € -12,087 to € -5,097). A significant difference in favor of the resection group in QoL was observed with the SF36 general health questionnaire, on the physical (MD 3.2, p=0.035) and the mental subscale (MD 4.1, p=0.036). Infliximab was stopped in 21 patients (30%) due to intolerance or insufficient response, 13 of whom underwent an ileocecal resection after a median time of 27 weeks (IQR 11-34). IBD related serious adverse events in terms of Clavien Dindo IIIb complications occurred in 3 patients (4%) in the laparoscopic ileocecal resection group and in 1 patient allocated to infliximab eventually going for surgery. In the resection group 3 patients (4%) were started on infliximab within 1 year. Readmissions (for flares or additional surgery/dilatation) during follow-up were comparable (21% in infliximab versus 18% in the resection group). Conclusions: Although IBDQ at 1 year was not significantly better, laparoscopic ileocecal resection can be considered an acceptable alternative for infliximab. Surgery improved general quality of life and was associated with a reduction in costs.

A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: the CRITICS study

R.M. van Amelsfoort, A. Cats, E.P.M. Jansen, N.C.T. van Grieken, N.K. Aaronson, H. Boot, P.A. Lind, E. Meershoek – Klein Kranenbarg, J.P.B.M. Braak, M. Nordsmark, H. Putter, A.K. Trip, J.W. van Sandick, K. Sikorska, I. Walraven, M.C. Hulshof, H.W. van Laarhoven, M.I. van Berge Henegouwen, H. van Tinteren, C.J.H. van de Velde, M. Verheij, on behalf of all CRITICS investigators. Cancer Institute/Antoni van Leeuwenhoek, Free University Medical Center, Leiden University Medical Center, Academic Medical Center, Karolinska University Hospital, Arhus University Hospital, The Netherlands

A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: the CRITICS study. The mainstay of potentially curative treatment of gastric cancer is radical surgical resection. Because most patients in the Western world present with advanced stage disease, long-term survival remains poor with a five-year survival rate of around 25%. Postoperative chemoradiotherapy (CRT) and perioperative chemotherapy (CT) have demonstrated a survival benefit over surgery alone. In the randomized phase III CRITICS-study (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach), it was investigated whether chemoradiotherapy after neoadjuvant chemotherapy and adequate (D2) surgery would improve overall survival (OS) in comparison with post-operative chemotherapy. Furthermore, toxicity of both treatment regimens was explored. Patients with stage Ib-IVa resectable gastric cancer were randomized after diagnosis. Neoadjuvant CT was prescribed in both arms and consisted of 3 courses of epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC). After gastric cancer resection, patients received another 3 courses of ECC/EOC or CRT (45 Gy in 25 fractions combined with weekly cisplatin and daily capecitabine). Primary endpoint was OS; secondary endpoints were event free survival, toxicity and quality of life. Between January 2007 and April 2015, 788 patients from The Netherlands, Sweden and Denmark were randomized (393 CT; 395 CRT). Base characteristics were well balanced between the two groups. Two-third of all patients were male and the median age was 62 years. 85% of the patients in the CT arm and 81% in the CRT arm received three cycles of chemotherapy before surgery. 47% of the patients in the CT arm and 54% in the CRT arm completed treatment according to protocol. After a median follow-up of 4.4 years, 418 patients died. OS did not show a statistically significant difference. Five year OS rates were 41% for the CT arm and 40% for the CRT arm. Toxicity was comparable after CT and CRT. Only neutropenia was significantly higher in the CT arm (34% vs 5% $p<0.001$). Conclusion: After neoadjuvant chemotherapy and surgery, no significant difference in overall survival was found between postoperative chemotherapy and postoperative chemoradiotherapy in patients with resectable gastric cancer.

T-Cell activation and signalling in Crohn's disease: from risk genes to molecular networks (MLDS-voordracht)

R. Weersma, Dept of Gastroenterology, UMC Groningen, The Netherlands

Background: CD is a chronic relapsing intestinal inflammatory disease resulting from a combination of genetic and environmental factors. A meta-analysis of genome wide association scans identified 231 genetic variants that each confer a small risk inflammatory bowel disease. Together they explain approximately 28% of the heritability. It is evident that risk genes can be grouped into functional classes: e.g. a set of risk genes implies a causal role for T-cell signalling and activation while other genes sets are involved in innate immune responses or mucosal barrier integrity. The challenge is to move from these genetic variants to the identification of disease mechanisms that can ultimately help improve diagnostics and treatment.
Objective: To define the molecular networks involved in the pathogenesis of Crohn's disease (CD) and analyze how these networks are influenced by genetic risk factors.
Results: we first investigated the functional consequences of risk SNPs for the Th17/IL23 pathway that is implicated in the pathogenesis of IBD . The Th17/IL23 pathway acts in Th17 cells, which are thought to play a role in chronic inflammatory processes. Next to the genetic associations, functional studies had also highlighted the role of the Th17/IL23 pathway in IBD. We generated expression data of both stimulated and unstimulated peripheral blood mononuclear cells from 40 healthy individuals, 40 CD and 40 UC patients for whom genome wide genotyping data was available. We then looked for a correlation between different risk profiles and gene-expression in the Th17/IL23 pathway. In addition 1,240 control individuals with whole-genome genotype and mRNA-expression data, were also assessed the correlation between genetic risk load and differential mRNA-expression and looked for *cis*-eQTL SNPs for all the currently known Th17/IL23 genes. Surprisingly and in contrast to our general hypothesis, we found little evidence for such genetic-gene-expression correlations in our dataset. In the next part we performed an extensive pathway analysis by protein-protein interaction (PPI) and co-transcriptional analysis, using both publically available and newly developed databases. In this part we focused on the complex IBD phenotype including its complications and extraintestinal manifestations. Hereby showing that the pathogenetic overlap between IBD and its EIM or complications extends beyond shared risk genes to distinctive shared biological pathways. We then used the genetic and protein-protein interaction information to determine potential drug targets for IBD treatment. First we confirm that proteins encoded by IBD candidate genes are targeted by approved therapies for IBD. Secondly, FDA approved drugs can possibly be repositioned for the treatment of IBD. Thirdly, investigational drugs could be further developed for the treatment of IBD. These findings could lead to improved IBD treatment at relatively low cost and low effort by using already existing drugs. Finally we used the information to prioritize genes for targeted re-sequencing to identify rare genetic variants that may have a deleterious impact on gene function. Pooled Resequencing of 122 Ulcerative Colitis Genes in a Large Dutch Population Suggests Population Specific Association of Rare Variants in *MUC2*.
Conclusion: Integrative analyses of genomic, network and transcriptomic information helped to identify novel causal genetic variants, shared pathogenetic pathways between IBD and EIM and potential drug targets for IBD treatment.

Unchanged Infliximab Serum Concentrations after Switching from the Reference Infliximab to the Biosimilar CT-P13 in Patients with Quiescent Crohn's Disease: a Prospective Study

A.S. Strik[1], W. van de Vrie[2], Y.J.B. van Megen[3], J.P.J. Bloemsaat-Minekus[3], T. Rispens[4], G.R. D'Haens[1]. [1]Dept of Gastroenterology, Academic Medical Center Amsterdam. [2]Dept of Gastroenterology, Albert Schweitzer Ziekenhuis, Dordrecht. [3]Mundipharma Pharmaceuticals BV, Leusden. [4]Sanquin Research, Sanquin Laboratory, Amsterdam, the Netherlands

The biosimilar infliximab (IFX) can reduce healthcare costs when patients are switched from the reference to the biosimilar IFX; however this switch has raised concerns about potential immunogenicity. The objective of the SECURE study was to demonstrate that the IFX serum concentrations of the biosimilar IFX were non-inferior to the IFX concentrations of the reference IFX 16 weeks after switch in subjects with rheumatoid arthritis, ulcerative colitis and Crohn's disease (CD) in stable remission for > 30 weeks. This abstract presents the preliminary results of CD patients only. In this prospective, open-label, interventional, non-inferiority, multicentre, phase IV trial, adult CD patients in clinical remission >30 weeks (Harvey Bradshaw Index; HBI ≤ 4) were switched from the reference IFX to biosimilar IFX at stable doses. Patients were followed for 16 weeks after switch (2 infusions at 8 week interval). The primary endpoint was the serum IFX trough level concentration measured by a bridging enzyme-linked immunosorbent assay (ELISA) 16 weeks after switch (non-inferiority margin of 15%). Secondary endpoints included antibodies to IFX (ATI), clinical disease activity (HBI score), C-reactive protein (CRP), fecal calprotectin and quality of life (EQ-5D score) 16 weeks after switch compared to reference IFX. In total 61 CD patients were enrolled in 9 centers and 44 patients were included in the per protocol analysis (PP); 17 patients were excluded due to violation of eligibility criteria (4), not compliant with the study protocol (5), early termination of the study (3) and missing IFX serum samples (5). Mean age of the patients was 42±16 years (50% male) and mean duration on IFX treatment 4.9±3.8 years. The LS mean serum IFX concentration (90% CI) was 2.97 (2.78-3.18) for the reference IFX and 3.25 (3.04-3.48) 16 weeks after switch, with an IFX ratio of 109.6% (99.7%-120.6%) demonstrating non-inferiority of the biosimilar IFX to the reference IFX. One patient developed ATI's after 2 infusions. At the end of the study 38 (86%) patients were still in remission (HBI ≤ 4). The CRP, fecal calprotectin and EQ-5D were not significantly different for the biosimilar at week 16 compared to the reference IFX. In the enrolled population (61 patients) 2 SAEs (3.2%) were reported (both perianal abscess). The adverse event profile was not changed compared to the reference IFX. This prospective, interventional study demonstrated that the IFX serum concentration of the biosimilar IFX was non-inferior to the IFX concentration of the reference 16 weeks after switching in patients with CD. Efficacy and tolerability were also similar.

- Daklinza in combinatie met sofosbuvir, inzetbaar bij volwassen patiënten met chronische hepatitis C*[3,4]
- Ook voor patiënten met HIV/HCV co-infectie, cirrose, pre- en post-lever-transplantatie[2,3,5]

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*Conform richtlijnen en product SmPC's.[3,4,5] Productinformatie zie elders in dit blad. 1392NL16PR10817

Optimal anti-TNF stop week during pregnancy depends on anti-TNF type

S.L. Kanis, A. de Lima and C.J. van der Woude. Dept of Gastroenterology and Hepatology of the Erasmus University Medical Center, Rotterdam, The Netherlands

The ECCO pregnancy guide provides recommendations regarding anti-TNF treatment during pregnancy that apply to all anti-TNF types. However, in our prospective cohort we found that women using adalimumab (ADA) had lower anti-TNF drug levels in cord blood compared to women using infliximab (IFX). We aimed to develop a stopping model for women using anti-TNF during pregnancy that can be used in clinical practice. Women with IBD were prospectively enrolled at our preconception outpatient clinic from Dec '08 until Jul '16 and were counseled according to the ECCO pregnancy guideline. During bimonthly visits, information on disease activity, medication use, weight gain and complications were recorded. If patients were in remission 6 months before conception until gestational week 20; anti-TNF treatment was stopped at week 22-24. At birth, anti-TNF was measured in cord blood and considered of low risk for the newborn when below 3µg/mL. A multiple linear regression was performed to determine independent predictors of the anti-TNF level in cord blood. In addition, a linear model was developed to predict anti-TNF cord blood drug level at birth. In total, 320 live births were documented of which 131 were exposed in utero to anti-TNF(73 IFX/58 ADA) born to 103 women (84(82%)CD,18(17%)UC,1(1%)IBDU). Concomitant treatment with thiopurines was more often used with IFX (n=29;40%) than with ADA (n=5;9%)(p=0.0001). Median anti-TNF stop week was the same for IFX and ADA: respectively 23.0(IQR21.0-31.5) and 23.0(IQR22.0-37.0)(p=0.56)).There was a trend towards more relapses during pregnancy in the ADA, furthermore, remission was less often regained before delivery in the ADA group compared to the IFX group, however, both differences were not statistically significant. There were 94 cord blood samples obtained(52IFX,42ADA). Median anti-TNF cord blood was significantly higher in IFX users (4.9µg/mL(IQR 1.9-14.7)) than ADA users (1.1µg/mL(IQR0.4-37.0))(p=0.0001). Also the median maternal anti-TNF was higher in IFX users(1.7µg/mL(IQR0.4-6.9)) than ADA users(0.6 µg/mL(IQR0.3-3.6)(p=0.05). The multiple linear regression model demonstrated that 2 variables had a significant influence on anti-TNF cord blood level, namely: type of anti-TNF and gestational anti-TNF stop week. In the final model, the optimal time to stop anti-TNF, defined as gestational anti-TNF stop week leading to a cord blood level of 3 µg/mL, was 24,6 weeks for IFX and 36,8 weeks for ADA.
In conclusion, these results suggest that the continuation of ADA up till the first half of the 3th trimester does not lead to high anti-TNF cord blood levels.

Switching from Remicade® to biosimilar CT-P13 in inflammatory bowel disease: One year follow-up of a prospective observational cohort study

L.J.T. Smits[1], A. Grelack[1], J.P.H. Drenth[1], D.J. de Jong[1], R.S. Boshuizen[2], A.A.J. van Esch[1], L.A.A.P. Derikx[1], F. Hoentjen[1]. [1]Inflammatory Bowel Disease Center, Dept of Gastroenterology and Hepatology, Radboud university medical center, Nijmegen. [2]Biologics Laboratory, Sanquin Diagnostic Services, Amsterdam, The Netherlands

The infliximab biosimilar CT-P13 is EMA and FDA approved, based on data extrapolated from phase III studies in rheumatoid arthritis and ankylosing spondylitis patients. Anti-tumor necrosis factor (TNF) naive IBD patients frequently start CT-P13 in current daily practice but the switch from Remicade® to CT-P13 is less common due to limited data on long-term clinical outcomes. Therefore, we aimed to prospectively investigate long-term efficacy, safety, pharmacokinetic profile and immunogenicity following an elective switch from Remicade® to CT-P13 in IBD patients. We performed a single-center prospective observational cohort study. All Remicade®-treated IBD patients were actively switched to CT-P13 regardless of disease activity. Primary endpoint was change in disease activity scores at week 52 compared to week 0 as measured by Harvey-Bradshaw Index (HBI) for Crohn's disease (CD) and Simple Clinical Colitis Activity Index (SCCAI) for ulcerative colitis (UC) and IBD unclassified (IBD-U). C-reactive protein (CRP), fecal calprotectin (FCP), infliximab trough levels and antidrug antibodies to infliximab (ADA) were measured at week 0, 16 and 52. Adverse events and reasons for discontinuation were documented during follow-up. Eighty-three patients were included, 57 CD, 24 UC, 2 IBD-U (28 male, median age 36, range 18-79) and 68 patients completed 1-year follow-up. Median change in disease activity was 0 (HBI, range -9 to +15, n=49) for CD and 0 (SCCAI, range -4 to +4, n=19) for UC/IBD-U. FCP and CRP levels did not significantly change during follow-up. CT-P13 dosing was adjusted in 20/68 (29%) of the patients and the proportion of trough levels within the therapeutic range (3.0-7.0 ng/ml) was 40% at base and 48% at week 52. In total 7 patients demonstrated detectable ADA during follow-up, 5/7 ADA titers were already detectable at baseline. Fifteen out of 83 patients (18%) discontinued CT-P13 during follow-up for reasons of clinical remission (n=2), loss of response (n=5) including 3/5 demonstrating detectable ADA, arthralgia (n=4), skin rash and itching (n=2) and migration to another hospital (n=2).
Conclusions: Eighty-two percent of the patients continued CT-P13 through 52 weeks after switching from Remicade®. Disease activity scores and inflammatory markers remained unchanged during follow-up and no CT-P13-related serious adverse events occurred. These 1-year data suggest that switching to CT-P13 in Remicade®-treated IBD patients is feasible.

Relapse risk and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-tnf therapy

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We aimed to investigate the incidence of relapse after anti-TNF withdrawal in a real-life cohort of Crohn's disease (CD) and ulcerative colitis (UC) patients in sustained clinical remission, to identify predictors for relapse and to assess the response to restart of anti-TNF retreatment. CD and UC patients in clinical remission receiving infliximab (IFX) or adalimumab (ADA) treatment for ≥ 1 year and discontinued treatment were included. Clinical relapse was defined as recurrence of symptoms and the need to (re)start anti-TNF therapy , immunomodulators and/or corticosteroids. Relapse risk and predictors for relapse were studied using cox proportional hazard analysis. In total, 92 patients discontinued anti-TNF treatment (69 CD, 23 UC). Median duration of anti- TNF therapy at the time of withdrawal was 53 months (IQR 24-87) and the median duration of follow-up was 13 months (IQR 8-16). IFX and ADA were discontinued in 52 (57%) and 40 patients (43), respectively. So far, a total of 47 patients (51%) experienced relapse (CD 33, UC 14), with a median time to relapse of 7 and 4 months in CD and UC, respectively. Of patients that were retreated with the same anti-TNF agents, 83% showed a clinical response. A serum concentration at trough ≥ 2 µg/ml (irrespective of the anti-TNF agent) within one year prior to anti-TNF discontinuation was associated with a significantly higher relapse rate (HR 3.6, 95%CI 1.2-10.6). Continuation of immunomodulatory treatment was not associated with a lower relapse rate in both CD and UC patients (HR 0.8, 95%CI 0.4-1.6; HR 0.6, 95%CI 0.2-1.7). Endoscopic remission in the previous year, bowel-related surgery, prior anti-TNF use, perianal disease, disease location, disease duration, duration of anti-TNF therapy and disease location were not associated with higher or lower relapse rates. Factors such as CRP and faecal calprotectin as predictors for relapse were not addressed, since they were within the normal range in most patients at the time of cessation of anti-TNF therapy.

Conclusions: Approximately 50% of patients in remission under anti-TNF treatment relapsed after anti-TNF withdrawal with a median time to relapse of 7 and 4 months in CD and UC, respectively. A trough level ≥ 2 µg/ml prior to discontinuation of IFX and ADA therapy was associated with an increased relapse risk. Continuation of immuno-modulatory treatment was not associated with a reduced relapse risk, which is in contrast to previous work. Retreatment with the same anti-TNF was successful in 83% of patients.

The therapeutic efficacy of anti-TNF requires Fc-gamma receptors and can be improved by antibody hypo-fucosylation

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Background Treatment with the IgG1 anti-TNF antibodies infliximab and adalimumab achieves complete mucosal healing in a considerable proportion of patients with Crohn's disease. In contrast, the Fab' fragment certolizumab showed only 4% endoscopic remission. These observations suggest that the Fc-region of anti-TNF contributes to the induction of mucosal healing. We have previously showed that anti-TNF induces CD206+ regulatory macrophages and that these macrophages were increased in the lamina propria of anti-TNF responders, but not in non-responders. Here, we investigate the importance of Fc-gamma receptor (FcgR) engagement by anti-TNF for achieving therapeutic efficacy in IBD.

Methods Rag1-/- mice lacking all activating FcgR were generated. We constructed hypo-fucosylated anti-murine TNF and hypo-fucosylated adalimumab. In vivo studies were performed in the T-cell transfer colitis model. For in vitro studies, T-cell proliferation and CD206+ macrophage percentages were measured in mixed lymphocyte reactions containing human PBMC from healthy donors.

Results Anti-TNF treatment achieved near complete intestinal healing in the T-cell transfer model. However, mice lacking FcgR were completely unresponsive to anti-TNF therapy. In with our previous human data, colons of mice treated with anti-TNF contained increased amounts of CD206+ macrophages, but this effect was completely abrogated in animals mice lacking FcgR. In vitro studies revealed that blocking FcgR III impaired the generation of human CD206+ macrophages. Further emphasizing the role of FcgRIII, CD206+ macrophage formation was increased in cultures composed of cells homozygous for high affinity FcgRIIIa158V compared to low affinity FcγRIIIa158F. Interestingly, hypo-fucosylation of the antibody Fc region enhances binding affinity specifically for FcgRIIIa. Indeed, hypo-fucosylation of anti-TNF increased the amount of CD206+ macrophages in vitro, especially for cells expressing low affinity FcgRIIIa158F. Finally, hypo-fucosylated anti-TNF increased the generation of CD206+ macrophages in the colon and displayed significantly improved therapeutic efficacy in vivo.

Conclusion FcgR engagement by anti-TNF is required for the therapeutic efficacy in IBD. Increasing the Fc binding affinity of anti-TNF with hypo-fucosylation significantly improved therapeutic outcome. Anti-TNF therapy currently achieves mucosal healing in less than 50% of patients, antibody glycoengineering could be an effective future strategy and might be of special interest for patients carrying the low affinity FcgRIIIa158F allotype.

Vedolizumab induces significantly higher endoscopic remission rates at week 16 in ulcerative colitis as compared to Crohn's disease

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Vedolizumab (VDZ) is approved for treatment of Crohn's disease (CD) and ulcerative colitis (UC). Reports on clinical response and remission in registration trials and real world cohorts have shown efficacy, however data on endoscopic response are limited. In this study, we assessed endoscopic response and remission at week 16 and 52. Adult patients with CD, UC and IBD unclassified (IBDU) who started VDZ between Oct. '14 and July '16 were prospectively included. Endoscopic disease activity was assessed at baseline, week 16 and week 52 using the simple endoscopic score (SES) in CD, Rutgeerts score for postoperative CD and MAYO score in UC and IBDU. Endoscopic scoring was randomly performed and blinded for patient characteristics and time points. Endoscopic response was defined as SES-CD reduction ≥50%, Rutgeerts reduction of ≥1 and MAYO score reduction of ≥1. Endoscopic remission was defined as SES-CD <4 or Rutgeerts score ≤1 for CD patients and MAYO score ≤1 for IBDU and UC patients. Generalized multivariate analysis were performed to identify predictors of endoscopic response and remission at week 16. In total, 58 (M24/F34) patients with median age of 39 years (IQR 29-47) were started on VDZ after a median disease duration of 11 years (IQR 6-16). The study population included 39 CD, 15 UC and 4 IBDU patients (included in the UC group for analysis). In total 57/58 (98%) patients received previous anti-TNF therapy. The start of VDZ was combined with induction therapy in 44/58 (79%) patients. Endoscopic response was achieved in 15/39 (40%) of CD and 10/19 (53%) of UC patients at week 16 (p=0.34). Endoscopic remission at week 16 was achieved in respectively 7/38 (18%) and 8/19 (42%) (p=0.05). At week 16, a significant decrease in mean SES-CD of 5 points was observed (p=0.01), 1 point decrease in Rutgeerts score(p=0.02) and similarly a mean MAYO score decrease of 1 point was observed(p=0.01). After clinical and endoscopic evaluation at 16 weeks, 32/58 (55%) patients continued VDZ. Endoscopic response at week 52 was achieved in 6/16 (38%) CD and 3/6(50%) UC patients(p=0.59). Endoscopic remission at week 52 was achieved in resp. 1/17 (6%) and 3/6 (50%)(p=0.01). In multivariate analysis, IBD phenotype of CD patients with perianal disease was associated with a decreased likelihood of endoscopic response at week 16 (p=0.03), whereas demographics, disease duration, smoking status, previous surgery and medication use were not.

Concluding, VDZ treatment induces endoscopic response at week 16 in 40% and endoscopic remission in 26% of IBD patients with anti-TNF refractory disease. In UC, endoscopic remission at week 16 is significantly higher as compared to CD.

Serological biomarkers of tissue turnover can early identify responders to infliximab in Crohn's disease

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Anti-TNFα agents such as Infliximab (IFX) are effective in inducing and maintaining remission in Crohn's Disease (CD). However, approximately 40% do not reach clinical remission and there are no serological biomarkers available that can predict adequate response. Inadequate response to IFX has been associated with increased submucosal fibrosis. Therefore, we investigated if serological collagen formation and degradation markers could predict for response to IFX. Markers for matrix metalloproteinase degraded collagens III and IV (C3M, C4M) and formation of collagens III, IV and V (Pro-C3, P4NP, Pro-C5) were measured using competitive ELISAs in serum from 60 CD patients with active disease, drawn before starting 5mg/kg IFX (week 0), and after 2, 6 and 14 weeks. Clinical disease activity was classified by physician's global assessment (PGA, 0: disease in remission, 1: mild disease, 2: moderate disease, 3: severe disease) and the Harvey Bradshaw Index (HBI). Clinical response was defined as a reduction of >1 in PGA and thereby induction of remission according to PGA and HBI during follow-up due to IFX. Clinical non-response was defined as <2 PGA decrease and IFX failing to induce clinical remission (in PGA and HBI) during follow-up. Patients with clinical response, who stopped IFX due to pregnancy or side effects, were defined as responder. Sixty patients started IFX after median disease duration of 9.3 years. Forty-four (73%) patients responded, whereas 16 (27%) patients did not respond (median follow-up 3.9 years). None of these patients had primary non-response before week 14. Levels of P4NP and C3M were lower after 2, 6 and 14 weeks in responders C4M (p: 0.012) levels were higher in non-responders after 14 weeks. Pro-C3 levels increased in responders after week 2 and 6 (p: 0.010, 0.002 respectively) whether non-responder levels remained stable. P4NP levels at week 2 were able to predict responders (AUC: 0.715). C3M, P4NP and Pro-C5 levels at week 14 were also able to predict responders (AUCs: 0.758, 0.827, 0.730 respectively).
Conclusions: Serological markers for collagen type IV formation (P4NP) and collagen type III degradation (C3M) can identify CD patients responding to IFX within the first 14 weeks of treatment. These markers could be used as early biomarkers for response to IFX and aid in early therapy decision-making.

Telemedicine enables a safe shift from examination room based care to personalised care for inflammatory bowel disease: a pragmatic randomised multicenter trial with my IBD coach

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Inflammatory bowel disease (IBD) is a group of chronic diseases with a heterogenic disease course and therapy response. Tight and personalised control of disease activity, with attention for all aspects influencing activity, is warranted to prevent long-term complications and improve quality of life (QoL). This is challenging given the increasing economic pressure on health systems, moreover since the incidence of IBD is increasing. We developed myIBDcoach: the first telemedicine system for IBD patients, regardless of phenotype, severity or treatment. We aimed to evaluate the effect of myIBDcoach on number of outpatient visits, patient-reported quality of care (PRQoC) and health outcomes in a pragmatic, randomised trial. From September 2014 to May 2015, all consecutive IBD outpatients in 2 academic and 2 non-academic hospitals in The Netherlands, aged 18 to 75 years, with internet-access and Dutch proficiency, were eligible for inclusion. Patients were randomised to use of myIBDcoach or standard care (1:1) and followed for 12 months. Patients using myIBDcoach were invited to visit the outpatient clinic at least once a year, or on demand. Data on outpatient visits, flares, corticosteroid use, hospitalisations, emergency visits and IBD-related surgery were collected from the electronic patient record and analysed using multivariate linear regression analysis. At base and 12 months, patients were requested to fill out a questionnaire including PRQoC, QoL (SIBDQ), adherence (MMAS-8) and self-efficacy (IBD-SES). Questionnaire data were analysed using linear mixed models. In total, 465 patients used myIBDcoach and 444 continued standard care. The mean number of outpatient visits during follow up was lower in the intervention group compared to the control group (1.55±1.50 and 2.34±1.64; p<0.001). After 12 months, both groups reported high scores on PRQoC on a VAS-scale, respectively 8.16±1.37 and 8.27±1.28 (p=0.411). The mean number of hospitalisations was lower in the intervention group compared to the control group (0.05±0.28 and 0.10±0.54; p<0.001). No differences were observed in flares, corticosteroid use, emergency visits or surgeries. Patients using myIBDcoach reported higher medication adherence rates (p<0.001), higher, but not significant, QoL (p=0.057) and similar self-efficacy scores (p=0.572). Conclusions: This pragmatic trial showed that telemedicine through myIBDcoach was safe, reduced outpatient visits and hospitalisations and improved medication adherence with equal PRQoC compared to standard care. MyIBDcoach monitors disease activity, patient reported outcomes and drug side-effects and may therefore be used to reorganise IBD-care enabling value based healthcare.

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Mucosal lymphocyte subsets in Ulcerative Colitis at diagnosis and during follow-up

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Background The initial immunologic processes that occur in the inflamed mucosa of patients with Ulcerative Colitis (UC) remain largely unclear. We aimed to investigate different mucosal lymphocyte subsets in patients at diagnosis and during follow-up to study the changes that might occur in different phases of disease activity. Methods A total of 35 newly diagnosed untreated adult UC patients and seven healthy controls (HC) were prospectively included. Colonic biopsy specimens of the inflamed areas were collected at diagnosis and, from the same colon segment, during follow-up. Flow cytometry was used to analyse lymphocyte subsets: T cells ($CD3^+$), CD4 ($CD3^+CD4^+$) and CD8 T cells ($CD3^+CD8^+$), regulatory T cells ($CD3^+CD4^+CD25^+Foxp^{3+}$), mucosal T cells ($CD3^+CD103^+$), naïve T cells ($T_N CD3^+CD27^+CD45RA^+$) central memory T cells (T_{CM} $CD3^+CD27^+CD45RA^-$) T cells re-expressing CD45RA (T_{EMRA} $CD3^+CD27^-CD45RA^+$) and effector memory T cells (T_{EM} $CD3^+CD27^-CD45RA^-$). Results Compared to HC, UC patients at diagnosis displayed higher percentages of $CD4^+$ (UC median 74% (interquartile range: 66-83) vs HC 40% (33-57)), T_{CM} (50% (39-58) vs 30% (21-36)) and lower percentages of $CD8^+$ (21% (16-29) vs 52% (33-55)), T_{EM} (21% (12-29) vs 52% (39-58)) and mucosal T cells (12% (6-18) vs 40 (32-60)) (all P values <0.05). Compared to diagnosis, an increase of mucosal T cells (36% (14-57)) and T_{EM} cells (56% (23-80)) was found in patients colon during remission at follow up (P<0.05). No differences compared to base percentages were observed in patients with an exacerbation at follow-up. UC patients in remission at follow-up had comparable lymphocyte subsets to HC (P values all >0.05), while patients with an exacerbation at follow-up had comparable findings to base and the same statistical significant differences in lymphocyte subsets were observed compared to HC.
Conclusions: Mucosal inflammation was associated with increased percentages of $CD4^+$ T cells and T_{CM} cells, and decreased percentages of $CD103^+$ T cells, $CD8^+$ T cells and T_{EM} cells. A trend towards normalization of the colonic T cell profile, with increase of $CD103^+$ and T_{EM} cells, is seen during remission; suggesting a positive role for these mucosal T cell subpopulations. These observations could question the efficacy of anti-CD103 treatment in UC patients. More research is needed to elucidate the pathological and regulatory effects of the different lymphocyte subsets, as well as their potential predictive role for response to therapy.

Therapeutic drug monitoring after thiopurine initiation improves drug efficacy

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Background: thiopurines are effective in the maintenance treatment of inflammatory bowel disease (IBD). However, 20-30% of IBD patients discontinue the thiopurine within 3 months after initiation due to adverse events or failure of therapy. Our aim was to evaluate the protocol of adjusting dose of Thiopurines, based on the level of metabolites (6-TGN and 6-MMP), on the percentage of patients continuing to use the drug. Method: This is a retrospective cohort study in adult IBD patients. Two groups of 50 patients were compared. Weight based dosage of mercaptopurine (1-1.5 mg/kg) in the control group (2012-2013) was compared to metabolite level based dosage of mercaptopurine in the therapeutic drug monitoring (TDM) intervention group (2015-2016). Primary outcome was the percentage of patients still using mercaptopurine 3 months after starting the drug. Secondary outcomes were the number of adverse events and the number of IBD patients with a corticosteroid-free clinical remission at 3 months. Results: Patients characteristics were similar in the two groups . The number of patients using a thiopurine after 3 months was 92% in the intervention group and 76% in the control group (p=0.029). Adverse events were reported in 46% of patients in the intervention group and in 66% of patients in the control group (p=0.044). Corticosteroid-free after 3 months were 70% of patients in the intervention group and 56% patients in the control group (p=0.147).
Conclusion: We conclude that therapeutic drug monitoring based dosage is superior to weight based dosage at the initiation of thiopurine therapy. 3 Months after starting treatment, in the therapeutic drug monitored group, more patients still use Thiopurines, less patients have adverse events and more patients are steroid free compared to weight based dosage group. Further evaluation is needed to study effect on long term remission of IBD.

MR Enterography in addition to ileocolonoscopy in newly diagnosed adults with Crohn's disease

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The value of Magnetic Resonance Enterography (MRE) in determining the extent and severity of Crohn's disease (CD) in addition to a complete ileocolonoscopy at the time of the primary diagnosis has been advocated in recent guidelines though not yet been studied. The aim of this study was to assess the additional value of MRE following initial diagnostic ileocolonoscopy in CD.Patients who underwent MRE within 3 months of primary ileocolonoscopy were retrospectively included in the analysis. Additional findings on MRE next to ileocolonoscopy were assessed including strictures, entero-enteral fistula, abscesses and extended small bowel disease activity. MRE findings were subsequently analyzed in different CD phenotypes.A total of 163 newly diagnosed CD patients were included in the analysis. MRE revealed additional findings in 28% (45/163) of all patients. Prevalence of additional MRE findings was 67% (21/32) in those cases in which ileum could not be intubated, compared to 18% (24/131) in patients with a complete ileocolonoscopy. In patients without ileitis at ileocolonoscopy no additional lesions were seen on MRE. Strictures, entero-enteral fistula and abscesses were mostly observed during MRE examination in patients with severely active ileitis at endoscopy.Prevalence of MRE findings next to ileocolonoscopy in newly diagnosed CD patients is high in endoscopically assessed stricturing disease and severe disease activity of the terminal ileum, corroborating the use of standard diagnostic MRE in these clinical circumstances.

The microbiome of inflammatory bowel disease and irritable bowel syndrome–a case-control study of 1792 individuals

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Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are two of the most common gastrointestinal (GI) disorders. Microbes play an essential role in maintaining a healthy gut. A large dysbiosis in the gut flora has been described in patients with IBD using the ribosomal 16S gene as a marker. However, this approach is not sufficient to understand the complexity of the gut microbial community. By using microbial whole-genomes sequencing, higher taxonomical resolution can be reached and microbial functional pathways can be inferred. Here, we present the largest gut microbiome case-control analysis in both IBD and IBS to date, using microbial whole-genome shotgun sequencing of stool samples from 1792 individuals. Taxonomy was determined for bacteria, viruses and micro-eukaryote. Bacterial gene families and pathways were determined using HUMAnN2. In addition, bacterial strain diversity and growth rates were inferred from the sequencing data. Furthermore, 213 phenotypes of patients with IBD, 222 phenotypes of patients with IBS, and 88 phenotypes of healthy controls (HC) were collected. Variance explained by each of these phenotypes on the overall microbiome composition was analyzed using a MANOVA-analysis. Associations between individual taxa and phenotypes were analyzed using the multivariate statistical framework MaAsLin. In the case-control analyses, and correcting for 25 previously identified microbiome-modifying factors, we observed 157 differentially abundant species associated with CD, 87 species associated with UC and 125 species associated with IBS. Intriguingly, the top 10 most strongly associated species, including Faecalibacterium prauznitzii, overlapped between IBS and IBD. We identified numerous factors, like diet or medication, influencing the gut microbiome composition in patients with IBD in terms of overall composition and relative abundance of microbial species and bacterial pathways. The absence of the ileocecal valve or disease localization were the most important, but also specific dietary factors and the use of vitamin D or vitamin B12. We observed reduced strain level diversity within F.prauznitzii and an increased strain diversity and a significant increase of the growth rate of opportunistic bacteria such as Escherichia coli and Bacteroides vulgatus in patients with IBD compared to HC. Prediction models for differentiating between IBS and IBD based on microbiome data are constructed and the influence of 231 IBD associated genetic variants will be assessed in all participants. In conclusion, we here present the largest microbiome case-control analysis to date in IBD and IBS.

SLC39A8 missense variant is associated with Crohn's disease but not with the gut microbiota composition

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Gene-microbiota interactions play an important role in aetiology and pathogenesis of inflammatory bowel disease (IBD), compromising Crohn's disease (CD) and ulcerative colitis. Results of gene-microbiota interaction studies often do not match. Therefore, it is of utmost importance that these studies are repeated in independent cohorts. In this study, we aim to replicate the recent finding describing the influence of the exonic SLC39A8 threonine [Thr]391 risk allele on the gut microbiota in patients with CD and healthy controls. We collected faecal samples, peripheral blood and extensive phenotypic data from 168 CD patients and 390 healthy controls. The 16S rRNA gene was tag-sequenced to determine the gut microbiota composition. The SLC39A8 missense variant information was obtained from whole exome sequencing data, generated using the Illumina HiSeq. The association of SLC39A8 carriership and disease status was tested using Wilcoxon-Mann-Whitney test. The associations between the microbiota composition and SLC39A8 carriership was determined using principal coordinate analyses and additive general linear models in MaAsLin in CD patients, healthy controls and both groups combined. The factors age, sex, body mass index, read-depth, PPI use, antibiotics and IBD medication (mesalazines, steroids, thiopurines, methotrexate and TNF-alpha inhibitors) were used as covariates in the multivariate model. We identified carriership of the SLC39A8 missense variant in 21/168 patients with CD and 27/390 healthy controls. Patients with CD were more often carrier of the SLC39A8 missense variant than healthy controls (P=0.03). However, when analysing the influence of this variant on the gut microbiota composition there were no statistically significant differences between the [Thr]391 risk allele carriers and non-carriers in the principal coordinate alayses of the gut microbiota composition in either patients with CD, healthy controls or both groups combined. On taxonomical level, neither the univariate nor the multivariate analyses identified any statistically significant relation between the risk allele and the microbial taxa in either patients with CD, healthy controls or both groups combined.
Conclusions: In this study, we show the importance of replicating previous gene-microbiota interaction studies. We could replicate the genetic [Thr]391 risk alle association with CD, but we could not identify any statistically significant association between the exonic missense variant in SLC39A8 and the gut microbiota composition in either patients with CD or healthy controls.

Inhibition of canonical WNT signaling pathway by β-catenin/CBP inhibitor ICG001 ameliorates liver fibrosis in vivo through suppression of stromal CXCL12

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Introduction: Hepatic fibrosis is the growing cause of mortality worldwide. In response to liver injury and altered wound healing response, quiescent hepatic stellate cells (HSCs) undergo characteristic morphological and functional changes and transformed to proliferative, contractile and ECM-producing myofibroblasts. In this study, we investigated implication of canonical Wnt signaling pathway in HSCs and liver fibrogenesis. Methods: Activation of canonical Wnt signaling pathway was examined in vitro in activated HSCs, 3T3 fibroblasts and in-vivo in liver fibrosis mouse model. Effects of canonical WNT signaling pathway using β-catenin/CBP inhibitor ICG001 on fibrotic parameters and contractility were evaluated in TGFβ-activated human HSCs and 3T3 fibroblasts. 3T3-conditioned medium studies were performed to assess the paracrine effects of ICG001 on macrophages and endothelial cells. Finally, ICG001 was evaluated for efficacy in CCl_4-induced liver fibrogenesis mouse model. Results: Canonical Wnt signaling pathway components were significantly up-regulated in TGFβ-activated HSCs and 3T3 fibroblasts, and liver fibrosis mouse model. In TGFβ-activated human HSCs and 3T3, ICG001 significantly inhibited expression of major fibrotic parameters, 3D-collagen gel contractility and wound healing. 3T3-conditioned medium studies showed increased 3T3-mediated macrophage and endothelial cells activation which was significantly inhibited by ICG001. In CCl_4-induced acute liver injury mouse model, post-disease intraperitoneal administration of ICG001 significantly attenuated collagen accumulation and HSC activation. Interestingly, ICG001 drastically inhibited macrophage infiltration, intrahepatic inflammation and angiogenesis. We further studied the mechanism involved in wnt-mediated effects and found role of stromal factor SDF1 or CXCL12. We observed complete inhibition of CXCL12 following Wnt inhibition suggesting potential role of CXCL12 in Wnt/β-catenin signaling during liver fibrogenesis. CXCL12 produced by activated HSCs potentiates macrophage infiltration and activation promotes liver inflamemation, and angiogenesis as confirmed by conditioned medium and CXCL12 antibody blocking studies.
Conclusion: Pharmacological inhibition of Canonical Wnt signaling pathway via suppression of CXCL12 suggests a potential therapeutic approach targeting activated HSCs in liver fibrosis.

Relaxin-coated iron-oxide nanoparticles as a novel theranostic approach for the diagnosis and treatment of liver fibrosis

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Background: Hepatic fibrosis is a growing health problem with no effective and clinically approved therapy. Hepatic stellate cells (HSCs) are the key cells involved in the pathogenesis of liver fibrosis. Upon activation, HSCs are transformed into contractile ECM-producing myofibroblasts leading to scar tissue formation. HSCs contraction contributes significantly to the portal hypertension thereby further impairing the liver function. Relaxin (RLN) has been shown to inhibit HSC activation and contraction thereby ameliorate liver fibrosis and portal hypertension. However, RLN has very poor pharmacokinetics and administration of high or frequent doses can lead to detrimental side effects e.g. vasodilation. Therefore, we aimed to develop a nanoparticle-based delivery system to improve pharmacokinetic profile and therapeutic efficacy of RLN for the diagnosis and treatment of liver fibrosis. Methods: We conjugated RLN to PEGylated iron oxide nanoparticles (RLN-MNP) and characterized the size, charge and stability using DLS. We examined relaxin conjugation and HSCs binding/uptake. We analyzed RXFP1 receptor expression on activated HSCs, CCl_4-induced liver fibrosis mouse models and human liver cirrhosis tissues using quantitative PCR and immunohistochemistry. Thereafter, we assessed the effects of RLN-MNP on human HSCs in vitro and on CCl_4-induced advanced liver fibrosis mouse model in vivo. Results: RLN-MNP was synthesized and RLN conjugation was confirmed using Dot-blot. RLN-MNP showed specific binding and uptake to TGFβ-activated human HSCs. In vitro, RLN-MNP and unconjugated RLN significantly inhibited TGFβ-induced 3D-collagen gel contraction and HSCs migration suggesting that RLN-MNP retained RLN binding and effects after conjugation. We found significant up-regulation of RLN receptor RXFP1 in TGFβ-activated HSCs and CCl_4-induced liver fibrosis mouse model. In vivo in established chronic liver fibrosis mouse model, both RLN and RLN-MNP strongly attenuated fibrosis by inhibiting HSC activation, ECM deposition and angiogenesis. Importantly, RLN-MNP but not unconjugated RLN increased Nitric oxide (NO) release by significant up-regulation of iNOS indicating inhibition of portal hypertension. On the other hand, unconjugated RLN induced systemic side effects by inducing systemic NO release (in serum) while RLN-MNP did not. MNP alone did not show any effect in vitro and in vivo.
Conclusion: This study presents a novel strategy to deliver relaxin specifically to HSCs, key pathogenic cells involved in liver fibrogenesis, for the diagnosis and treatment of liver fibrosis.

HBV synthetic long peptide can boost CD4 + and CD8 + T cell responses in chronic HBV patients ex vivo

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Background & aims: T cells play a crucial role in viral immunity. Patients chronically infected with HBV(CHB) have poor HBV-specific T cell responses. So far, HBV-specific immunotherapy fails to decisively improve therapeutic results. Vaccination with Synthetic Long Peptides (SLP) could be a promising new treatment strategy, since SLP have the ability to induce both CD4+ T(Th) cell and CD8+ T(CTL) cell responses as shown for several pathogens in preclinical models and patients. Therefore, the present study investigated the ability of a prototype HBV core sequence (HBc)-derived SLP to boost HBV-specific T cell immunity in CHB patients. Methods: HBc-SLP was synthesized and used to assess cross-presentation by HLA-A2+ monocyte-derived DC (moDC) and BDCA1+ blood DC to an HBc-CTL clone. Autologous SLP-loaded and TLR ligand-activated DC were used to examine SLP-induced natural HBc-specific CTL and Th cell immunity in patient-derived T cells. Results: CHB patient-derived BDCA1+ DC cross-presented HBc-SLP to the HBc-CTL clone as efficient as DC from healthy control(HC). Addition of TLR1/2-adjuvant Amplivant or TLR3L PolyI:C significantly enhanced cross-presentation of SLP by DC from CHB and HC up to 3 fold. Autologous SLP-loaded DC significantly increased patient-derived HBc-CTL, in both frequency and absolute number (up to 9 fold after 12days; n=12), which were functional as demonstrated by TNF-α and IFN-γ secretion upon antigen-specific re-stimulation. Despite the fact that HLA class II typing of CHB patients was not performed and hence the chance of Th cell activation was not optimal, SLP-loaded moDC increased cytokine producing Th cells up to 2.3-fold in all CHB patients (n=6), demonstrating the strength of a SLP-based vaccine to induce both Th cell and CTL responses without HLA restriction. Interestingly, in 5/7 patients, especially those with a moderate, but not high PD1-expression on day-12 CTL, blockade of PD-L1 further increased HBV-specific CTL proliferation in response to SLP. Conclusion: CHB patient-derived DC efficiently cross-present SLP-which can be boosted by Further adjuvants. This single prototype HBV SLP not only enhanced functional HBc-specific CTL, but ook Th cell responses in the patient's CHB ex vivo. In some, but not all patient-derived cultures, additional PD-L1 blockade improved SLP vaccine immunogenicity. These results pave the way for the development of a therapeutic SLP-based vaccine to induce effective HBV-specific adaptive immune responses in CHB patients. Keyword: HBV, cross-presentation, peptide vaccine, T cell response, PD-L1 blockade Disclosure of Interest: None Declared

Multifaceted interaction and regulation of hepatitis E virus infection by mitochondria

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Mitochondria are essential organelles to generate energy and regulate various important cellular processes. Liver cells have the highest copies (2000/cell) of mitochondria. Mitochondrial dysfunctions in hepatitis patients have been reported in many clinical studies. However, the molecular interactions of mitochondria with hepatitis E virus (HEV) infection (causing an emerging global health issue) have not yet been studied. Thus, we aimed to delineate the interaction and regulation of HEV infection by mitochondria in respect to their unique properties, including mitochondrial DNA (mtDNA), mitochondrial respiratory chain machinery and mitochondrial dynamics. In this study, human liver Huh-7 cells were used to model HEV infection and relative viral replication were analysed by quantitative real-time polymerase chain reaction (qPCR). The interaction and regulation of HEV replication by mitochondrial unique properties were respectively determined through pharmacological or gene silence approaches. We identified that inhibition of mtDNA replication through 2 specific inhibitors or knockdown of mtDNA polymerase γ (POLG) facilitated HEV infection accompanied by decreased ATP production. Furthermore, inhibition of mtDNA gene transcription by downregulation of mitochondrial transcription (co-)activators also significantly enhanced HEV infection. Impairment of mitochondrial respiratory chain resulted in decreased oxygen consumption rate, ATP generation and mitochondrial intensity, meanwhile facilitated HEV infection. In conjunction, these data suggested the integrity of mitochondrial is necessary in efficient defense against HEV infection. Mitochondrial morphology is dynamic and closely related to mitochondrial function. Intriguingly, HEV infection altered mitochondrial morphodynamics by inducing fusion to form elongated mitochondria. Gene silencing of key mitochondrial fusion regulators OPA1 and Mfn1 prevented HEV-triggered mitochondrial elongation and concurrently inhibit viral replication through enhanced cell-autonomous antiviral immunity and attenuating HEV induced autophagy, suggesting HEV is able to dampen host immunity by altering mitochondrial morphodynamics. In conclusion, host cells use mitochondria for defense against HEV; whereas the virus is able to corrupt these mechanisms by altering mitochondrial morphodynamics. Hence mitochondria may constitute a novel target for developing rational therapeutic avenues aimed at combating HEV infection.

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Cathepsin D regulates lipid metabolism in murine steatohepatitis

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Despite the globally increased prevalence of non-alcoholic steatohepatitis (NASH), the mechanisms that govern the inflammatory aspect of this disease are not fully understood. Recent evidence points towards the role of lysosomes in mediating inflammatory responses. In line, we previously found a correlation between plasma cathepsin D (CTSD), a lysosomal enzyme, and the level of hepatic inflammation in NASH patients. So far, the exact function of CTSD in NASH is unclear. We hypothesized that proteolytic inhibition of CTSD leads to reduced steatohepatitis. Ldlr$^{-/-}$ mice, fed a high-fat, high-cholesterol diet for 3 weeks, were injected with pepstatin A (PepA), an inhibitor of aspartyl proteases, in the final week of the experiment. Additionally, by incubating oxidized LDL-loaded wild type (Wt) bone marrow-derived macrophages (BMDMs) with PepA for 4hr, we also assessed the effect of inhibiting CTSD in vitro. In addition to diminished hepatic inflammation, inhibition of CTSD activity dramatically improved lipid metabolism, as demonstrated by decreased plasma and liver levels of both cholesterol and triglycerides. Mechanistically, CTSD inhibition resulted in an increased conversion of cholesterol into bile acids and an elevated excretion of bile acids via the feces, indicating that CTSD influences lipid metabolism. Consistent with these findings, treating Wt BMDMs with PepA in vitro showed a similar decrease in inflammation and an analogous effect on cholesterol metabolism.
Conclusions: CTSD is a key player in the development of hepatic inflammation and dyslipidemia. Therefore, aiming at the inhibition of the activity of CTSD may lead to novel treatments to combat NASH.

2'-C-methylcytidine inhibits hepatitis E virus replication but antagonizing Ribavirin

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Hepatitis E virus (HEV) infection has emerged as a global issue, whereas no approved medication is available. Although ribavirin is effective as off-label treatment for chronic hepatitis E, a substantial proportion of patients develop resistance and eventually fail to clear the virus. The viral polymerase inhibitor 2'-C-methylcytidine (2CMC) has been shown capable of inhibiting a variety of RNA viruses, including hepatitis C virus (HCV).This study aims to investigate the effect of 2CMC on HEV replication and its combinatory effect with ribavirin. We first validated the antiviral activity of 2CMC in an HCV replicon model containing a luciferase reporter. 2CMC (10μM) showed a remarkable inhibitory effect on HCV replication by 99.7±0.004%(n=4 , P<0.05) after 72h treatment. In the sub-genomic HEV model, 2CMC exerted specific anti-viral activity, without affecting cell viability (IC50,1.64 μM and CC50,111.2 μM). In the infectious HEV model, 2CMC (10μM) significantly inhibited HEV replication by 63.4±0.018% (n=4, P<0.05). This was further confirmed in the PLC liver cell that 2CMC (10μM) inhibited HEV replication by 69.5±0.011% (n=4, P<0.05). Since various extra-hepatic manifestations in particular neurological and renal injuries have been recently reported to be associated with HEV infection, we further evaluated the effects in the 293T kidney cell line, the MRC-5 lung cell and the U87 brain cell line. 2CMC (10μM) inhibited HEV replication by 81.2±0.017% (n=4, P<0.05) in 293T cells, 43.5±0.061% (n=4, P<0.05) in MRC-5 cells and 87.2±0.013% (n=4, P<0.05) in U87 cells with the HEV infectious model. Furthermore, long-term treatment of 2CMC in both infectious and sub-genomic models resulted in more potent antiviral effects. Unexpectedly, combination of 2CMC with ribavirin showed a moderately antagonistic anti-HEV effect, with an antagonism of -36.93 μM^2%.
CONCLUSION: 2CMC could effectively inhibit HEV replication but showed a moderate antagonism with ribavirin. Thus, targeting viral polymerase represents as a viable option for developing anti-HEV therapy and 2CMC could serve as a starting point for drug design

Mesenchymal stromal cells prevent progression of liver fibrosis in a zebrafish embryo model

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Chronic exposure of the liver to injuring circumstances results in the secretion of multiple mediators that activate multiple cell types, usually resulting in hepatic fibrogenesis. Key features are proliferation and activation of hepatic stellate cells, accompanied by progressive deposition of extracellular matrix. Zebrafish embryo models are widely accepted and frequently used to study a variety of diseases and therapeutics. The aim of our study was to translate the commonly in mice used carbon tetrachloride (CCL4) and thioacetamide (TAA) liver fibrosis models into the zebrafish embryo. In addition, we studied the efficiency of bone marrow-derived mesenchymal stromal cells (MSCs) to modulate the fibrotic process. Zebrafish embryos, 2 days post fertilisation (dpf), were exposed for 6 days to increasing concentrations of TAA or received 1 to 2 injections of CCL4 in the yolk sac 2- and 4 dpf. After 6 days of exposure (8 dpf) the fish were fixed and paraffin embedded for Sirius red staining and RNA isolation to study the extent of fibrosis. RNA levels of fibrosis-related (Collagen1α1, Hand, and Acta-2) and tissue damage-related genes (TGFβ and SDF1a, SDF1b) were determined. Approximately 100 RFP expressing MSCs or fibroblasts from mice, the latter as control, were injected 5 dpf in close proximity to the liver. The highest concentration of CCL4 resulted in acute toxicity with no surviving embryos. Lower CCL4 dosages were less toxic, but did not result in the upregulation of the fibrotic- and tissue damage-related genes. In with these findings no matrix deposit structures in the liver were observed. TAA treatment resulted in a dose-dependent upregulation of collagen in the zebrafish embryos but only in the intermediate TAA treatment group the fibrotic markers Hand and Acta-2 were elevated, suggesting more proliferation and activation of hepatic stellate cells. Higher mRNA levels of tissue damage related genes TGFβ, SDF1a and SDF1b was also observed. Furthermore, collagen-deposition structures in the liver could be visualised with Sirius red staining. These data indicate the onset of a fibrotic process by the TAA treatment. Local treatment with MSCs at 5 dpf in the TAA model resulted in strongly reduced matrix deposition and up to 47% less upregulation of fibrotic genes. The injected MSCs could still be traced at the end of the experiment (8dpf). In contrast to the MSCs, fibroblasts did not affect the fibrosis.
In conclusion, TAA induces liver fibrosis in zebrafish embryos, thereby providing a promising model for future mechanistic and therapeutic studies. Furthermore, injection of MSCs seems to prevent progression of liver fibrogenesis in the zebrafish.

Fibroblast-specific endoglin knockout enhances polyp formation by affecting stromal interactions

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Endoglin, a transforming growth factor-β (TGF-β) co-receptor, is highly expressed on angiogenic endothelial cells in solid tumors. However, we also observed endoglin expression on cancer associated fibroblasts (CAFs), specifically at the invasive borders of colorectal cancer (CRC). Caf-specific endoglin expression correlates with decreased metastasis-free survival in stage-II CRC patients. To further examine the role of endoglin on CAFs we generated tamoxifen-inducible, fibroblast-specific endoglin knockout (KO) mice (CreERT2-Collagen1α1.ENGfl/fl). Tumor formation was induced using the carcinogen azoxymethane (AOM), followed by three cycles of dextran sodium sulphate (DSS) to induce colitis. At the end of the experiment (day 84) mice were sacrificed. Surprisingly, we found significantly more lesions (adenomas with high grade dysplasia) in the KO group compared to non-induced controls (average number of lesions 20 vs 6 respectively, P<0.0001). Flow cytometry analysis of the lesions revealed that, although the total CD45+ immune infiltrate was not changed, increased infiltration of Ly6C- macrophages and Ly6G+ neutrophils was observed in KO mice, compared to controls. Immunohistochemical analysis confirmed increased infiltration of these cells. Further analysis showed increased proliferation of epithelial cells in the adenomas compared to histologically normal tissue, but no difference in the number of proliferating or apoptotic cells in the lesions of control and KO mice was observed. In contrast, the total stroma content (vimentin positive), as well as the number of activated α-smooth muscle actin positive fibroblasts was increased in KO mice (P<0.001 and P<0.05 respectively). Tissue mRNA expression analysis of the lesions revealed increased Chemokine Ligand-2 (CXCL2, a neutrophil attracting chemokine, 49% upregulation) expression in lesions from the KO mice. In-vitro experiments using endoglin KO murine embryonic fibroblasts (MEFs) showed that mRNA expression of various chemokines and cytokines including Chemokine Ligand 1 (CXCL1, p<0.001) and bone morphogenetic protein-6 (BMP-6, P<0.05) was down regulated (80% and 74% respectively). Paracrine effects of MEFs on epithelial TGF-β and BMP signaling, but not difference in proliferation was observed using reporter assays. Together these data suggest a role for endoglin on fibroblasts during early stages of CRC tumorigenesis possibly via altered recruitment of macrophages and neutrophils. Currently, our ongoing research is focusing underlying mechanism regulating paracrine interactions in the tumor microenvironment.

Blockade of LAG-3 or PD-L1 enhances the functionality of tumor-infiltrating T cells in liver metastasis from mismatch-repair proficient colorectal cancer

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Targeting the PD-1/PD-L1 immune checkpoint co-inhibitory pathway has been shown to be a promising novel therapeutic approach for several types of cancer including mismatch repair (MMR)-deficient colorectal cancer (CRC), but not effective in MMR-proficient CRC so far. Liver metastasis (LM) is a leading cause of CRC-related mortality. They are present in 20%-25% of patients at diagnosis and develop in another 25% of patients during the course of the disease. Therefore, we aimed to determine which co-inhibitory pathways can be targeted to enhance the functionality of intra-tumoral T cells in liver metastasis from CRC (LM-CRC). We measured the expression of co-inhibitory receptors and their ligands on leukocytes freshly isolated from paired resected metastatic liver tumors, tumor-free liver tissues (TFL) and peripheral blood of patients with LM-CRC by flow cytometry, and studied the effects of blocking co-inhibitory pathways on the responses of tumor-infiltrating lymphocytes (TIL) in ex vivo assays. Finally, we compared the intra-tumoral expression of co-inhibitory molecules among MMR-proficient LM-CRC, peritoneal metastasis from CRC (PM-CRC) and primary CRC tissues. Co-inhibitory receptors PD-1, TIM-3 and CTLA-4 were expressed on significantly higher proportions of CD4+ T helper cells, while PD-1, TIM-3 and LAG-3 were expressed on significantly higher proportions of CD8+ cytotoxic T cells in LM-CRC tumors than in TFL and blood. Dendritic cells, monocytes and B cells in tumors expressed their ligands. Compared to the TIL without co-inhibitory receptor expression, CD4+ and CD8+ TIL expressing those co-inhibitory receptors displayed a more activated phenotype but similar or reduced effector cytokine production. Importantly, blocking LAG-3 or PD-L1 with neutralizing antibodies increased ex vivo proliferative and cytokine responses of CD4+ and CD8+ TIL to polyclonal and tumor antigen stimulation. Interestingly, CD8+ TIL in MMR-proficient LM-CRC expressed more PD-1 than those in MMR-proficient primary CRC and expressed more TIM-3, LAG-3 and CTLA-4 than those in MMR-proficient PM-CRC; while CD4+ TIL in MMR-proficient LM-CRC expressed more LAG-3 and CTLA-4 than those in MMR-proficient PM-CRC Conclusion: Increased co-inhibitory receptor expression on CD8+ TIL in LM-CRC suggests that MMR-proficient LM-CRC may respond better to PD-1/PD-L1 blockade than MMR-proficient primary CRC. Blocking LAG-3 or PD-L1 enhances the ex vivo functionality of tumor-infiltrating T cells from MMR-proficient LM-CRC. Therefore, these two co-inhibitory pathways may be promising immunotherapeutic targets for the most prevalent secondary liver cancer.

Cripto an indicator of a more aggressive hepatocellular carcinoma phenotype

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Hepatocellular carcinoma (HCC) is the third cause of cancer-related death worldwide. Despite increasing treatment options, prognosis remains poor. CRIPTO is a GPI-anchored signaling protein with diverse actions as a regulator of stemness. In addition to its physiological roles in stem cells, Cripto is expressed at high levels in human tumors and promotes the oncogenic phenotype. In HCC, CRIPTO expression was correlated to poor patient outcome, however the underlying mechanism(s) are still unknown. In this study, we aimed to elucidate the underling mechanisms and explore the effect of CRIPTO expression in HCC. Paraffin embedded and frozen tissue samples were used to evaluate CRIPTO expression on protein and RNA level. Functional and molecular effects exerted by CRIPTO in HCC were studied in a stable lentiviral transduced CRIPTO overexpressing HepG2 cell line. RNA levels of CRIPTO related pathway, epithelial to mesenchymal transition (EMT) pathways and cancer stem cell (CSC) genes were measured. Migratory and proliferative capacities were tested with standard wound healing, transwell and proliferation assays. Tumour take was assessed by subcutaneous implantation of cells in immunocompromised a mouse and duct of Cuvier injection in zebrafish embryos.
CRIPTO immunostaining of 80 pairs of HCC and adjacent tissue samples identified a subpopulation (28%) of tumours expressing higher CRIPTO levels than adjacent tissue. In vitro studies with HepG2-CRIPTO cells revealed increased expression levels of GRP78 and NODAL pathway members (NODAL, ALK4, LEFTY). Moreover, proliferation and migration were increased in HepG2-CRIPTO cells compared to HepG2-MOCK cells. Consistently HepG2-CRIPTO cells showed downregulation of E-CADHERIN, upregulation of EMT markers (VIMENTIN, ZEB-1, ZEB-2, TWIST and SNAIL-2) and increased CSC marker (EpCAM, BMI-1 and CD44) expression. Zebrafish embryos injected with HepG2-CRIPTO cells contain more HCC foci compared to HepG2-MOCK cells which indicate a better cell survival. Subcutaneously implanted HepG2-CRIPTO cells formed larger tumours (13 mm) compared to HepG2-MOCK cells (4 mm). These data indicate elevated CRIPTO expression in a subpopulation of HCC tumours. Furthermore, CRIPTO overexpressing cells exhibit a more aggressive phenotype, which may indicate that CRIPTO is involved in HCC progression.

Identification of specific subpopulations of Tumor Associated Macrophages in Esophageal Adenocarcinoma is associated with poor survival

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Lately it has been shown that immune modulation e.g., by inhibition of the T-cell cancer interaction, can greatly improve cancer response. Tumor-associated-macrophages (TAMs) are other key cellular players within the tumor microenvironment which can present both tumor promoting and tumor suppressive functions. Although several anti-TAM therapies reduce tumor growth and metastasis in preclinical cancer models, strategies that aim at specifically eliminating the protumoral TAMs or TAM signals are lacking. This study aimed at identifying specific TAM populations within the tumor microenvironment of Esophageal adenocarcinoma (EAC). EAC is a highly aggressive cancer that presents high intratumoral heterogeneity and dismal prognosis. To determine whether TAM infiltration is associated to low survival and high recurrence in EAC, we analyzed the transcriptomes of 56 EAC by RNAseq of pre-treatment biopsy specimens. We found that high RNA expression of CCL2 (a tumor-derived chemokine that stimulates the recruitment of monocytes to the tumor microenvironment) was associated with poor overall survival in EAC patients. Additionally, several canonical markers and effectors, including MARCO, CXCR4 and TGF-beta, that are known to mediate specific TAM functions in cancers, were associated to poor survival These data therefore hints towards the existence of different TAM subpopulations with diverse tumorigenic functions. Bone Morphogenic Proteins have more recently been identified as signaling molecules involved in aggressive tumor behavior and involved in the tumor stroma cross talk. In this study we have found that BMPs regulate the oncogenic functions of several TAM subpopulations. In the RNA seq data, in particular BMP2 and BMP4 correlated with the presence of TAM. Also the TAM related CCL2 expression was positively correlated with BMP2/4 expression. In vitro, we have also demonstrated that both epithelial cells as well as TAM-like macrophages not only secrete BMPs but are responsive to BMP signals, suggesting that a bidirectional BMP crosstalk between TAMs and cancer cells, may increase the aggressiveness of EAC. Our studies demonstrate the presence of different malignant subpopulations of TAMs in EAC. It also supports the role of BMPs in the cross talk between the TAM subpopulations and tumor cells. Future inhibition of the BMP signal might represent a novel anti-TAM strategy with the potential to ameliorate the malignant behavior of aggressive esophageal cancers.

Smooth muscle cell contractile phenotype and cachexia in pancreatic cancer patients: a pilot study

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Muscle loss in cachectic pancreatic cancer patients is most obvious in skeletal muscle, but clinical symptoms suggest that cachexia may manifest itself also in smooth muscle, a tissue that is responsible for the contraction of the gastrointestinal tract. Under pathological conditions, smooth muscle cells (SMCs) switch to a less contractile stage, which is characterized by decreased smooth muscle-specific contractile marker proteins. To investigate whether intestinal SMC contractile phenotype is affected in cancer cachexia, we studied the abundance of several contractile SMC protein markers in the jejunum of cachectic pancreatic cancer patients. We randomly selected nine jejunum tissue sections from a retrospective cohort of 133 pancreatic cancer patients who underwent surgery between 2008 and 2013 at the MUMC+. Tissue sections were immunohistochemically stained for the SMC contractile protein markers α-smooth muscle actin (α-SMA), SM22α, and smoothelin. Staining intensity of the two intestinal SMC layers was separately analyzed by ImageJ software. Elastic van Gieson staining was performed to visualize extracellular matrix components. Skeletal muscle mass (L3 muscle index) as well as skeletal muscle radiodensity were assessed by CT-image analysis. Patient characteristics were: age 71±8.1 yrs, BMI 24±2.9 kg/m^2, plasma CRP 10.7±10.3 mg/L, plasma albumin 42.8±30.0 g/L, L3 skeletal muscle index 43.0±6.7 cm^2/m^2, muscle radiodensity 32.7±15.4 Hounsfield Unites (HU). All SMC contractile markers were detectable in both intestinal SMC layers in all patients. SM22α staining intensity in the longitudinal intestinal smooth muscle layer was strongly correlated with skeletal muscle radiodensity (r_s=0.733, p=0.025). Furthermore, a trend towards a significant correlation between α-SMA staining intensity in the longitudinal smooth muscle layer and the L3 muscle index was observed (r_s=0.567, p=0.112). High plasma CRP levels were associated with increased extracellular matrix tissue in jejunal smooth muscle.
In conclusion, both intestinal smooth muscle contractile protein expression and extracellular matrix content are associated with cancer cachexia-related parameters. These data suggest that cancer cachexia is not only associated with skeletal muscle wasting but also affects intestinal smooth muscle contractile phenotype.

The impact of EUS in staging of locally advanced esophageal cancer patients following PET-CT

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Background: Current guidelines for preoperative staging in esophageal cancer recommend integrated computed tomography (CT), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). The role of endoscopic ultrasound (EUS) is debatable. EUS has a high sensitivity regarding local resectability (T-stage) and locoregional lymphadenopathy (N-stage). Limited data is available regarding the value of EUS in guiding treatment decisions. Therefore, we investigated the role of EUS in treatment decisions when performed routinely after FDG-PET/CT investigation. Methods: In this prospective single center study we investigated the role of EUS in patients with suspected curable esophageal cancer referred to the University Medical Hospital Groningen between January 1st and December 1st 2016. In all patients, we performed an integrated FDG-PET/CT scan and subsequent EUS. We used a standard EUS protocol in which we performed fine needle aspiration (FNA) of all lymph nodes with the slightest suspicion of malignancy outside the radiotherapy field (≥3cm proximal or distal from the tumor). Treatment decisions were made after complete staging in our multidisciplinary team. We studied the impact of EUS results on decision making in addition to the FDG-PET/CT results alone. Results: 61 patients were included. All patients underwent staging with FDG-PET/CT and subsequent EUS. In 7/61 patients (11%) EUS lead to alteration of the treatment plan. In 24/61 patients FNA of detected lymph nodes was performed. In 5/24 a positive FNA was seen. In 2 patients the preoperative radiotherapy field was altered. In 1 patient the tumor was staged incurable. In 2 patients a curative endoscopic mucosal resection (EMR) was performed instead of surgery. In 2 patients the tumor was downstaged and found suitable for curative treatment.
Conclusion: Standard EUS +/- FNA after FDG-PET/CT altered treatment decisions in 11% of the esophageal cancer patients referred for curative treatment. Larger studies are needed to clarify the optimal position of EUS in the staging of locally advanced esophageal cancer patients.

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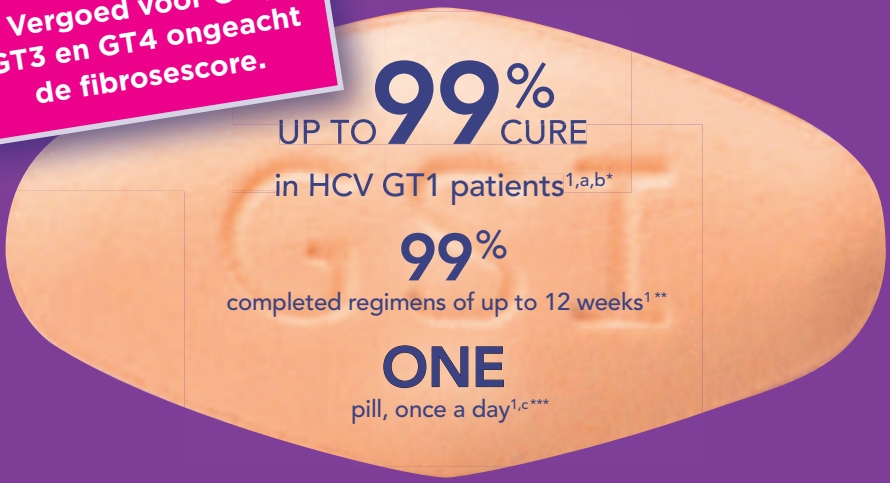

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[b] EASL define cure as SVR12.
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Referenties en productinformatie elders in deze uitgave.

HAR/NL/15-09/PM/1789

Identification of three distinct biological subtypes in esophageal and junctional adenocarcinoma by RNA sequencing

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Esophageal adenocarcinoma (EAC) is a highly aggressive malignancy with poor prognosis. Advances in therapy have achieved incremental improvements in overall outcome in EAC, but over- and undertreatment of undefined subgroups of patients might undermine these benefits (Courrech Staal, 2010). The biological diversity of EAC complicates patient selection and treatment stratification and impedes the development of new targeted agents. Further insight into the heterogeneous molecular pathology of EAC and a possible relation to outcomes and response to current treatment strategies is urgent.

We included ~90 patients with EAC and junctional adenocarcinomas between 2012 and 2017. All patients with resectable locally advanced cancer received neoadjuvant chemo-radiotherapy (nCRT) with carboplatin and paclitaxel followed by surgical resection (CROSS). Pre-treatment tissue samples of the tumor and healthy adjacent mucosa were collected during upper gastrointestinal endoscopy. RNA was extracted from all tumor biopsies and a subset of matched healthy biopsies. Samples were sequenced using Illumina sequencing technology. Count files were obtained, which served as input into the R language and environment for statistical computing for further analyses. We performed unsupervised hierarchical clustering on the tumor RNA profiles. To estimate the optimal number of endotypes we combined cumulative distribution functions, silhouette width analysis and cophenetic distance correlation analysis. We could identify three distinct subtypes. One of the subtypes was associated with poor response to therapy. We have developed a subtype classifier to validate our results in different databases. Currently, we are using this classifier to perform subtype prediction in a cohort from the TCGA database. Our studies support the existence of three distinct EAC/junctional subtypes associated with different response to therapy. Based on these subgroups, we developed an EAC subtype classifier that might enable better patient selection and treatment stratification and subsequently improve outcomes. Moreover, we will use the identified EAC subtypes to develop better targeted therapies.

The expression of the MHC-I pathway correlates with poor patient's survival and it is regulated by microRNA in esophageal adenocarcinoma

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Esophageal adenocarcinomas (EAC) are highly aggressive cancers, which generally have poor response to chemo-radiotherapy and surgery. It is thought that novel therapies, such as immune checkpoint inhibitors, will improve patient outcomes. However, biomarkers and potential immune modulators for selecting and optimizing treatment for EAC patients need to be explored. Here, we investigated which microRNA regulate the expression of MHC class I pathway genes and whether we could identify a subgroup of EAC patients that could benefit from immune therapies. EAC tumor biopsies analyzed for several MHC-I pathway components by qPCR, and validated in the RNA-sequencing dataset from The Cancer Genome Atlas (TCGA), showed differential expression of MHC class I pathway genes between patient groups. In the patient biopsies, the MHC-I status correlated with the expression of other immune-related genes which are known to sustain both a supportive and suppressive tumor immune-micro environment. Interestingly, the high expression of several of the MHC-I pathway genes correlated with poor therapeutic response and poor disease free survival. The EAC cell lines, OE33 and OE19 with respectively “high and “low” MHC-I pathway gene expression, were analyzed for eighty-eight miRNAs involved in the regulation of immunopathology pathways and two microRNA were found to be associated with decreased expression of MHC class I pathway genes. In EAC biopsies, expression of the candidate microRNAs by in situ hybridization (ISH) correlated with expression of the target genes. Furthermore the analysed microRNAs could regulate several of the MHC-I pathway genes as evaluated in vitro by luciferase reporter gene assay and a functional cytotoxicity T-cell assay against the cancer cells. Based on these results we advocate that EAC patients with proficient MHC class I gene expression can benefit from treatment with immune checkpoint inhibitors. Additionally, the microRNA-target identified interactions could serve as unique novel targets for potentiating immune therapeutic strategies.

High mRNA expression of splice variant SYK short correlates with hepatic disease progression in untreated lymph node negative colon cancer patients

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Introduction: In lymph node negative (LNN) colon cancer 20% of the patients will develop recurrence of disease. Identification of these patients is an unmet need. SYK, a protein kinase, has been ascribed a tumor promoter and suppressor role in epithelial cancers. The prognostic value of SYK and its splice variants, largely unknown in colorectal cancer, was explored in a clinically well-defined prospectively collected cohort of colon cancer patients (MATCH-study). Methods: Total mRNA expression of SYK [SYK(T)] and its two splice variants SYK short(S) and SYK long(L) were measured using RT-qPCR in 240 colon cancer patients (n=160 untreated LNN and n=80 adjuvant treated lymph node positive [LNP] patients). mRNA expression levels were related to microsatellite instability (MSI), mRNA expression of epithelial (EPCAM), stromal (BGN, FAP, INHBA) and infiltrate markers (VEGFA, CD45), known CRC mutations (n=238), and disease free (DFS), hepatic metastasis free (HFS) and overall survival (OS). Results: Increased SYK levels were associated with stage I/II, a left-sided located primary tumor and MicroSatellite Stability (MSS). However, these associations and their interrelation differed significantly between SYK(T), SYK(S) and SYK(L) implicating an added value for measuring mRNA expression of the splice variants separately. A significant positive correlation with the expression of EPCAM and VEGFA suggested a higher expression of SYK in epithelial-rich, stromal-poor tumors. SYK(T) and SYK(S) expression was significantly lower in tumors with a BRAF or PTEN mutation (mt) compared to wild type (wt) tumors. Although others reported differential expression of SYK between KRAS-dependent and KRAS-independent cell lines and KRAS mt versus wt tumors in 221 TCGA-samples (p=0.008), we observed no significant differences for expression of SYK(T), SYK(S) and SYK(L) between KRAS--mutant (mt) and KRAS-wild type (wt) tumors. In the LNN group, using univariate Cox regression analysis increasing mRNA expression of SYK(T) (HR=2.05 95%CI=1.01-4.17 p=0.047) and SYK(S) (HR=1.83 95%CI=1.09-3.05 p=0.021) was associated with worse HFS, which remained significant for SYK(S) when correcting for the number of assessed lymph nodes (HR=1.83; 95% CI=1.08-3.12; p=0.026 and HR=1.27; 95%CI=1.009-1.60; p=0.042).
Conclusion: this study suggests a different role for SYK(S) and SYK(L) in colon cancer, and within colon cancer in hypermutated and nonhypermutated tumors. In our untreated LNN colon cancer cohort SYK(S) is a pure prognostic marker for HFS. These results may help to identify LNN patients at overall low risk to develop liver metastases.

Pooled incidence of fecal occult blood test interval cancers in colorectal cancer screening; a systematic review and meta-analysis

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Worldwide, many organized colorectal cancer (CRC) screening programs use non-invasive fecal occult blood tests (FOBTs). Although the interval colorectal cancer (iCRC) rate is an important performance indicator of a screening program, data on iCRC after negative FOBTs are limited. We therefore performed a systematic review and meta-analysis to estimate the overall pooled incidence rate (IR) of FOBT iCRCs in population-based screening programs, and compared the pooled IRs of guaiac FOBT (gFOBT) and fecal immunochemical test (FIT) iCRCs. Ovid Medline, Embase, The Cochrane Library, the Science Citation Index, PubMed publisher and Google scholar were searched up to May, 2016. All studies reporting on incidence of FOBT iCRCs in average-risk CRC screening populations were included, without language restrictions. Main outcome was pooled IR of FOBT iCRCs per 100,000 observed person-years (p-y). FOBT iCRC was according to international standards defined as cancer diagnosed after a negative FOBT and before the next FOBT was due. Pooled IRs were obtained by fitting random effect poisson regression models with the logarithm of p-y as offset variable. The between-study heterogeneity of effect-size was quantified using the I^2. The search identified 5,873 records, of which 413 full-text articles were assessed for eligibility and 30 studies were included in both qualitative and quantitative syntheses. Meta-analysis comprised data of 5,252,563 screening participants. Follow-up for iCRC was 22 million p-y, with a mean follow-up of 4.2 years per study, in which 14,030 screen-detected CRCs (1,858 gFOBT- and 12,172 FIT iCRCs) and 5,398 iCRCs (1,395 gFOBT- and 4,003 FIT CRCs) were documented. Incidence rates of iCRC between studies ranged from 0 to 106 per 100,000 p-y. The overall pooled IR of FOBT iCRC was 27 per 100,000 p-y (95% confidence interval (CI) 20-36; I^2=96%). The pooled IR of gFOBT iCRC and FIT iCRC were 40 (95%CI 26-61; I^2=93%, n=14 studies) and 20 (95%CI 14-28; I^2=94%, n=19 studies) per 100,000 p-y respectively. The pooled incidence rate ratio of FIT iCRC versus gFOBT iCRC was 0.50 (95%CI 0.30-0.84, n=30 studies). ICRCs were located distal from the splenic flexure in 68% (95%CI 63%-73%; I^2=8%, n=7 studies) and staged Dukes II-IV in 79% (95%CI 70%-86%, I^2=51%, n=8 studies).

Conclusion This is the first study to show the overall and test-specific incidences of gFOBT and FIT iCRC in screening setting. Incidence of gFOBT iCRC is twice as high as FIT iCRC. This finding supports the use of FIT over gFOBT as a primary CRC screening test. It further highlights the importance to adequately inform screenees that a negative FOBT does not completely rule out CRC.

Validation and pathway analysis of a metastasis specific microRNA signature in primary colon cancer

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Introduction: In lymph node negative (LNN) colon cancer 20% of the patients develop disease recurrence. Identification of these patients is needed. MicroRNAs (MiRNAs) can have a tumor promotor or suppressor role. Hur recently found 6 differentially expressed MiRNAs in primary versus matched metastatic colorectal cancer (CRC) tissues (MiR 320, MiR 221, MiR 30b, MiR 10b, MiR 885 5p, Let 7i). The expression of 2 MiRNAs was significantly correlated with distant metastasis (low Let 7i expression and high MiR 10b) in primary CRC. When split at the median and combined into a signature (Let 7i high and MiR 10b low [n=22] vs. Let 7i low and/or MiR 10b high[n=122]), the first group showed 100% metastasis free survival (MFS). We assessed the prognostic value of these MiRNAs and the signature in a clinically well defined cohort of primary colon cancers. Methods: Expression of the 6 MiRNAs were measured using RT qPCR in a cohort of 232 colon cancer patients (n=155 untreated LNN and n=77 adjuvant treated lymph node positive [LNP] patients) selected from the MATCH cohort. Expression levels were related to microsatellite instability (MSI), and MFS, hepatic metastasis free (HFS) and overall survival (OS). Results: In univariate Cox regression analysis, MiR 30b was significantly associated with MFS (HR=2.07 p=0.008), and MiR 30b and Let 7i were associated with HFS (HR=2.94 p=0.005 and HFS HR=0.28 p<0.001, respectively) in the LNN group. These associations remained significant when correcting for MSI. Pathway analysis for MiR 30b and Let 7i with the GSEA hallmark gene sets between the 50 samples with the highest and 50 samples with lowest expression revealed a significantly higher expression of the TGF beta pathway in the MiR 30b high group, and a significantly higher expression of the EMT pathway in the Let 7i high group. MiR 30b and Let 7i expression was split at the median level and combined into two groups ('Let 7i high and MiR 30b low' vs. 'Let 7i low and/or MiR 30b high'). The 'Let 7i high and MiR 30b low' group in the total group (n=74) had a significantly better 5 yr HFS (100% vs 87.4% p=0.002), and had a significantly better 5 yr MFS (91.7% vs 78% p=0.036) and HFS (100% vs 87.8% p=0.01) in the LNN group (n=52). Conclusion: in our cohort and more specifically the LNN group, we confirmed Let 7i and identified MiR 30b as a prognostic factor for MFS and HFS. We did not confirm the prognostic value of Mir 10b. The combination of Let 7i and MiR 30b identified a group with a 100% HFS. Pathway analysis showed higher expression of the TGF beta pathway in the MiR 30b high group, and higher expression of the EMT pathway in the Let 7i high group.

Locally advanced colorectal cancer: true peritoneal penetration as a predictive factor for peritoneal metastases

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Background: T4 colorectal cancer (CRC) is a risk factor for developing peritoneal metastases (PMCRC). Heterogeneity regarding peritoneal involvement of T4 tumours might explain the wide range of reported PMCRC incidences (8 to 50%). Hyperplastic and mesothelial inflammatory reactions complicate the evaluation of the exact primary tumour involvement of the peritoneal layer. The aim of this retrospective cohort study was to assess the association between the extent of peritoneal involvement of the primary tumour and the risk of PMCRC. Methods: All patients who underwent resection of a pT4 CRC between January 2010 and July 2013 were included. Pathologists systematically categorized the peritoneal involvement of the primary tumour into peritoneal reaction with tumour within 1 mm of the peritoneal surface or true peritoneal penetration. Results: In total 159 pT4 CRC patients were included. Peritoneal reaction with tumour within 1 mm was present in 43 and true peritoneal penetration in 116 patients. Overall, 29 patients (18%) had synchronous PMCRC and 30 patients (23%) developed metachronous PMCRC. True peritoneal penetration, as opposed to peritoneal reaction with tumour within 1 mm of the peritoneum, was associated with an increased risk of PMCRC in multivariable analysis (OR:2.518 (1.038-6.111); p=0.041), as well as lymph node involvement (N1:OR:1.572 (0.651-3.797) N2:OR:4.046 (1.549-10.569); p = 0.014).
Conclusion: Patients with T4 CRC with histological confirmed true peritoneal penetration constitute a high risk subgroup for PMCRC. In current TNM classification systems, the evaluation of the exact peritoneal involvement of the tumour is not incorporated. With evolving treatment strategies that aim to treat PMCRC in an earlier phase, identification of high risk patients becomes of high clinical importance.

Adherence to food guidelines of the World Cancer Research Fund & American Institute for Cancer Research and pancreatic cancer risk

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Pancreatic cancer is one of the most lethal cancers, with an increasing incidence and limited treatment options. Prevention of this cancer, through lifestyle management, might improve the burden of this disease. We aimed to study whether, adherence to dietary and lifestyle guidelines of the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR), is associated with the risk of pancreatic cancer. This study was embedded in the Rotterdam Study, a longstanding, prospective, population-based cohort study. Data on dietary intake were collected at baseline, through a frequent food questionnaire. We excluded subjects of whom we had no or unreliable food data. We constructed a score, b.ased on the WCRF/AICR recommendations on weight management, foods and drinks that promote weight gain, plant and animal foods, alcoholic drinks, and use of dietary supplements. We used Cox Proportional Hazard Models to estimate the association between the score and pancreatic cancer risk. Next we evaluated the risk of pancreatic cancer for each individual component of the WCRF/AICR score. At base 14,922 participants were at risk of developing pancreatic cancer. For 9778 participants dietary data was available. During a median follow-up time of 20.1 years, 77 patients developed pancreatic cancer. Adherence to the WCRF/AICR recommendations was significantly associated with a reduced risk of pancreatic cancer (HR: 0.74, 95%CI: 0.57-0.97). This effect persisted after excluding all participants with less than two years of follow-up. Further analysis of the separate recommendations showed that this effect was mainly driven by refraining from taking dietary supplements (HR: 0.53, 95% CI: 0.34-0.84).

Conclusion: Our finding support, that adherence to dietary and lifestyle recommendations of the World Cancer Research Fund and American Institute for Cancer Research, decreases the risk of pancreatic cancer. Promoting these recommendations to the general population could help reduce pancreatic cancer incidence.

The prognostic impact of radical resection margins on the Recurrence of Crohn's Disease

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Background: Up to 85% of Crohn's patients will undergo surgical resection during the course of their disease. The majority of these resections involve ileocoecal resection. Smoking, fistulizing disease, and young age have been identified as risk factors for clinical and surgical postoperative recurrence. The prognostic impact of radicality of resection has been a matter of debate for decades, but so far current guidelines do not specifically recommend performing a radical resection. In contrast, they only emphasize the importance of a limited resection. The aim of this study is to analyze the prognostic impact of pathological findings in the resection margins of ileocoecal resection specimens in Crohn's disease. Methods: A consecutive series of 43 patients with Crohn's disease undergoing primary ileocoecal resection for medically refractory disease between 2006 and 2009 at the Academic Medical Center (AMC) in Amsterdam were included. Resection margins were histologically scored for several inflammatory parameters (e.g. architectural changes, eosinophils and neutrophils in lamina propria, crypt destruction, erosions and ulcerations, granulomes, and fissures). The score was based on the adjusted Geboes score. Pathological findings were correlated to clinical results that have been collected in a prospectively maintained database. Clinical recurrence was defined as endoscopic recurrence necessitating medical treatment. Results: There were 12 men and 31 women with a median age of 33.3 years. Median follow-up time was 71 months, with a minimum of 58 months. A radical resection was performed in 65.1% of patients. No association between clinical parameters and non-radical resection could be demonstrated. Overall clinical recurrence rate was 41.9%, with a lower recurrence rate in the radically resected group (32.1% versus 67.9% in the non-radical group, p=0.06 log-rank). Kaplan Meier curves showed that the median time to recurrence was 18 months for both groups. The incidence of surgical recurrence was too small (n=1) to perform statistical analysis. Conclusion: The presence of active microscopic inflammation in the resection margin after ileocoecal resection seems to be related to recurrent Crohn's disease. The high incidence of clinical recurrence in the non-radical group (68%) justifies a renewed discussion about the clinical importance of a radical surgical resection in these patients.

Smooth Seton® for perianal fistulas: a knot-less solution

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Perianal fistulas are a common incapacitating problem. Many patients with perianal fistulas are treated by seton drainage to prevent recurrent abscess formation. For centuries, a vessel loop or suture has been used for seton drainage and the knot is well known for causing complaints interfering with daily quality of life. To inventory complaints associated with knotted setons, a web-based questionnaire was performed by the Dutch Crohn and Ulcerative Colitis Association. Twenty-four out of 46 patients (52%) reported to have daily complaints caused by the knot. Medishield B.V. designed a knotless seton drain, the Smooth Seton, in order to decrease these complaints. With this study we aim to determine the advantages of a Smooth Seton for patients with perianal fistulas. A prospective cohort study was performed in a consecutive series of fistula patients. All patients ≥ 18 years, with perianal fistulas and a seton in situ, or patients presenting with a new perianal fistula, and no defunctioning stoma, were eligible. Existing setons were replaced at the outpatient clinic whereas new setons were placed at the operating room in day care setting. The primary outcome was seton failure (loosening of the connection). Secondary outcomes were complications, and quality of life measured by the PDAI ('Perianal Disease Activity Index'). For the patient group with seton replacement, preoperative PDAI was compared to postoperative PDAI. Results were analysed using the paired t-test. Twenty patients (40% male, mean age 42 (SD 12.81)) were included between August and November 2016. Seventeen patients had perianal fistulas due to Crohn's disease and 3 had fistulas of cryptoglandular origin. In one patient, the outpatient replacement failed, and the Smooth Seton was placed subsequently in theatre. The median number of Smooth Setons placed per patient was 2 (range 1-3). Follow-up was performed in 17 patients with a median of 23 days (range 11-71). Loosing of the connection occurred in one of the patients. Mean PDAI in patients with a knotted seton was 11.36 versus 8.69 after Smooth Seton placement (P=0.006). Looking at each of the 5 subscales of the PDAI, only pain and restriction of activities significantly decreased (P=0.003). Ten out of 16 patients (63%) reported less cleaning problems with the Smooth Seton when compared to the regular knotted seton. No postoperative complications occurred during the study period. The Smooth Seton is a feasible novel technique for patients with new and recurrent perianal fistulas with promising short term results. Replacement of the conventional knotted seton by the Smooth seton significantly decreases complaints measured by the PDAI.

[RETHINK PBC]

The GLOBE score: ALP, bilirubin, age, albumin and platelet count are markers of disease progression in PBC

Inadequately treated primary biliary cholangitis (PBC) can lead to liver transplantation or death[1,2]

Up to 40% of patients taking, or intolerant to, ursodeoxycholic acid (UDCA), may not be achieving an adequate response to treatment, as indicated by a GLOBE score of >0,30. So it is important to monitor your patients regularly[3]

Alkaline phosphatase (ALP), bilirubin, age, albumin and platelet count are markers of both disease progression and response to therapy.[3] A GLOBE score of >0,30 in PBC patients is associated with significantly shorter times of transplant-free survival than matched healthy individuals (P < 0,0001)[3]

EASL recommends checking your patients' response to therapy one year after starting therapy[4]

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Perianal fistulas and the lift procedure: predictive factors for success

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The treatment of a perianal fistula is difficult due to the possibility of fecal incontinence (FI) as a result of sphincterotomy and recurrence. LIFT is the most promising sphincter saving procedure with success rates ranging from 57% to 94%. The aim of this study was to find predictors for a favorable outcome after a LIFT procedure. Furthermore, we evaluated postoperative FI and the impact of FI on the quality of life and compared all our results with the literature. Patients who underwent LIFT surgery between 2013-2015 were searched for in the patient's electronic patient file of our clinic. Medical data concerning medical history, complaints, physical examination, 3D anal ultrasound, surgical findings and follow up were retrieved. The fistula related characteristics were described with physical examination, 3D anal ultrasound and during surgery. All patients received questionnaires regarding their post-operative FI status (Wexner) and the impact of their current fistula related symptoms on their quality of life (QOL) by the Patient Reported Outcome Measurement (PROM). A total of 49 patients (21 man, age 41years (range 24-67) were included. In 41 (84%) patients a complex fistula was present; 32 (65%) patients were referrals with previous fistula surgery. The initial success rate was 43%. Of the recurrences, 33% were downgraded and had a favorable outcome with subsequent management, thus bringing the success to 57%. Only the height of the internal fistula opening was statistically significant (≥15mm (68%), ≥18mm (81%) both $p<0.03$. The LIFT procedure didn't negatively affect the continence status. Recurrence was associated with a higher Wexner score (mainly flatus and soiling) ($p<0.04$) and showed a trend with the PROM ($p=0.07$). Compared with the literature we had more complicated fistulas and referred patients, as do others with moderate results.
Conclusion : Recurrence after LIFT is related to the height of the internal fistula opening. FI does not alter after LIFT. Furthermore, recurrence is associated with FI and diminished QOL. Favorable results in the literature are related to their patient population.

Late anastomotic leakage and chronic presacral sinus following low anterior resection. Incidence and predisposing factors in a population based cohort

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Abstract Introduction Little is known about late detected anastomotic leakage after low anterior resection for rectal cancer, as well as the proportion of leakage that turns into a chronic presacral sinus. Methods In this collaborative snapshot research project, data from registered rectal cancer resections in the Dutch Surgical Colorectal Audit (DSCA) in 2011 were extended with additional treatment and long term outcome data. Independent predictors for anastomotic leakage were determined using a binary logistic model.
Results A total of 71 out of the potential 94 hospitals participated. From the 2095 registered patients, 998 underwent a low anterior resection, of whom 88.8% received any form of neoadjuvant therapy. Median follow-up was 41 months (IQR 25-47). Anastomotic leakage was diagnosed in 13.4% within 30-days, with an increase to 20.0% (200/998) beyond 30-days. Non-healing of the leakage occurred in 47.5%, resulting in an overall proportion of chronic presacral sinus of 9.5%. Independent predictors for anastomotic leakage were neoadjuvant therapy and a distal tumor location (≤ 3 cm), with corresponding odds ratios of 2.85 (95% CI 1.00-8.11) and 1.88 (95% CI 1.02-3.46), respectively.
Conclusion This cross-sectional Dutch population study of low anterior resection for rectal cancer in 2011, with almost routine use of neoadjuvant radiotherapy, shows that one third of anastomotic leakage is diagnosed beyond 30-days and almost half of the leakages eventually do not heal. Chronic presacral sinus is a significant clinical problem that deserves more attention.

Vacuum assisted early transanal closure of leaking low colorectal anastomoses, the CLEAN-study

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Introduction: This study aimed to investigate the efficacy of early transanal closure of anastomotic leakage after pretreatment with the Endosponge® therapy in rectal cancer patients having a leak of a low colorectal anastomosis. Methods: In this prospective, multiCenter, feasibility study, patients with a leaking colorectal anastomosis were treated with a vacuum assisted early transanal closure strategy. Primary outcome was the amount of patients with a healed anastomosis at six months following the transanal closure. Furthermore, healing rates at the end of follow-up, continuity, chronic sinus rate, direct medical costs, functionality and quality of life were analysed. Results: Between July 2013 and July 2015, 30 patients with a leaking low colorectal anastomosis were included. Neoadjuvant therapy was applied in 22/30 (73.3%) patients. The median follow-up was 14 (7-29) months. Median duration of Endosponge® therapy was 13 (5-51) days. At six months following transanal closure in 16/30 (53.5%) patients the anastomosis had healed, which increased to 21/30 (70%) at the end of follow-up. Continuity was achieved in 20/30 (66.7%) of the patients. When Endosponge® therapy commenced within three weeks after the TME procedure, continuity was achieved in 73.3% of the patients. Chronic sinus rate was observed in 10/29 (34.5%) patients and in 3/14(21.4%) when started within three weeks following the index operation. At the end of follow-up 12/15 (80.0%) experienced a major LARS-score. The direct medical cost of the vacuum treatment and early closure were a mean of €8933,- (95% CI 7.268-10707) per patient

Conclusion Vacuum assisted early transanal closure of a leaking colorectal anastomosis showed that acceptable anastomotic healing rates and stoma reversal rates can be achieved. Early diagnosis and start of treatment is crucial. This treatment strategy could serve as first therapy in an anastomotic salvage protocol.

Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis: a pooled analysis of individual data for 1980 patients

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Objective Minimally invasive including endoscopic necrosectomy compared with open necrosectomy might improve outcomes in necrotising pancreatitis, especially in critically ill patients. Evidence from large comparative studies is lacking. Design We combined original and newly collected data from 15 published and unpublished patient cohorts (51 hospitals; 8 countries) on pancreatic necrosectomy for necrotising pancreatitis. Death rates were compared in patients undergoing open necrosectomy versus minimally invasive or endoscopic necrosectomy. We adjusted for confounding by three types of analyses: logistic regression, stratification according to predicted risk of death at base (low: <5%, intermediate: ≥5% to <15%, high: ≥15% to <35%, and very-high: ≥35%), and propensity-score matching. Results Among 1980 patients with necrotising pancreatitis, 1167 underwent open necrosectomy, and 813 underwent minimally invasive surgical (n=467) or endoscopic (n=346) necrosectomy. There was a lower risk of death for minimally invasive surgical necrosectomy (odds ratio, 0.53; 95%-CI, 0.34 to 0.84; P=0.006) and endoscopic necrosectomy (odds ratio, 0.19; 95%-CI, 0.06 to 0.61; P=0.005). After risk stratification and propensity-score matching, minimally invasive surgical necrosectomy remained associated with a lower risk of death than open necrosectomy in the very-high-risk group (42/111 versus 59/111; risk ratio, 0.70; 95%-confidence interval, 0.52 to 0.95; P=0.02). Endoscopic necrosectomy was associated with a lower risk of death than open necrosectomy in the high-risk group (3/40 versus 12/40; risk ratio, 0.27; 95%-CI, 0.08 to 0.88; P=0.03) and in the very-high-risk group (12/57 versus 28/57; risk ratio, 0.43; 95%-CI, 0.24 to 0.77; P=0.005).
Conclusion In high-risk patients with necrotising pancreatitis, minimally invasive surgical and endoscopic necrosectomy reduced death rates compared with open necrosectomy.

High hospital mortality after pancreatoduodenectomy explained by failure to rescue rather than major complications in a nationwide audit

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Failure to rescue (FTR) is death of a patient after a major complication. The Dutch Pancreatic Cancer Audit is a mandatory nationwide audit of pancreatic surgery. Our aim was to to compare major complication and failure-to-rescue rates (FTR) between high- and low mortality hospitals after pancreatoduodenectomy, and to develop a prognostic model for FTR. Patients undergoing pancreatoduodenectomy in 2014 and 2015 were included. Hospitals were divided into quartiles based on in-hospital mortality rates. The risk of a major complication (Clavien-Dindo ≥III) and death after a major complication (i.e. FTR) were compared between these quartiles. A nomogram was developed based on patient- and hospital characteristics that were independently associated with FTR in multivariable logistic regression analysis. Out of 1,342 patients, 391 (29%) developed a major complication. FTR occurred in 56 (14.3%) patients. Mortality was 0.9% in the first hospital quartile (4 hospitals, 327 patients), and 8.1% in the fourth (5 hospitals, 310 patients). Major complication rate increased by 40% (35.2% vs 25.7%) between the fourth and the first hospital quartile, whereas the FTR rate increased by 560% (22.9% vs 3.6%). Independent predictors of FTR were male sex (OR=2.1, 95% confidence interval (CI) 1.2-3.9), age >75 years (OR=4.3, 95%CI 1.8-10.2), BMI ≥30 (OR=2.9, 1.3-6.6), histopathological diagnosis of periampullary cancer (OR=2.0, 1.1-3.7), and hospital volume <30 (OR=3.9, 1.6-9.6). The nomogram identified groups with 2%, 4%, and 12% risk of FTR. Concluding, differences between hospitals in mortality after pancreastoduodenectomy seems to be explained mainly by differences in FTR, rather than the incidence of major complications. The nomogram can be used to identify patients at high risk of FTR.

Minimally invasive versus open distal pancreatectomy for ductal adenocarcinoma (DIPLOMA): a pan-European propensity score matched observational study

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Background Systematic reviews have shown excellent outcomes after minimally invasive distal pancreatectomy (MIDP) compared with open distal pancreatectomy (ODP) for non-malignant pancreatic disease. However, a recent survey revealed that a third of the European surgeons have concerns about the oncological outcomes of MIDP for pancreatic ductal adenocarcinoma (PDAC). A large retrospective observational study was performed to compare oncological outcomes of MIDP with ODP. Methods A pan-European observational study including all consecutive patients from participating centers who underwent MIDP or ODP for PDAC between 2007 and 2015 was performed. MIDP patients were matched to ODP patients in a 1:1 ratio based on propensity scores (obtained via multivariable logistic regression including only preoperatively variables: sex, age, BMI, ASA, history of abdominal surgery, surgery year, tumor location, and tumor size).

Primary outcome was radical (R0) resection. Secondary outcomes were pancreatic fistula, major morbidity, 90-day mortality, hospital stay, lymph node retrieval, adjuvant chemotherapy, and survival.

Results In total, 1336 patients were included from 33 centers in 11 countries. Out of 369 (28%) MIDP patients (25 (7%) robot-assisted procedures), 239 could be matched to an ODP patient. The conversion rate was 21% (n=44). Splenectomy was performed in almost all patients (98% (n=233) of MIDPs vs. 99% (n=237) of ODPs (P=0.3)) and multivisceral resection was performed in 14% (n=33) of MIDPs and 21% (n=50) of ODPs (P=0.04). The pancreatic fistula grade B/C rate was 18% (n=43) vs. 20% (n=48) (P=0.64), the major complication rate (Clavien-Dindo grade 3 or higher complications) was 16% (n=36) vs. 24% (n=53) (P=0.06), the 90-day mortality was 1% (n=2) vs. 2% (n=4) (P=0.44), and median hospital stay was 7 days (IQR=5-10) vs. 9 days (IQR=7-14) (P<0.001), for MIDP and ODP respectively. Oncological outcomes showed an R0 resection rate of 66% (n=152) for MIDP and 52% (n=119) for ODP (P=0.002), lymph node retrieval was 13 nodes (IQR=7-23) for MIDP and 19 nodes (IQR=12-26) for ODP (P<0.001). The use of adjuvant chemotherapy (72% vs. 67%, P=0.28) and median overall survival (31 vs. 26 months, P=0.51) did not differ significantly between MIDP and ODP.

Conclusion: This pan-European propensity score matched analysis suggests MIDP to be non-inferior to ODP in terms of postoperative outcomes and more specifically in terms of oncological outcome. Given the difficulty to match patients and differences in R1 resections and lymph node retrieval, a randomized controlled non-inferiority trial is needed to confirm the oncologic outcome of MIDP vs. ODP for PDAC.

Nationwide outcomes in patients undergoing surgical exploration without resection for pancreatic cancer

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Background Despite improvements in diagnostic imaging and staging of pancreatic cancer, unresectable pancreatic cancer is still encountered during surgical exploration with curative intent. This nationwide study investigates outcomes for unresectable pancreatic cancer found during surgical exploration Methods All 10 595 patients diagnosed with primary pancreatic (adeno)carcinoma (2009-2014) in the Netherlands Cancer Registry were included. Predictors for unresectability, 30-day mortality, and poor survival were evaluated using logistic and Cox proportional hazard regression analysis. Results The rate of patients undergoing surgical exploration increased from 20 to 27 per cent (P<0.001). Among 2536 explored patients, the resection rate increased from 62 to 71 per cent (p<0.001), whereas the contribution of M1 disease (19 per cent) remained stable. Compared with resected patients, patients not undergoing resection had an increased 30-day mortality (7.8 vs 3.8 per cent, p<0.001). In non-resected patients with M0 (n=383) and M1 (n=436) disease at surgical exploration, 30-day mortality was 4.7 versus 10.6 per cent (P = 0.002), median survival was 7.2 and 4.3 months (p<0.001), and 1-year survival 28 and 13 per cent, respectively. Among other factors, low hospital volume (0-20 resections/year) was an independent predictor for not undergoing a resection, but also for 30-day mortality and poor survival after not undergoing resection.
Conclusion Despite nationwide increasing exploration and resection rates, one-third of patients undergoing surgical exploration for pancreatic cancer did not undergo resection, with doubled 30-day mortality compared with patients undergoing resection. Improved preoperative staging strategies are urgently needed.

Diagnostic laparoscopy, a safe and useful tool in the preoperative screening of patients considered for cytoreductive surgery + HIPEC

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No standard pre-operative workup exists in patients with peritoneal carcinomatosis (PC). Previous literature describes underdiagnosing PC on imaging up to 10%. An usefool tool might be diagnostic laparoscopy (DL) and could help managing patients expectations. This study reviews the value of a DL in patients considered eligible for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC). This single-center, retrospective cohort study examines all patients who underwent laparotomy for peritoneal carcinomatosis of colorectal disease in the period of January 2005 until June 2016. Data of tumor characteristics, peroperative and postoperative reports were collected. A total of 333 patients undergoing explorative laparotomy were included. Sixty patients underwent DL in the preoperative screening for CRS and HIPEC. In one patient the DL was unsuccessful because the inability to create a pneumoperitoneum due to dense adhesions. All remaining 59 procedures were performed in daycare surgery. Complications were recorded in one patient (2%). A serosal tear at the trocar site was sutured directly without further sequelae. Seventy-six out of 333 patients (23%) were excluded for CRS and HIPEC at laparotomy because of extensive tumor dissemination: 10 out of 60 patients (17%) undergoing a preoperative DL and 66 out of 273 (24%) patients undergoing primary exploratory laparotomy (p-value = 0,22). Conclusions: diagnostic laparoscopy is a safe tool in the preoperative screening of patients considered for cytoreductive surgery and HIPEC. DL may prevent unnecessary exploratory laparotomies and it may contribute to better preoperative patient counselling and management of patients expectations, however open & closure procedures are still expected. The diagnostic value of laparoscopy should be researched prospectively.

The influence of partial hepatectomy on the post-operative course of bile salts and FGF19: a cohort study on novelregulators of liver regrowth

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Background and Aims: Systemic and hepatic bile salt levels rise shortly after partial hepatectomy (PHx) in rodents, likelyproviding input signals for the regenerative response. Deficiency of the nuclear bile salt receptor FXR or its target geneFgf15/FGF19, results in delayed liver regeneration (LR) and mortality after PHx. This is due to dysregulated bile salthomeostasis and attendant bile salt toxicity in the remnant liver, and is reminiscent of impaired LR in patients withperihilar cholangiocarcinoma (pCCA) and cholestasis. Little is known about the role of bile salt/FGF19 signaling in humanLR. Here, we explored the post-resectional course of these signaling molecules in patients with different hepatobiliarymalignancies.Methods: Data was collected of adult patients who underwent minor (<3 segments) or major hepatectomy (≥3 segments)at the Uniklinikum Aachen between 01.06.2013 and 01.02.2016 for colorectal liver metastases (CRLM), pCCA andintrahepatic CCA (iCCA). Levels of bile salts and FGF19 (regulator of bile salt synthesis, and hepatocellular mitogen) insystemic plasma were determined preoperatively and on postoperative days (POD) 1, 3 and 7.Results: Data of 121 consecutive patients were obtained (CRLM; n=88, pCCA; n=18 and iCCA, n=15). Patients withCRLM underwent minor (n=39) or major PHx (n=49), whereas all other patients underwent major PHx. At baseline, bilesalt levels were 4-fold higher in patients with pCCA in comparison with the other patient groups ($p<0.025$).Preoperatively, FGF19 was 2.7-fold higher in patients with pCCA in comparison to patients with CRLM ($p=0.018$). AfterPHx, bile salts declined on POD1 and remained low thereafter in patients with pCCA, but were not affected in the iCCAgroup. In contrast, bile salts were elevated in patients undergoing PHx for CRLM from POD3 onwards, with the largestincrease after major resection. Plasma FGF19 was transiently elevated at POD1 in patients undergoing major PHx forCRLM, with no changes in this group during the course after minor resection. Postoperatively, Fgf19 decreasedsignificantly in both pCCA and iCCA groups.
Conclusions: PHx in the CRLM group was accompanied by an increase in circulating bile salts, potentially providing astimulus for the regenerative machinery. In contrast, major resection in the pCCA group caused a pronounced dec ofcirculating bile salts and FGF19. The cause of this divergent response and possible functional consequences requirefurther investigation.

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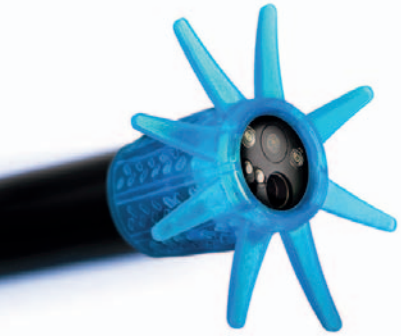

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Seventeen-Year Outcome of a Randomized Clinical Trial Comparing Laparoscopic and Conventional Nissen Fundoplication: A Plea for Patient Counselling and Clarification

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Objective: To analyze long-term outcome of a randomized clinical trial comparing laparoscopic (LNF) and conventional Nissen fundoplication (CNF) for the treatment of gastroesophageal reflux disease (GERD). Background: LNF has replaced CNF, based on positive short- and mid-term outcome. Studies with a follow-up of over 15 years are scarce, but desperately needed for patient counselling. Methods: Between 1997 and 1999, 177 patients with proton pump inhibitor (PPI)-refractory GERD were randomized to CNF or LNF. Data regarding the presence of reflux symptoms, dysphagia, general health, PPI use and need for surgical reintervention at 17 years are reported. Results: A total of 111 patients (60 LNF, 51 CNF) were included. Seventeen years after LNF and CNF, 90% and 95% of the patients reported symptom relief, with no differences in GERD symptoms or dysphagia. Forty-three and 49% of the patients used PPI's (NS). Both groups demonstrated significant improvement in general health (77% vs. 71%, NS) and quality of life (75.3 vs. 74.7, NS). Surgical reinterventions were more frequent after CNF (18% vs. 45%, P=0.002), mainly due to incisional hernia corrections (3% vs. 14%, P=0.047).
Conclusions: The effects of LNF and CNF on symptomatic outcome and general state of health remain for up to 17 years after surgery, with no differences between the two procedures. CNF carries a higher risk of surgical reintervention, mainly due to incisional hernia corrections. Patients should be informed that 17 years after Nissen fundoplication, 60% of the patients are off PPI's, and 16% require reoperation for recurrent GERD and/or dysphagia.

Long term quality of life in patients after total gastrectomy versus Ivor Lewis esophagectomy

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Treatment of gastroesophageal junction (GEJ) cancers is challenging. The therapy for these cancers mainly consist of (neo)adjuvant chemo(radio)therapy and surgery. Different surgical approaches exist and there is no evidence which is the preferred approach in terms of oncology, morbidity and quality of life. The aim of this study was to investigate the difference in the long-term quality of life in patients undergoing total gastrectomy versus Ivor Lewis esophagectomy (IL) in a tertiary referral center. Consecutive patients after either total gastrectomy or IL for distal oesophagus, GEJ or proximal gastric carcinoma were asked to fill in EORTC QLQ-C30 and EORTC QLQ-OG25 questionnaires to evaluate quality of life during the period of 2014 October – 2016 December. EORTC QLQ-INFO25 quality of life questionnaire was used to evaluate information needs of patients in both groups. All answers with a long (> 2 year) follow up after surgery were analysed. Median follow up was 4 years for total gastrectomy (N=11) and 2.5 years for IL (n=29), the median age was 64.5 years. Complaints of dyspnoea and coughing were significantly lower in the total gastrectomy group (p=0.039, 95% CI 1.02 – 8.63; p=0.003, 95% CI 7.65 – 35.40). Patients had significantly fewer complains of dry mouth after IL esophagectomy (p=0.03, 95% CI -44.26 – -2.65). There was no significant difference in global health status or physical, social or emotional functioning. Furthermore there was no difference in symptoms of dysphagia, nausea, fatigue or pain and discomfort between IL and total gastrectomy groups. After IL esophagectomy patients received more information about their disease and found the overall information more helpful (p=0.001, 95% CI 9.91 – 35.48; p=0.044, 95% CI 0.43 – 30.36). Conclusion: After a long follow up no differences in global health status or functional scales between total gastrectomy and IL esophagectomy were found. However, significant differences in some symptom scales were observed. These findings should be taken into consideration when deciding between a total gastrectomy and Ivor Lewis esophagectomy in patients where both procedures are feasible.

Factors Influencing Quality Of Life After Curative Gastrectomy For Cancer

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Objective: Gaining insight in predictive factors for HRQoL will assist in clinical decision-making and inform patients about the long-term consequences of surgery. This study aimed to evaluate health-related quality of life (HRQoL) and find predictive factors associated with HRQoL in patients who underwent gastrectomy for cancer. Methods: This cross-sectional study used prospective databases from 7 Dutch centers to include patients who underwent gastrectomy for cancer. European Organization for Research and Treatment of Cancer HRQoL questionnaires QLQ-C30 and QLQ-STO22 were sent to all patients that were alive without recurrence. The QLQ-C30 scores were compared to a Dutch reference population using one-sample t-test. Spearman's rank was used to correlate time since surgery to HRQoL, and multivariable linear regression was performed to identify predictors for better HRQoL. Results: A total of 222/274 (81.0%) patients completed the questionnaires. Median follow-up was 29 months (range 3-171); 86.9% of the responders had a follow-up >1 year. The majority of patients underwent neoadjuvant treatment (n=143), and a total gastrectomy (n=117). Minimally invasive procedure was performed in half of the cases (n=111). Compared to the Dutch reference population, patients scored significantly worse on most functional and symptom scales ($p<0.001$), and slightly worse on global HRQoL (78 vs. 74, $p=0.012$). Time since surgery did not correlate to global HRQoL (Spearman's $\rho=0.06$, $p=0.384$). Partial gastrectomy, neoadjuvant therapy, and minimally invasive surgery were associated with higher HRQoL scores ($p<0.050$). Conclusion: After gastrectomy, patients experience only a slightly impaired global HRQoL. Partial gastrectomy, neoadjuvant therapy and minimally invasive surgery are associated with HRQoL benefits.

Impact of the number of resected nodes on survival in patients treated with neo-adjuvant chemoradiotherapy and esophagectomy – a population-based cohort study in The Netherlands

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Objective To evaluate the impact of the number of resected lymph nodes on survival in patients treated with neoadjuvant chemoradiotherapy and esophagectomy. Summary background data The indication for an extended lymphadenectomy after neoadjuvant chemoradiotherapy is debated. Recent reports show no relationship between the number of resected nodes and survival. These data have not yet been evaluated in larger cohorts. Methods All patients who underwent neoadjuvant chemoradiotherapy and esophagectomy were identified from the Netherlands Cancer Registry (2005-2014). The association of the number of resected nodes on overall survival was analyzed using multivariable Cox regression analyses with stepwise backward elimination, adjusted for age, cN-stage, radicality, ypT-stage, and ypN-stage. Analyses were performed with the number of resected nodes as categorized variable (<15 vs. ≥15 resected nodes) and per 10 additionally resected nodes. Results A total of 2.698 patients were included with a median overall survival of 20 months [range 0-118]. The median number of resected nodes was 16 [interquartile range 11-22]. The number of resected nodes was significantly associated with overall survival for both the categorized variable (≥15 vs. <15 resected nodes, hazard ratio (HR) 0.83, 95% confidence interval (95%CI) 0.73-0.94) as per 10 additionally resected nodes (HR 0.90, 95%CI 0.83-0.97). The association between the number of resected nodes and overall survival was strong for adenocarcinoma (≥15 vs. <15 resected nodes; HR 0.78, 95%CI 0.68-0.91, per 10 additionally resected nodes; HR 0.88, 95%CI 0.80-0.96), and absent for squamous cell carcinoma (≥15 vs. <15 resected nodes; HR 0.95, 95%CI 0.73-1.24, per 10 additionally resected nodes; HR 0.93, 95%CI 0.81-1.07).
Conclusions This large population-based cohort study demonstrates an association between the number of resected nodes and survival, indicating a therapeutic value of extended lymphadenectomy during esophagectomy. Therefore, an extended lymphadenectomy should be the standard of care after neoadjuvant chemoradiotherapy.

A single blinded randomized controlled trial comparing semi mechanical with hand sewn cervical anastomosis after esophagectomy for cancer (SHARE-study)

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Objective: The aim of this study was to compare the leak rate between a semi-mechanical anastomosis (SMA) with the hand sewn end-to-end anastomosis (ETE) after esophagectomy with gastric tube reconstruction. Background data: The optimal surgical technique for the creation of an anastomosis in the neck after esophagectomy is unclear. No randomized controlled studies have been performed that compare a hand sewn ETE anastomosis with a SMA. Methods: Patients with esophageal cancer were scheduled for esophagectomy with gastric tube reconstruction and cervical anastomosis were eligible for participation. Patients were randomized in a 1:1 ratio to an ETE or SMA anastomosis. The primary endpoint was anastomotic leak rate defined as external drainage of saliva from the site of the anastomosis or an intra-thoracic manifestation of a leak. Secondary endpoints included anastomotic stricture at one year follow up, number of dilations, dysphagia score, hospital stay, morbidity and mortality. Patients were blinded for the type of anastomosis. Results: Between August 2011 and July 2014, 174 patients with esophageal cancer underwent esophagectomy of which 93 patients were randomized to ETE (n=44) and SMA (n=49) groups. Due to slow accrual, the study was stopped prematurely. Anastomotic leak occurred in 9 of 44 patients (20%) in the ETE group and 12 of 49 patients (24%) in the SMA group (p=0.804). There was no statistically significant difference in dysphagia at one year postoperatively (ETE 25% vs. SMA 20%; p=0.628). There was no difference in in-hospital stay, morbidity or mortality. Conclusion: SMA and hand sewn ETE technique have similar leak and stricture rates after esophagectomy with gastric tube reconstruction.

Postoperative outcomes of minimally invasive gastrectomy during the early introduction in The Netherlands: a population-based cohort study

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Objective: Between 2011 and 2015, the use of MIG increased from 4% to 53% in the Netherlands. This study aimed to compare the postoperative outcomes of minimally invasive gastrectomy (MIG) to open gastrectomy (OG) for cancer during the introduction of MIG in the Netherlands. Methods: This population-based cohort study included all patients with curable gastric adenocarcinoma that underwent gastrectomy between 2011-2015, registered in the Dutch Upper GI Cancer Audit. Patients with missing data, and patients in whom no lymphadenectomy or reconstruction was performed were excluded. Propensity score matching (PSM) was applied to create comparable groups of MIG and OG, using year of surgery and other potential confounders. Morbidity, mortality and hospital stay were evaluated. Results: Of the 1.700 eligible patients, 788 were discarded after PSM; 456 and 456 patients who underwent MIG and OG, respectively, remained. Conversions occurred in 10% of the patients during MIG. Although the overall postoperative morbidity (40% vs. 44%, p=0.254) and mortality rates (6% vs. 4%, p=0.235) were comparable between the 2 groups, patients who underwent MIG experienced less chyle leakage (1% vs., 4%, p=0.004) and wound complications (2% vs. 5%, p=0.015). Anastomotic leakage occurred in 9% of the patients after MIG, and in 6% after OG (p=0.163). The median hospital stay declined over the years for both procedures (11 to 8 days, p<0.001), but was shorter after MIG (8 vs. 10 days, p<0.001).
Conclusion: MIG was safely introduced in the Netherlands, with overall morbidity and mortality comparable to OG, less wound complications and faster recovery.

Targeted Next-Generation Sequencing of Commonly Mutated Genes in Esophageal Adenocarcinoma patients with Long-term Survival

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Objective Survival of patients with esophageal adenocarcinoma (AC) remains poor and individual differences in prognosis remain unexplained. This study investigated whether gene mutations can explain why a subset of patients with high-risk (pT3-4, pN+) esophageal AC survive past 5 years after esophagectomy. Methods A prospective database was used to identify consecutive patients who underwent resection without neoadjuvant therapy for high-risk esophageal AC and to select 6 long-term survivors (LTS) (≥5 years survival without recurrence) and 6 short-term survivors (STS) (<2 years survival due to recurrence). Targeted next-generation sequencing of 16 selected genes related to esophageal AC was performed. Mutations were compared between the LTS and STS using the Mann-Whitney U test and Fisher's exact test. Furthermore, the mutation rate in the LTS and STS was described in comparison with literature. Results A total of 48 mutations in 10 genes were identified. In the LTS, the median number of mutated genes per sample was 5 [range 0-5] and the samples together harbored 22 mutations in 8 genes: APC (n=1), CDH11 (n=2), CDKN2A (n=2), FAT4 (n=5), KRAS (n=1), PTPRD (n=1), TLR4 (n=8) and TP53 (n=2). The median number of mutated genes per sample in the STS was 4 [range 1-8] and in total 26 mutations were found in 6 genes: CDH11 (n=5), FAT4 (n=7), SMAD4 (n=1), SMARCA4 (n=1), TLR4 (n=7) and TP53 (n=5). CDH11, CDKN2A, FAT4, TLR4 and TP53 were mutated in at least 2 LTS or STS, exceeding mutation rates in literature.

Conclusion Mutations across the LTS and STS were found in 10 of the 16 genes. The results warrant future studies to investigate a larger range of genes in a larger sample size. This may result in a panel with prognostic genes, to predict individual prognosis and to select effective individualized therapy for patients with esophageal AC.

Association between waiting time from diagnosis to treatment and survival in patients with curable gastric cancer - a population-based study in The Netherlands

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Objective: In the Netherlands, a maximum waiting time from diagnosis to treatment (WT) of 5 weeks is recommended for curative cancer treatment. This study aimed to evaluate the association between WT and overall survival (OS) in patients undergoing gastrectomy for cancer. Methods: This nation-wide study included data from patients diagnosed with curable gastric adenocarcinoma between 2005-2014 from the Netherlands Cancer Registry. Patients were divided into 2 groups; patients who received neoadjuvant therapy followed by gastrectomy or patients who underwent gastrectomy as primary surgery. WT was analyzed as a categorical (≤5 weeks [reference], 5-8 weeks and >8 weeks), and as a discrete variable. Multivariable Cox regression analysis was used to assess the influence of WT on OS. Results: Among 3.778 patients, 1.701 received neoadjuvant chemotherapy followed by gastrectomy, and 2.077 underwent primary gastrectomy. In the neoadjuvant group, median WT to neoadjuvant treatment was 4.6 weeks [interquartile range (IQR)3.4-6.0], and median OS was 32 months. In the surgery group, median WT to surgery was 6.0 weeks [IQR4.3-8.4], and median OS was 25 months. For both groups, WT did not influence OS (neoadjuvant: 5-8 weeks, hazard ratio (HR)0.81, p=0.061; >8 weeks, HR0.84, p=0.324; each additional week WT, HR0.96, p=0.065; surgery: 5-8 weeks, HR0.91, p=0.175; >8 weeks, HR0.92, p=0.314; each additional week WT, HR0.99, p=0.264).
Conclusion: Longer WT until the start of curative treatment for gastric cancer is not associated with worse OS. These results could help to put WT into perspective as indicator of quality of care and reassure patients with gastric cancer.

A high lymph node yield is associated with prolonged survival in elderly patients undergoing curative gastrectomy for cancer – a Dutch population-based cohort study

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Objective: This study aimed to evaluate the influence of lymph node yield (LNY) on postoperative mortality and overall survival in elderly patients with gastric cancer. Methods: This population-based study included data of patients who underwent curative gastrectomy for adenocarcinoma between 2006-2014 from the Netherlands Cancer Registry. Patients were divided into groups based on age (<75: young, and ≥75: elderly). LNY was analyzed as a categorical (low: <15, intermediate: 15-25, and high: >25 nodes), and as a discrete variable. Multivariable analysis was used to evaluate the influence of LNY on 30-day and 90-day mortality, and overall survival. Results: A total of 3.764 patients were included; 2.387 (63%) were young, and 1.377 (37%) were elderly. The median LNY was 14 in young, compared to 11 in elderly patients (p<0.001). In elderly patients, 851 (62%) had a low, 333 (24%) an intermediate, and 174 (13%) a high lymph node yield. Multivariable analysis demonstrated that in the elderly patients, a higher LNY was associated with a prolonged overall survival (low: reference; intermediate HR 0.74, 95%CI [0.62-0.88], p<0.001; high HR 0.59, 95%CI [0.45-0.78], p<0.001), but not with 30-day (p=0.940) and 90-day mortality (p=0.573). For young patients, these results were comparable.
Conclusion: In young as well as elderly patients, a high LNY is associated with prolonged survival but not with an increase in postoperative mortality. Therefore, an extensive lymphadenectomy is the preferred strategy for all patients during gastrectomy to provide an optimal oncological result.

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A propensity score matched analysis of open versus minimally invasive transthoracic esophagectomy in The Netherlands

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Randomized controlled studies have shown that minimally invasive esophagectomy (MIE) is associated with reduced pulmonary complications and shorter hospital stay as compared to open esophagectomy (OE). The aim of the study was to compare OE with MIE in a population based setting. Patients who underwent transthoracic esophagectomy for cancer between 2011 and 2015 were selected from the national Dutch Upper GI Cancer Audit. Excluded were hybrid, transhiatal or emergency procedures. Propensity score matching was used to correct for differences in patient characteristics. The primary endpoint was pulmonary complications within 30 days after the operation and secondary endpoints were morbidity, mortality (30 day and/or in hospital), convalescence after surgery and pathology. Patients in the OE (N=500) group had more advanced TNM stage and tended to have more comorbidities compared to MIE (N=1227). After propensity score matching, the percentage of patients with one or more complications was 62.6% in the OE group (N=433) and 61.9% in the MIE group (N=433) (p=0.833). Mortality was 3.5% in the OE group and 5.3% in the MIE group (p=0.184). The rate of pulmonary complications was not different between the groups: 35.1% (OE) versus 35.6% (MIE) (p=0.887). Anastomotic leak rates were 15.2% for OE and 22.2% for MIE (p=0.009). Median hospital stay was shorter for the MIE group (12 versus 14 days (p<0.001) but the readmission rate was higher: 16.9% (MIE) versus 12.2% (OE) (P=0.052). Percentages of R0 resections (93%) did not differ between the groups. The median lymph node count was 18 (OE) versus 20 (MIE) (P<0.001). Mortality and pulmonary complications were similar for OE and MIE. Anastomotic leaks was more frequent in patients after MIE. MIE is associated with a shorter hospital stay but at the cost of higher readmission rate.

Impaired postprandial colonic response in the presence of coordinated propagating colonic contractions suggests an extrinsic neuropathy in children with intractable functional constipation

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High-resolution colonic manometry (HR-CM) enables detailed description of colonic motor patterns. In a recent study using HR-CM, a novel motor pattern was described in healthy adults; pan-colonic pressurizations. This motor pattern consists of pressure events that occur simultaneously across all colonic sensors, are associated with anal sphincter relaxation and increase in number after a meal. In adults with intractable functional constipation (FC) this motor pattern was significantly less common. In children, pan-colonic pressurizations have not been described yet. Our aim was to determine whether pan-colonic pressurizations could be identified in children with intractable FC. We performed a retrospective analysis of children with FC who underwent HR-CM. A solid-state catheter with 36 sensors (spaced at 3 cm intervals) had been placed into a prepared colon. Colonic manometry recordings lasted 2 hours before and after a meal, followed by 1 hour of recording after bisacodyl was infused into the proximal colon. To describe the postprandial response, dominant frequencies of contractile activity were quantified for 1 hour before and after initiation of the meal. All recordings were examined for the presence of pan-colonic pressurizations (peak amplitude <50mmHg, occurring simultaneously across all colonic sensors) and high amplitude propagating contractions (HAPCs; peak amplitude ≥75 mmHg, migrating aborally over ≥15 cm). We included 23 children (median age 11.6 years, 13 male). The normal post-prandial increase in distal colonic 2–4 cycle per minute activity was diminished or absent. We were unable to find evidence of pan-colonic pressurizations. In most children (n=20, 87%) antegrade rapidly propagating pressure waves were observed. These motor patterns (previously labeled as a long single motor patterns) were recorded at a median of 2.9/hour (IQR 1.5-16.0) prior to the meal and their number did not increase after the meal; 4.4/hour (IQR 0.9-10.6). HAPCs were observed in 4 & 6 children before and after the meal respectively and in 18 children after bisacodyl. In all 5 children without HAPCs, long single motor patterns were recorded and in all 3 children without long single motor patterns, HAPCs were observed.
Conclusion: Our data indicate that pan-colonic pressurizations are absent in children with intractable FC. However, we recorded coordinated propagating motor patterns (long single motor patterns, HAPCs or both) in all children, indicating a preservation of neural pathways within the enteric nervous system. The impaired colonic response to a meal supports the hypothesis that an extrinsic neuropathy may exist in children with intractable FC.

Esophageal stasis on barium esophagogram in achalasia patients without symptoms after treatment does not predict symptom recurrence

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After achalasia treatment, some patients have poor esophageal emptying without having symptoms. There is no consensus on whether or not to pre-emptively treat these patients. We hypothesized that, if left untreated, these patients will experience earlier symptom recurrence than patients without stasis. We aimed to compare asymptomatic patients with and without stasis (no barium column after 5 min) after treatment. We retrospectively reviewed the prospectively collected data of 99 adult achalasia patients who were in clinical remission (Eckardt ≤ 3) at 3 months after treatment. Patients were divided into two groups, based on presence or absence of esophageal stasis on a timed barium esophagogram performed after 3 months. Patients were treated with pneumodilation, peroral endoscopic myotomy or Heller myotomy. Before initial treatment, there was no difference in age, gender, achalasia subtypes, treatment allocation, Eckardt score, LES relaxation, barium column height and maximum esophageal diameter between the groups. After three months, the median barium column height at 5 min was 4.4 cm (IQR 2.6 – 6.2) in the group with stasis. The distal esophagus was significantly wider in patients with stasis (2.5 cm (IQR 2 – 3.9)) than in patients without stasis (2 cm (IQR 1.7 – 2.3)), $p < 0.001$. The Eckardt score and the number of patients with inadequate LES relaxation after treatment were comparable between the groups. Two years after initial treatment, in patients with stasis, the esophageal diameter had increased from 2.5 to 3.0 cm, which was significantly wider than in patients without stasis (1.8 cm; IQR 1.5-2.7), $p < 0.001$. Also, they still had significantly more stasis (3.5 cm; IQR 1.9-5.6) than the no-stasis group (still 0 cm; IQR 0-0) $p < 0.001$. The proportion of patients that received additional treatment was identical in the stasis group (8/46 (17%) patients) and the no-stasis group (10/53 (19%) patients), $p = 1.00$. Also, median time to retreatment was comparable between patients with stasis (8 months; 95% CI 5.1 – 10.9) and patients without stasis (13 months; 95% CI 4.7 – 21.3); $p = 0.893$. After two years, there was still no difference in Eckardt score, quality of life and reflux symptoms between the two groups.

Conclusion Although patients with stasis initially had a wider esophagus and two years after treatment also had a higher degree of stasis and a more dilated esophagus, compared to patients without stasis, they did not have a higher chance of requiring retreatment. We conclude that stasis in symptom-free achalasia patients after treatment does not predict treatment failure within two years and can therefore not serve as a sole reason for retreatment.

Development of a new diagnostic test for esophageal food sensitization in EoE patients: the Esophageal Prick Test (EPT)

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Skin and serum IgE tests perform poorly as tools to guide elimination diets in eosinophilic esophagitis (EoE). We hypothesize that a test detecting local esophageal sensitization will have better clinical relevance in EoE. The aim of this study was to investigate the feasibility of testing sensitizations on esophageal tissue by local allergen challenge; the Esophageal Prick Test (EPT). In this prospective study we included adult EoE patients and controls. Specific serum IgE and skin prick tests (SPT) were performed for the same allergens as the EPT. During gastroscopy 6 diluted allergen extracts (wheat, milk, soy and 3 allergens based on history), a negative control (0.9% NaCl) and a positive control (diluted histamine) were injected at different sites in the esophagus, using an injection needle. Local reactions were recorded up to 20 minutes. A second gastroscopy was performed after 24 hours to evaluate delayed responses. For an in vitro allergen challenge 8 biopsies per subject were placed in HBS solution. Tryptase release in the solution was measured by ELISA at base and after 20 minutes of allergen incubation. We included 8 EoE patients, age 49 (22 – 54) years, of whom 6 (75%) had an atopic background and 3 healthy controls. Skin and serum test were positive for 24 allergens in 6 patients and negative in all controls. No systemic anaphylactic reactions occurred in response to the EPT. In 5/8 patients an acute response (< 2 min) consisting of complete luminal obstruction and blanching of the mucosa was observed after esophageal injection (soy, banana, apple, oats, hazelnut). During the next endoscopy the obstruction was dissolved. In two other patients an erythematous wheal was visible at the injection site (peach and walnut). The EPT was negative in controls. Tryptase levels were increased by at least 2-fold in the medium of 21/77 (27%) in vitro challenged biopsies and in 0/11 of the biopsies that were challenged with 0.9% NaCl. Only 6/24 allergens that were tested positive on skin or serum corresponded with the positive tested allergens on the in vitro challenge. This study shows that an allergy test based on esophageal tissue is safe, feasible and may have additional value above conventional allergy tests based on serum and skin. Both acute and delayed responses were observed. The allergens that triggered an acute response on EPT were in agreement with the reported implicating foods but different from those that triggered a delayed response. The EPT deserves further exploration as it can potentially guide elimination diets.

Acid and non-acid reflux as a cause of chronic unexplained cough

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Persistent cough is a frequent problem which often results in limitations of quality of life. Gastroesophageal reflux is considered to be a significant contributing factor to chronic unexplained cough. Patients presumed to have reflux-induced cough are treated as such despite the limited treatment efficacy in this population. The aim of this study was to assess the yield of 24-hour ambulatory pH-impedance-pressure monitoring in finding a causal relationship between chronic cough and reflux. Twenty-four-hour ambulatory pressure-pH-impedance monitoring was used to study 192 patients with chronic cough. Patients were recruited through the outpatient clinic and through referral in three different centers. Manometric tracings were used to detect all cough bursts and pH-impedance monitoring was used to detect reflux episodes, including non-acid reflux. A cough burst was defined as ≥2 rapid simultaneous pressure peaks. The symptom association probability (SAP) was used to determine a temporal relationship between reflux and cough. In the 192 patients studied (70.3% female, median age 57.5 years) a total of 7472 reflux episodes were detected, of which 71.5% were acidic. A total of 6442 cough burst episodes were detected manometrically, of which only 59% were registered by the patients. The majority of the patients (52.1%) did not report typical reflux symptoms. Pathological distal acid exposure time (>6%) was found in 21.4% of the patients. A total of 21.9% of all cough burst episodes were temporally associated with reflux, with 48.6% of these being reflux-cough episodes and 51.4% cough-reflux episodes. A diagnosis of reflux-induced cough (positive SAP for reflux-cough sequence) was made in 25.5% of the patients. Interestingly, if only acid reflux episodes were used, 22.4% of these patients would not have been diagnosed. Significantly more patients diagnosed with reflux-induced cough had a pathological distal acid exposure time and typical reflux symptoms in comparison to patients without the diagnosis. A diagnosis of cough-induced reflux was made in 24.0% of the patients. In approximately one quarter of the patients with chronic unexplained cough, reflux can be identified as a probable causative factor. This explains the observation that the vast majority of patients with unexplained chronic cough does not benefit from anti-reflux therapy. Ambulatory 24-hour pH-impedance-pressure monitoring provides a means to identify patients who are likely to have reflux-induced cough.

Age-related changes in abdominal pain in healthy individuals and IBS patients

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The world population is aging, resulting in increased prevalence of age-related comorbidities and health care costs. Limited data are available on intestinal health in elderly populations. Structural and functional changes, including altered visceroperception, may lead to altered bowel habits and abdominal symptoms in healthy individuals and irritable bowel syndrome (IBS) patients. Our aim was to explore age-related changes in gastrointestinal symptoms and abdominal pain scores. Base data of an intervention study comparing 52 healthy young adults (18-40 yrs) versus 48 healthy elderly (65-75 yrs) was used. In 10 young adults and in 10 elderly, gene transcription of transient receptor potential Ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1), visceral pain-associated receptors, were investigated by quantitative RT-PCR in sigmoid biopsies. GAPDH was used as reference gene. Moreover, IBS patients (n=445) diagnosed using the Rome III criteria and controls (n=205) participating in the Maastricht-IBS cohort, were divided into three age groups: young adults (20-39 yrs), middle-aged adults (40-59 yrs), and elderly (60-79 yrs). A subset of 241 IBS patients and 100 controls underwent a rectal barostat procedure to assess visceral hypersensitivity. Demographics and gastrointestinal symptom scores were collected in both studies using validated questionnaires. Relative TRPA1 gene transcription was significantly lower in healthy elderly compared with healthy young adults (1.20 ± 0.030 vs 1.25 ± 0.031, $p<0.01$), whereas no significant difference was found for TRPV1. In all study populations, elderly groups showed significantly lower scores for abdominal pain ($p<0.001$) and indigestion ($p<0.05$) compared with young adults. In addition, older IBS patients had significantly lower scores for diarrhea ($p<0.001$) and constipation ($p<0.05$) compared with young IBS patients. Visceral hypersensitivity was less common in older IBS patients compared with young IBS patients (57.4% vs 26.5%, $p<0.001$). Our findings show an age-related decrease in abdominal pain perception. This may be attributed to biological changes, such as decreased TRPA1 receptor expression in intestinal epithelium, or to altered coping strategies during aging. Further studies are needed on underlying mechanisms and the association with intestinal health.

The predictive value of colonic transit time for colonic motor abnormalities on colonic manometry in patients with chronic constipation

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Colonic manometry (CM) is of additive value in the diagnostic workup of colonic motility in chronic constipated patients. However, CM is an invasive, demanding procedure and is not readily available in all centers. Colonic transit time (CTT) as measured with radio-opaque markers is a less invasive procedure but it is claimed that colonic motor disturbances occur in both normal- and slow-transit and therefore, the relationship between colonic motor disturbances on CM and colonic transit time remains unclear. The aim of this study was to assess the predictive value of CTT for colonic motor abnormalities on 24-hours colonic manometry in patients with chronic constipation in order to evaluate whether CTT studies might be helpful in determining for which patients CM is indicated.Prospectively collected data from patients undergoing both a CTT study as well as 24-hours CM in our tertiary referral center were reviewed. Healthy volunteers were studied to obtain control values. CTT was measured using radio-opaque markers (X ray at day 4 after ingestion of 20 markers at day 0). A catheter with 6 solid-state pressure sensors was positioned endoscopically and clipped to the mucosa in the right colon in order to perform 24-hours ambulatory CM. CM was defined as abnormal when less than three high-amplitude propagating contractions (HAPC's), i.e. propagating waves with amplitude ≥80 mmHg over at least three sensors, were identified. Results are shown as means±SD and proportions and were compared using independent-samples T-test and chi square statistics. Data of 71 patients (62 women; 44.6±14.7 years) and 12 healthy controls (10 women; 47±14.4 years) were evaluated. Slow colonic transit (SCT) was based on CTT. Mean number of HAPC's per 24 hours was significantly lower in patients showing SCT compared to patients with normal colonic transit and controls (1.9±2.3 vs. 4.8±1.6 and 5.25±3.0, $p<0.001$ and $p<0.001$ respectively). In total, 59 patients showed SCT, of which 40 (67.8%) showed abnormal CM. All 12 patients with normal colonic transit at CTT had normal CM. Therefore, the positive predictive value (PPV) of CTT for colonic hypomotility was 67.8% and the negative predictive value (NPV) was 100%. This study shows that in the evaluation of patients with chronic constipation normal colonic transit, as measured by radio-opaque marker study, excludes abnormal colonic manometry (i.e. based on number of HAPC's), whereas slow transit is a strong indicator for finding motor disturbances on colonic manometry. Therefore, colonic transit studies seem helpful in selecting patients with chronic constipation for colonic manometry to further characterize colonic motility.

Development, Content Validity and Cross-Cultural Adaptation of a Patient-Reported Outcome Measure for Real-time Symptom Assessment in Irritable Bowel Syndrome: MEASuRE

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End-of-day questionnaires, which are considered the gold standard for assessing abdominal pain and other gastrointestinal (GI) symptoms in Irritable Bowel Syndrome (IBS), are influenced by recall and ecological bias. The Experience Sampling Method (ESM) is characterized by random and repeated assessments in the natural state and environment of a subject, and herewith overcomes these limitations. An explorative study from our group demonstrated that ESM measures IBS symptom patterns more accurately compared to retrospective end-of-day questionnaires. Hereafter, we conducted focus group interviews in order to develop a patient-reported outcome measure (PROM) suitable for symptom assessment using ESM. This report describes the further development, content validity and cross-cultural adaptation of this momentary PROM. In addition to focus group meetings an expert meeting with international experts in the fields of neurogastroenterology and pain was arranged in order to obtain experts' input on the relevance of all individual items and the potential necessity for additional items. Back-to-back translation of the selected items to English for the UK and USA and to Swedish was performed. Cognitive interviews with individual, native-speaking IBS patients (ROME III criteria) were performed to assure on patients' understanding with the PROM in each language. Finally, a smartphone-based application was developed specifically for this electronic PROM using experience sampling methodology. Focus group interviews originally revealed 43 items, categorized into five domains: physical status, defecation, mood and psychological factors, context and environment, and nutrition and substance use. Experts reduced the number of items to 32, taking into account the relevance of each item with regards to momentary assessment of individual symptom patterns. Cognitive interviewing after translation resulted in a few slight adjustments regarding linguistic issues, but not regarding content of the items. The different translations were implemented in the smartphone application (i.e. MEASuRE). In this study the further development of an ESM-based PROM, suitable for momentary assessment of IBS symptom patterns was described, taking into account content validity as well as cross-cultural adaptation. This instrument has the advantage to capture the complexity of individual IBS symptom patterns in daily life rather than just a snap shot. It also has the potential to implement personalized therapeutic strategies with increasing patient empowerment. An international, multicenter study aiming to validate this PROM in a large, heterogeneous IBS population is currently ongoing.

Large Increase in Incidence of Eosinophilc Esophagitis over the Last 20 Years in the Netherlands: Results from a Nationwide Pathology Database

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Since EoE was first described as a distinct entity, its incidence has increased over the past decades. Large differences in incidence have been reported. Most epidemiologic data have been acquired from single center studies over a short period of time, which may explain the heterogeneous incidence figures. Therefore, the aim of our study was to estimate nationwide incidence of EoE over the last 20 years in the Netherlands. The Dutch national database of pathology (PALGA) was queried to identify all pathology reports describing esophageal eosinophilia over the last 20 years. Cases were eligible if EoE was confirmed by the pathologist and/or if biopsy specimens sampled from the proximal, mid- and distal esophagus showed more than 15 eosinophils per high power field (HPF). Using the annual population data of the Netherlands, the incidence of EoE was calculated. Between 1996 and 2015, the search yielded 11,068 pathology reports describing esophageal eosinophilia. Consequently, EoE was diagnosed in 2161 patients, of whom 1796 (83%) were male and 365 (17%) children. The mean age at diagnosis was 37.5 (SD 19) years. The incidence of EoE increased from 0.01 (95% CI 0-0.02) in 1996 to 2.1 (95% CI 2.05-2.23) per 100,000 persons in 2015. Incidence was higher in males than females, 3.02 (95% CI 2.66-3.41) versus 1.14 (95% CI 0.93-1.38) per 100,000 persons, odds ratio (OR) 2.66 (95% CI: 2.10-3.36) and higher in adults than in children, 2.23 (95% CI: 1.99-2.49) versus 1.46 (95% CI: 1.09-1.91) per 100,000 persons, OR 1.78 (95% CI 1.32-2.40). The highest incidence of 5.35 per 100,000 persons (95% CI 3.93-6.78) was observed in males between 30 and 40 years of age in 2015. Remarkably, 46% of all EoE cases were diagnosed in the last three years (2013-2015). There was no seasonal variation in the number of newly diagnosed cases of EoE.
In conclusion, the nationwide incidence of EoE in the Netherlands has increased in the last 20 years more than 200 times and still continues to rise. With the current incidence rates, EoE cannot be designated as an orphan disease anymore.

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PEG-J for gastroparesis; the ultimate solution?

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Gastroparesis is characterized by abnormal gastric motor function with delayed gastric emptying in the absence of mechanical obstruction. In our tertiary referral patients are treated with a stepwise approach, starting with dietary and lifestyle advice and prokinetics followed by pyloric botulinum toxin. When these initial measures fail, in the presence of malnutrition, one of the following interventions are considered: three months naso-duodenal tube feeding with 'gastric rest' and placement of a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). Our primary aim was to evaluate the effect of nutritional treatment entities in patients with gastroparesis who fail previous treatments, on weight and Body Mass Index and symptoms. Prospectively collected data of all referred gastroparesis patients between 2008 and 2016, were reviewed. A total of 101 gastroparesis patients (71% female, 20-86yrs, mean 55yrs) were analyzed. Etiologies were idiopathic (37%), diabetes mellitus (30%), post-surgical (27%) and other (7%). Of the 101 patients, 51 patients had adequate responses to dietary advice and prokinetics, not requiring further therapeutic interventions. For the remaining 60 patients, various treatments were used. With respect to nutritional interventions, 36 patients were treated with three months of gastric rest by complete nasoduodenal tube feeding. Enteral tube feeding was well accepted, occlusion occurred in 8% of patients. Mean weight gain in symptom responders was 3.5% (2.4kg, p=0.02), in non-responders 3.7% (2.4kg, p=0.01). These 19 patients with insufficient symptomatic response after 3 months gastric rest continued treatment with enteral feeding through PEG-J. mA significant weight gain of 8.2% was seen (mean 5.0kg, range -6% to +29%), p=0.003) within 3-6 months after PEG-J placement. Thereafter only 3 patients (16%) have been able to resume complete oral intake and the PEG-J was removed after 11 months. In 84% of patients the PEG-J is still in use, with a mean treatment time of 894 days. Over 75% of patients report adequate effect on symptoms. Most frequent complication was luxation of the jejunal extension to the stomach (32% of patients). Other complications were peristomal infection (11% within 30 days, 16% after 30 days) and buried bumper (16%). This study describes the sequelae of a large group of tertiary referral patients treated with PEG-J treatment. In gastroparesis patients who failed all previous treatment, PEG-J is an excellent option to regain and maintain adequate nutritional status with marked symptom control.

Impact of anorectal complaints on quality of life in patients with inflammatory bowel disease: a survey of the Dutch National Crohn's and Colitis organization

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Anorectal complaints occur in a considerable group of patients with IBD. There is a dearth of evidence relating to the impact of these complaints on IBD patients' lives. We aimed to survey the effect of anorectal complaints on quality of life in a large cohort of patients who engaged in the Dutch Crohn's and Colitis organisation (CCUVN). In October 2016, the CCUVN had a membership database of 10.047 patients. A comprehensive study questionnaire was sent out on by the CCUVN in January 2015 and October 2016 to a voluntary panel, which consisted of 1.710 CCUVN patients. The panel is represented by patients who voluntary participate in on surveys with regard to disease related subjects. Inclusion criteria were age over 18 years old and a self-reported diagnosis of Crohn's disease (CD), ulcerative colitis (UC) or IBD-unclassified (IBD-U). The survey included the St. Marks incontinence score, peri-anal disease activity index, faecal incontinence quality of life (FI-QOL) questionnaire and the SF-36 questionnaire. Multiple imputation was used for covariates with missing data. Multivariate regression analysis was performed. A total of 1094 patients (64%) responded the on survey. Mean age was 47 years (range 18-87), CD diagnosis was predominant (621 CD patients (57%), 431 UC patients (39%) and 42 IBD-U patients(4%)) and diagnosis was established for a mean period of 13 years (interquartile range 3 – 19 years). Active perianal disease was present in 243 CD patients (39%) and perianal surgery (abscess- or fistula-related) was previously performed in 153 (25%). Faecal incontinence (≥ 1 episode per month) was reported in 305 CD (58%), 230 UC (56%) and 20 IBD-U (51%) patients. Weekly episodes occurred in 41 CD (8%), 22 UC (5%) and 3 IBD-U (8%) patients (mean St. Marks incontinence score 14). FI-QOL scores were not different between the different diagnoses. Multivariate regression analysis (adjusted for gender, diagnosis and previously performed abdominal operations) showed a reduced total SF-36 score in patients with faecal incontinence (β -8.57 [-11.33; -5.81]; p<0.0001) and active perianal disease (β -4.13 [-7.35 ; -0.91]; p=0.01). A better score was reported in UC patients compared to CD patients (β 3.53 [0.48 – 6.58]; p=0.02). Previously performed perianal surgery was not associated with SF-36 score in the multivariate analysis. Conclusions: Anorectal complaints have a substantial impact on the quality of life in patients with IBD, with a (usually unmet and) clear need to treat. More awareness for this highly distressing and most commonly cumbersome treatable disease manifestation is needed.

Risk of malignant and non-malignant complications of the rectal stump in patients with Inflammatory Bowel Disease

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A considerable number of patients with inflammatory bowel disease (IBD) have refractory disease and therefore often require a subtotal colectomy with construction of an ileostomy. When pouch surgery is not appropriate this can be a definitive procedure. Due to the potential risk of pelvic nerve damage and pelvic septic complications, the rectum is often left in situ. The primary objective of this study was to assess the incidence rate of non-malignant and malignant complications of RS patients with IBD. Secondary objectives were to evaluate the management strategies after colectomy in IBD patients. In a single tertiary referral Center, a diagnostic coding system was used to identify all patients with IBD and a history of colonic resection. Patients were stratified according to the presence of intestinal continuity (ileorectal anastomosis [IRA] and ileal pouch anal anastomosis [IPAA]) or discontinuity (ostomy with or without remaining RS). Additional demographic and clinical data were collected for patients with bowel discontinuity. Endoscopically confirmed diversion colitis, stenosis or shortening of the colon were defined as benign RS complications. Neoplasia was defined as the presence of low-grade dysplasia (LGD), high-grade dysplasia (HGD) or carcinoma in the RS. Out of 1787 patients with IBD, 352 had 1 or more colonic resections. The final anatomical status was IRA in 25 patients (7.1%), IPAA in 89 patients (25.3%) and a colo-/ileostomy in 238 patients (67.6%). In 197 patients a RS had been in situ for more than 1 year. Out of these 197 patients, 48 had UC (24.4%), 140 had CD (71.0%) and 9 had IBD-unclassified (4.6%). Sixty-nine patients were male (35.0%) and the mean age at colectomy was 38.8 years. Out of 144 patients with endoscopic follow-up, diversion colitis occurred in 115 patients (79.7%) and RS stenosis occurred in 56 (38.9%) patients. In patients with follow-up of the RS (median: 8 years, range 0-39), 5 carcinomas, 1 case of HGD and 6 cases of LGD occurred. Incidence rates were 3.0 and 7.1 per 1000 patient-years of follow-up, for cancer and all neoplasia, respectively. In 45 patients with a RS (22.8%) a completion proctectomy was performed. The main reasons for excision of the RS were treatment or prevention of carcinoma in 7 patients (15.6%) and persisting complaints of the RS such as bloody and mucopurulent rectal discharge in 31 patients (68.9%).
Conclusions: In patients with IBD and a retained RS after colectomy a high prevalence of diversion colitis and RS stenosis was observed during endoscopic follow-up. Cancer occurred in 5 out of 197 patients with an incidence rate of 3.0 per 1000 patient-years.

Long-term outcomes after restorative proctocolectomy and ileal pouch-anal anastomosis in children compared to adults

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Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for therapy refractory ulcerative colitis and familial adenomatous polyposis (FAP). There are only a few studies addressing the outcome of IPAA in children compared to adults. This complicates decision making in children with therapeutic refractory UC or FAP. Therefore, we aimed to compare adverse events and pouch function between pediatric and adult patients who underwent IPAA. METHODS: In this cohort study, all consecutive children (<18 years) and adults with a diagnosis of inflammatory bowel disease or FAP that underwent IPAA were included (2000–2015). The IPAA's were performed in a Dutch tertiary referral center by the same team of colorectal surgeons in all subjects in this time period (IPAA's 30–35/year). Demographic and surgical characteristics, and adverse events were obtained by chart review. Pouch function was assessed by phone interview using the Pouch Function Score (PFS, scale 0–30). Differences in adverse events between pediatric and adult patients were analyzed using multivariate regression analysis, corrected for the moment of enrollment during the study period. RESULTS: In total, 445 patients underwent IPAA: 41 pediatric (median age 15 years) and 404 adult patients (median age 39 years). Median follow-up was 24 months (IQR 8–68). In pediatric patients, overweight, previous abdominal surgeries, open procedures (i.e. colectomy) and defunctioning ileostomy were less prevalent compared to adult patients ($p<0.05$). All other characteristics, including type of diagnosis and duration of follow-up, were similar ($p>0.05$). The occurrence of anastomotic leakage, surgical related fistulas, chronic pouchitis and Crohn's of the pouch (in IBD patients) was not associated with pediatric age, neither was pouch failure on the long-term. Pediatric age at IPAA was an independent risk factor for developing anastomotic strictures (OR: 4.2 [95%CI: 1.1 – 15.8]; $p = 0.032$). These strictures were successfully treated through a single dilatation in all pediatric and 73% of adult patients. Current pouch function was similar between pediatric and adult patients (median PFS 5.0 vs. 6.0, $p = 0.164$).
CONCLUSION: Long-term pouch failure rates and pouch function were similar between pediatric and adult patients. There is no need for a more cautious attitude in the application of IPAA in pediatric patients based on concerns of poor outcome on the long term.

Pregnancy in IBD: direct effect of sex-hormones on epithelial barrier function

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Background Inflammatory bowel disease (IBD) is a chronic inflammatory diseases of the gastrointestinal tract. The epithelial barrier is known to be compromised in active IBD. Previously we have demonstrated that some of the patients can stop maintenance therapy during pregnancy without a disease relapse. While pregnancy is an immune-tolerant state, the direct effect of pregnancy hormones on epithelial barrier cells is unknown but might play an important role in the favorable disease course during pregnancy. We aimed to study the direct effect of pregnancy hormones on barrier cells and their function. Methods The effect of progesterone and estrogen on intestinal epithelial cell barrier functions was investigated using human colonic adenocarcinoma cell lines (CACO2 and HCT116) as model system. Endoplasmic reticulum (ER) stress (earlier shown to induce epithelial cell death, barrier dysfunction and pro-inflammatory responses in IBD) was induced by treatment of cells with tunicamycin, followed by Western blot analysis of the ER stress marker GRP78. Epithelial barrier function was analyzed by transepithelial electrical resistance measurement (TEER), wound healing was determined by scratch assay, and cell viability was measured by MTT assays. IL-8 production by CACO2 cells was determined by enzyme-linked immuno sorbent assay (ELISA). Results Progesterone and estrogen were able to reduce tunicamycin-induced ER stress in intestinal epithelial cells. This effect was dependent on the amount of ER stress induced and GRP78 reduction was most efficient in CACO2 cells (progesterone p=.029, estrogen p=.02). Scratch assays showed a faster wound closure in the presence of pregnancy hormones (estrogen and progesterone double treatment, p=.034 for CACO2 cells and p=.019 for HCT116 cells). This was not due to increased proliferation, as determined by MTT assay. Barrier function as determined by TEER measurement improved in the presence of estrogen and progesterone. IL-8 cytokine production by CACO2 cells increased in the presence of progesterone alone and in combination with estrogen.
Conclusion Our study shows that estrogen and progesterone alleviate ER stress, increase IL-8 production, stimulate wound healing and increase barrier function of epithelial cells, thereby suggesting that in toto these pregnancy hormones can have beneficial effects on disease activity by positive modulatory action on the intestinal epithelial lining.

Fecal calprotectin accurately predicts symptomatic relapse in children and adolescents with inflammatory bowel disease in clinical remission

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In children and adolescents with inflammatory bowel disease (IBD) in clinical remission, it is difficult to predict when a relapse will occur. Reliable data on the value of biomarkers of inflammation for predicting relapse in these young patients are lacking. Therefore, we aimed to investigate the predictive value of fecal calprotectin (FC) and CRP for symptomatic relapse in pediatric IBD in clinical remission. METHODS: In this cross-sectional cohort study, patients aged <18 years with Crohn's disease or ulcerative colitis in clinical remission ≥3 months were included. At baseline, clinical and biochemical disease activity were assessed using the abbreviated-Pediatric Crohn's Disease Activity Index (aPCDAI) or Pediatric Ulcerative Colitis Activity Index (PUCAI), and FC and CRP, respectively. Clinical remission was defined as an aPCDAI or PUCAI <10. Disease course over the subsequent 12 months was retrospectively assessed. Symptomatic relapse was defined as an aPCDAI or PUCAI score ≥10, with the need for treatment intensification. Multivariate Cox regression analysis was performed to evaluate whether FC and CRP were independent predictors for symptomatic relapse. RESULTS: In total, 114 patients in clinical remission were included (56% males; median age 14.9 years). Base FC level was higher in patients that developed a relapse compared to patients without symptomatic relapse (median 367µg/g vs. 117µg/g, p=0.014). FC level was an independent predictor for symptomatic relapse within 6 months from base (HR per 100µg/g: 1.15 [95%CI: 1.06–1.24], p<0.001), corresponding to a 15% increase in the probability of relapse per 100 µg/g increment, with fair predictive accuracy (AUC: 0.77, p<0.001). The optimal FC cut-off was 350 µg/g, with a sensitivity and specificity of 76% and 78%, respectively. Base CRP level did not differ between patients with or without symptomatic relapse. CRP level was an independent predictor for symptomatic relapse within 6 months from base (HR per 1mg/L: 1.10 [95%CI: 1.01–1.19], p=0.025), corresponding to a 10% increase in the probability of relapse per 1 1mg/L increment, with poor predictive accuracy (AUC: 0.67, p=0.036). The optimal CRP cut-off was 0.6 mg/L, with a sensitivity and specificity of 88% and 38%, respectively. CONCLUSIONS: Levels of FC and CRP were both independent predictors of symptomatic relapse in pediatric IBD in clinical remission, with superior predictive test characteristics of FC. High FC levels at routine measurement justify careful disease monitoring and evaluation of current treatment.

Fecal Loss of Infliximab is Underestimated due to Proteolysis

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Patients with acute severe ulcerative colitis (ASUC) often do not respond to Infliximab (IFX) induction therapy. In an earlier study we showed that IFX could be measured in feces of these patients, with the highest fecal IFX concentrations in the first days after the first infusion. This 'fecal loss' of IFX is believed to contribute to primary non-response. The mucosa of patients with inflammatory bowel disease is characterized by overexpression of proteases (metalloproteinases (MMPs) and high levels of proteases are found in feces. Therefore fecal IFX concentrations from patients with ASUC may be underestimated due to proteolysis. Fecal samples of 5 patients with ASUC not receiving biological therapy, were homogenized (0.2 gram/ml) in buffers containing general protease inhibitors (EDTA free, Sigma-Aldrich®), Marimastat, broad spectrum MMP inhibitor ((Sigma-Aldrich®), a combination of the two, or no protease inhibitors at all. Ten µg/ml IFX was added to the fecal supernatants, after which samples were stored at different temperatures (4°C, 22°C and 37°C) for 24 hours. IFX concentrations were measured using validated ELISA technology by Sanquin Laboratories (Amsterdam, The Netherlands). In samples without protease inhibitors stored at 37°C IFX concentrations were (median, IQR) 0.2 µg/ml (0.1-5.2). After addition of protease inhibitors, higher IFX concentrations were observed: 0.7 µg/ml (0.5-5.9) for the general protease inhibitor, 0.2 µg/ml (IQR 0.1-4.1) for Marimastat and 0.6 µg/ml (IQR 0.5-3.4) for the combination (figure 1). In samples without protease inhibitor, the highest concentrations were measured after incubation at a temperature of 4°C (0.8 µg/ml; 0.3-7.5) compared to the lowest concentrations measured after incubation at 37°C (0.2 µg/ml; 0.1-5.2). Overall, the IFX concentrations that were measured were > 10 times lower than what was 'spiked' to the samples. Degradation of IFX by fecal proteases is highly relevant, since <10% of IFX added to feces could be measured with an ELISA test. This indicates that fecal loss of IFX in these patients is strongly underestimated. In order to maximize measurements of fecal IFX in patients with IBD samples should be processed in the presence of regular protease inhibitors and at a low temperature (4°C), to minimize proteolytic degradation. In real life, most of the degradation however may already take place in the gut before defecation.

Thiopurine dose adjustment during pregnancy in inflammatory bowel disease: a case series

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Backgroud Inflammatory bowel disease (IBD) is a group of chronic diseases of the gastrointestinal tract that affects men and women in their young and reproductive years of life. We showed that preconceptional counseling improves adherence to drugs, which was related to excellent pregnancy and child outcome. Although several studies showed that thiopurine use during pregnancy is of low risk, females with a pregnancy wish are still reluctant to continue thiopurines because they are afraid to harm their offspring. To counsel females more adequate on the risks of stopping thiopurines we investigated the effect of stopping thiopurine before or during pregnancy on disease activity during pregnancy. Methods We analyzed data from our prospectively followed-up pregnancy cohort, were we collect clinical, biochemical and endoscopic details. Twenty-five patients (17 Crohn's Disease (CD; 68%) and 8 Ulcerative Colitis (UC; 32%)) adjusted or stopped thiopurines in the preconceptional period, or during pregnancy. Flares were defined as Harvey Bradshaw Index for CD > 5 and Simplified Clinical Colitis Activity Index for UC >2, and/or fecal calprotectin >200 ug/g. Results Average disease duration was 7.8 (5.6-10) years at conception. Three (12%) patients used 6-mercaptopurine and 23 (88%) used Azathioprine. Twelve patients stopped thiopurine: 7 stopped in the first trimester, 1 in the second and 4 in the third trimester. Thirteen women adjusted thiopurine (all Azathioprine) dose during the pregnancy with a mean thiopurine dose of 1.82 mg/kg before adjustment and 0.70 mg/kg after adjustment (p<.000). Reasons for reducing or stopping the thiopurine dose included high blood levels (14 patients), thiopurine-related anemia (2 patients), elevated liver enzymes (2 patients), other side effects (2 patients) or the patients were afraid it might harm the baby (5 patients). Of the patients that stopped, 2(17%) experienced a relapse during second and third trimester. Two patients had an ongoing relapse which started before conception and therefore these patients were not taken into account for the total number of relapses. Of the adjusted dose patients, 3(23%) experienced a relapse during first, second and/or third trimester, 1 patient had an ongoing relapse and was therefore excluded (1 endoscopic and 7 clinical diagnosis). Patients were treated with either prednisone or mesalazine during a flare, all with favorable outcome. Child outcome was not affected: al women gave live birth; mean gestational age was 38(37.2-38.8) weeks. Conclusion In this case series we show that 20% of patients that stop or adjust thiopurine therapy at time of conception or during pregnancy experience a relapse during pregnancy.

High rate of advanced neoplasia after detection of low-grade dysplasia in Inflammatory Bowel Disease patients with primary sclerosing cholangitis

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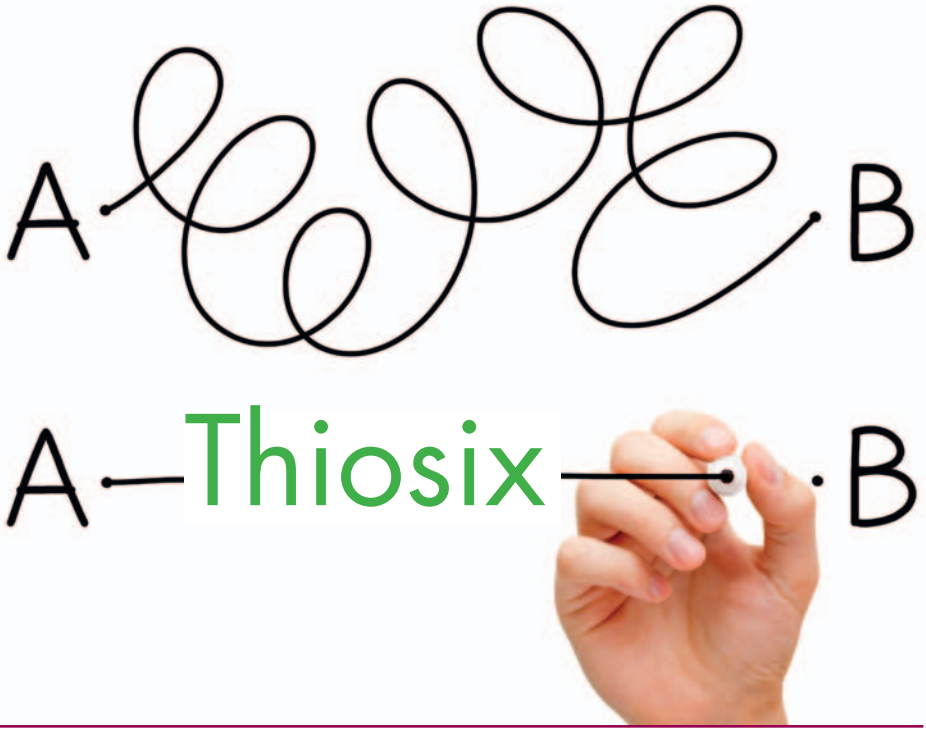
Primary sclerosing cholangitis (PSC) is the strongest risk factor for colorectal neoplasia (CRN) in inflammatory bowel disease (IBD). While prior studies in this population have estimated the prevalence of advanced CRN (aCRN) (high-grade dysplasia or colorectal cancer), little is known about the incidence rate of aCRN after a diagnosis of low-grade dysplasia (LGD) to, and its potential risk factors. PSC-IBD patients were identified from two existing large surveillance databases (the Mount Sinai Hospital Surveillance Database (2005-2015) and the Dutch multiCenter surveillance database (2000-2013)) and compared to non-PSC IBD patients. All patients had undergone at least two surveillance colonoscopies. Clinical information, as well as endoscopic and histologic data were recorded. The prevalence of LGD and aCRN and the incidence of aCRN after an index LGD lesion (first LGD within study period) were compared between groups. Cox-regression was used to determine predictors of dysplasia progression. Results: 301 patients with PSC-IBD were compared to 1100 non-PSC IBD patients. Patients with PSC-IBD were younger at IBD diagnosis [median 24y(range 69) vs 28y (72), p=0.003], more frequently male (69% vs 50%, p<0.001), and had a shorter IBD duration (median 10y [51] vs 14y [52], p<0.001). Median time of follow-up for the total cohort was 4.8 years. PSC-IBD patients had a statistically significant increase in the frequency of aCRN as compared to non-PSC IBD patients (Hazard ratio [HR] 3.1, 95%CI 1.7–5.8). The overall incidence rate of developing aCRN in PSC-IBD compared to non-PSC IBD patients was 1.3 versus 0.4 per 100 patient-years follow-up (pty). Despite similar frequencies of LGD between PSC-IBD and non-PSC IBD patients (20.3% versus 21%, p=0.8, Table 1), the rate of developing aCRN following detection of LGD was higher in PSC-IBD patients (HR 2.8, 95% CI 1.2–6.5). The incidence rate of aCRN after a diagnosis of LGD was 7.4/100pty for PSC-IBD patients compared to 2.3/100pty for non-PSC IBD patients. Using Cox-regression analysis, older age at study entry and a history of prior neoplasia were significant risk factors for development of CRN (LGD, or HGD, or CRC) among PSC-IBD patients; there was a non-significant trend for an association of multifocal dysplasia with higher risk of developing aCRN after an LGD diagnosis (HR 3.2, 95%CI 0.8–11.8, p=0.086). Conclusions: PSC-IBD patients have a similar incidence of LGD compared to non-PSC IBD patients, but the risk of developing aCRN after a diagnosis of LGD is significantly higher in PSC-IBD patients. Our findings substantiate recommendations for annual surveillance in this very high-risk population.



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Postoperative surgical recurrence in Crohn's Disease decreases significantly in the biologic era

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A large proportion of Crohn's disease (CD) patients undergo bowel resection within 10 years after diagnosis. Previous reports estimated postoperative surgical recurrence rates around 30-50% within 10 years. However, pre- and postoperative treatment paradigms have shifted significantly over the past decades. In this study, we aimed to assess recent time trends of ileocecal resection (ICR) in CD patients and postoperative surgical recurrence. Adult CD patients who underwent ICR in the period from January 1991 to December 2015 were identified in PALGA, the Dutch nationwide histopathology archive. Histology reports on oncologic resections and tissue revision were excluded. Data on demographics, ICRs and subsequent bowel resections were recorded. Surgical recurrence was defined as a re-resection of the colon, small bowel or rectum. Follow-up data were evaluated to December 2015. Survival data on patients without follow-up in the database were imputed using survival data of the general Dutch population. Patients were divided into four groups according to year of ICR to evaluate time trends. Risk of surgical recurrence was assessed using Kaplan-Meier survival statistics. Hazard ratios were assessed using Cox regression. The identified cohort comprised 2614 CD patients (M 979/ F 1635), who underwent ICR at a median age of 31.0 years (IQR 25-45). An increase in the absolute number of ICRs was observed during the study period, from 471 in the period 1991-1996, 610 in 1997-2002, 605 in 2003-2008, to 928 in 2009-2015. A total of 542 patients underwent re-resection after a median follow-up of 5.6 years (IQR 2.2-10.1). The overall risk of re-resection after 5, 10 and 20 years was 7.7%, 15.7% and 28.0% respectively. The 5-year risk of re-resection after ICR decreased significantly during the study period from 13.6% in 1991-1996 to 7.0% in 1997-2002 (HR 0.56), 6.7% in 2003-2008 (HR 0.50) and 4.8% in 2009-2015 (HR 0.38). The 10-year risk decreased from 24.7% in 1991-1996 to 14.0% in 1997-2002 (HR 0.53) and 13.8% in 2003-2008 (HR 0.37).

Concluding, CD patients have an overall risk of postoperative surgical recurrence of 8% within 5 years and 16% within 10 years after ICR. The risk of surgical recurrence within 5 years has declined significantly with an absolute risk reduction of 9% during the period from 1991 to 2015. This observation might be explained by implementing improved (post)operative treatment strategies, including availability of biologicals.

Inter-observer agreement of the Paris classification in pT1b esophageal adenocarcinoma

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In early esophageal adenocarcinoma (EAC), the depth of tumor invasion in the submucosa (pT1b) correlates with the risk of lymph node metastasis. The assessment of depth can be classified by subdividing the submucosa (sm) in 3 equal layers (sm1/sm2/sm3). In endoscopic resection (ER) specimens however, this classification may not be reliable, as full thickness of the sm cannot be assessed. This has led to the development of a more quantitative approach, where the depth of sm invasion is measured in micrometers, with sm1 defined ≤500µm and sm2/3 >500µm (Paris classification). The reproducibility of this approach has yet to be determined. We aimed to evaluate the inter-observer agreement (IOA) of the Paris classification for the assessment of submucosal tumor invasion in surgical and ER specimens. Between 1989-2014, all patients with pT1b EAC treated by either primary surgery or ER, were identified from the institutional database of a tertiary referral center. All H&E-stained slides were reexamined, and additional immunohistochemical double staining for desmin and pankeratin (D&P) was done on the paraffin block with the deepest invasion, to more accurately visualize the muscularis mucosa as well as invasiveness. From both slides, the deepest level of sm invasion was recorded in µm. Additionally, tumor grading (G) and presence of lymphovascular invasion (LVI) were recorded. All samples were independently reviewed by three expert GI-pathologists, who were blinded from the original diagnosis and clinical outcome. The IOA was determined using the intraclass correlation coefficient (ICC) for continuous variables and Fleiss' kappa (κ) for categorical variables. In total, 78 patients with pT1b EAC were included, 34 treated by ER and 44 by primary surgery. When determining the depth of sm invasion, the IOA between three pathologists was good (ICC=0.64, 95% CI 0.52 – 0.74) in H&E-slides, and good (ICC=0.76, 95% CI 0.63 – 0.86) in D&P-slides. When slides were assessed according to the Paris classification, the IOA was moderate (κ=0.59, 95% CI 0.47 – 0.72). In single slide assessment, the IOA was good for G (κ=0.680, 95% CI 0.583 – 0.777) and moderate for LVI (κ=0.429, 95% CI 0.301 – 0.557). Conclusion: There is good agreement between expert GI-pathologists in determining the depth of sm invasion in pT1b EAC, further improved by implementation of immunohistochemistry. The Paris classification has a moderate accuracy, which can be explained by slight variations around the 500µm cut-off-level. Our data suggest that the quantitative approach has a good reproducibility, which is essential for the treatment strategy and prognosis after a complete ER of low-risk sm1 EAC.

Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma

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Current guidelines advise to refer patients with submucosal esophageal adenocarcinoma (EAC) for surgical treatment, given the supposed risk for lymph node metastases reported in up to 46% of patients based on in surgical series. However, not all patients are candidates for surgical treatment due to comorbidity or age. Recent studies in endoscopically treated patients with submucosal EAC showed that risk of lymph node metastasis in this group might be much lower than previously assumed. The study aim was therefore to evaluate the rate of lymph node metastases in patients with a submucosal EAC treated endoscopically, with subsequent endoscopic follow-up. We retrospectively identified all patients undergoing endoscopic resection (ER) for submucosal EAC between December 2011 and December 2015 in two centers in The Netherlands. We only included submucosal EAC patients who underwent endoscopic follow-up after ER by means of regular upper endoscopies, and endoscopic ultrasounds (EUS), with a minimum FU of 12 months. Primary outcome was the rate of lymph node metastases; secondary outcomes included intraluminal recurrences and disease-free survival. Twenty-six patients (median age 69 years, median BE C2M5) were included. Twelve of 26 tumors (46%) were classified as a low-risk submucosal EAC (superficial submucosal invasion <500nm, G1-G2, no lymphovascular invasion [LVI]), and 14/26 (54%) as a high-risk submucosal EAC (deep submucosal invasion >500nm, and/or G3-G4, and/or LVI, and/or a tumor-positive deep resection margin [R1]). After a median follow-up of 24 (IQR 16-37) months in which patients underwent a median of 6 (IQR 5-7) endoscopies and a median of 5 (IQR 2-7) EUS procedures, none of the included patients developed lymph node metastases. Two (8%) patients developed a local intraluminal recurrence 18 and 21 months after ER; both could be treated endoscopically by means of argon plasma coagulation (n=1) and endoscopic submucosal dissection (n=1) respectively. Median disease-free survival was 22 (IQR 16-36) months. During follow-up, one patient (4%) died due to a non-tumor related cause. Conclusions: The results of this study suggest that endoscopic therapy in patients with a low-risk submucosal EAC is safe, given the minimal risk of lymph node metastases. In patients with a high-risk submucosal EAC, the risk of lymph node metastases is lower than previously assumed. Selected high-risk patients might be eligible for endoscopic therapy and follow-up.

Safety and efficacy of endoscopic Focal CryoBalloon Ablation for the treatment of esophageal squamous cell intraepithelial neoplasia

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Eighty percent of all esophageal cancer cases are esophageal squamous cell cancer (ESCC), arising from esophageal squamous cell intraepithelial neoplasia (ESCIN). Patients with ESCC have poor prognosis, but when diagnosed at the stage of ESCIN curative endoscopic treatment can be performed. ESCIN mainly occurs in developing countries like central Asia and eastern Africa, which often have limited endoscopic expertise and resources. Therefore an easy-to-use, low-cost treatment for ESCIN would be of great value. Focal Cryoballoon Ablation therapy (FCBA) is an endoscopic ablation therapy that comprises a through-the-scope catheter with a confirmable balloon, obviating the need for sizing, a handle and a small disposable cryogen cartridge. The balloon is cooled with nitrous oxide from the cartridge, resulting in ice patches of ±2cm^2. FCBA is easy to use and requires no capital equipment. Early studies for FCBA of Barrett's esophagus have shown promising results, however, limited data are available for FCBA of ESCIN. We aimed to assess the safety and efficacy of FCBA for eradication of ESCIN. In this ongoing multi-center prospective trial in China, patients with one flat type (Paris 0-IIb) unstained lesion (USL) on Lugol's chromoscopy, <6 cm in length and <50% of circumference, with a confirmed diagnosis of Moderate or High Grade Intraeptihelial Neoplasia (MGIN/HGIN) were enrolled. At baseline, side-by-side ablations were performed on USLs. Treatment was repeated every 3 months until eradication of neoplasia was confirmed. Outcomes: safety, tolerability (VAS for pain), complete response (CR) rates (absence of MGIN or worse in biopsies), neoplastic progression and adverse events. Of 43 patients (34 MGIN, 9 HGIN) enrolled, 40 (93%) were successfully treated. Three patients developed superficial, self-limited mucosal lacerations upon balloon inflation; one of them was successfully treated 3 months later. At base median 5 (IQR 3.5-6.5) adjacent ablations were performed per patient. Mean ablation time was 9 (±6) mins, with overall procedure time of 32 (±11) mins. The post-procedure median VAS was 2 (IQR 0-3) at day 2, and 0 (IQR 0-0) at days 7 and 30. Three patients (7%) developed fever shortly after treatment and were treated with aspirin. As of November 2016, 40 of 41 patients completed 3 month follow-up endoscopy. 35/40 patients (87.5%) showed endoscopic and histologic CR. Five patients had residual USL and were ablated again. No strictures were noted on follow-up. Conclusions - Early results of our multicenter cohort study suggest that FCBA of ESCIN is safe, well-tolerated and highly effective in inducing endoscopic and histologic remission.

A novel fully covered double-bump stent for anastomotic leaks after bariatric surgery: a retrospective analysis

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Anastomotic leakage after bariatric surgery can be treated with endoscopic placement of a self-expandable stent. The success of stent placement is often hampered by stent migration. The Niti-S Beta stent (TaeWoong medical) is a self-expandable fully covered double-bump stent that is specifically designed to prevent migration. This study aimed to evaluate the success and complication rate of the Niti-S Beta stent in treating anastomotic leakage after bariatric surgery. A retrospective study was performed in three high-volume bariatric Centers. All consecutive patients between 2009 and 2016 who underwent placement of a Beta stent for anastomotic leakage after bariatric surgery were included. Primary outcome was resolution of the leakage. Secondary outcome was the complication rate including migration. Thirty-eight patients were included, with 50 stent placements in total. Twenty-three (61%) underwent Roux-en-Y gastric bypass, 13 (34%) sleeve gastrectomy and 2 a different type of bariatric surgery. In 12 patients stent placement was the initial therapy for the anastomotic leakage and in 26 patients a stent was placed after surgical repair with oversewing of the leak had failed. Twenty-five patients (66%, 95%CI 50 - 79) had resolution of the leakage. Nineteen patients (50%) were successfully treated with one stent and 6 (16%) after consecutive stent placement. Stent treatment as initial treatment showed higher success rate than stent placement after failed surgical repair, 100% (12 out of 12) versus 50% (13 out of 26) respectively (p = 0.003). The chance of success of a consecutive stent did not differ from the first stent (6 out of 14 versus 19 out of 36, p = 0.529). Fourteen patients (37%) experienced one or more complications of stent placement. Migration occurred in 13 stents (26%) in 12 different patients (32%), including 8 out of 31 stents in LRYGB patients (26%) and 3 out of 16 stents in patients with LSG (19%, p = 0.588). There were 2 serious complications requiring surgical treatment: one stent migrated through the leak to the retroperitoneal area and had to be removed surgically, the second case was an aorto-oesophageal fistula caused by pressure of the stent, requiring placement of an endovascular aortic stent. There was one death in this series, due to persistent leakage despite stent placement. Conclusions: The double-bump Niti-S Beta stent for anastomotic leakage after bariatric surgery showed a success rate of 66%. Migration occurred in 26% of stents. Despite the novel design, the success as well as the migration rate seem comparable to other stents in previous studies.

Esophageal stent placement for upper gastrointestinal leaks: a prediction model for successful leakage control

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Upper gastrointestinal leaks cause severe morbidity and even mortality. Sealing the defect by endoscopic stent placement allows healing in 44-94% of patients. We aimed to develop a prediction model that predicts the chance of successful stent therapy. All patients treated with esophageal stent placement for anastomotic leakage, iatrogenic/spontaneous perforation or esophago-respiratory, -cutaneous or -pleural fistula were retrospectively included. Patients with active malignant disease were excluded. The primary outcome was successful leakage control, defined as absence of persisting symptoms of leakage after stent removal, or as successful leakage control in case the stent was left in permanently. We developed the prediction model from the derivation cohort that consisted of patients from three Dutch hospitals using logistic regression. We used a pre-specified model including six clinical parameters: etiology of leak (anastomotic / perforation / fistula), history of radiotherapy (yes / no), delay between diagnosis and stent placement (days), defect size (< 1cm / 1-2cm / > 2cm), highest CRP-level (mg/L) in the 7 days before stenting and location of defect in the esophagus (proximal / mid / distal). Missing values were imputed by multiple imputation. We calculated the predicted chance of successful stent therapy for each individual patient and assessed the model performance. The model was also validated in an external cohort. A total of 145 patients were included in the derivation cohort and 59 patients in the validation cohort. Stent therapy was successful in 55.9% and 67.8% of patients with a median follow-up period of 316 (IQR 97-742) days and 143 (IQR 40-692) days in the derivation and validation cohort, respectively. The prediction model consisted of 6 clinical parameters. With these parameters, the chance of successful stent therapy was calculated for each individual patient. The predicted chance of success was significantly higher in success patients compared with failure patients in both the derivation ($p<0.001$) and validation cohort ($p=0.001$). When the model predicted ≥ 75% chance of success, 73.9% and 87.0% of patients in the derivation and validation cohort actually had a successful outcome of stent therapy. When the model predicted ≤ 55% chance of success, 65.6% and 83.3% of patients actually failed on stent therapy, respectively. In conclusion, this novel prediction model, consisting of 6 clinical parameters, can identify patients with upper gastrointestinal leakage who are likely to benefit and fail on stent therapy. The model can thereby support the physician in clinical decision-making and informing patients.

Esophageal self-dilation for therapy-resistant benign strictures: towards a structured and standardized approach

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Therapy-resistant benign esophageal strictures (TRBES) have a major impact on the physical, psychological and social well-being of patients. These patients generally require repeated endoscopic dilations. For selected patients, self-dilation with dilation bougies may allow patients to regain autonomy and reduce the number of endoscopic dilations. Our aim is to develop a structured and standardized approach for patients with TRBES. We retrospectively analyzed the clinical course and outcomes of all patients with TRBES who started self-dilation at our center since 2013. To learn self-dilation, patients were seen on a weekly basis at the outpatient clinic. They received an instruction video and started self-dilation using Savary-Gilliard dilators under the supervision of a specialized nurse. Weekly endoscopic dilations were continued until patients were able to perform self-dilation adequately. We evaluated the technical success, the number of endoscopic dilations, the bougie diameter and frequency of self-dilations and dysphagia scores. We defined technical success as being able to perform self-bougienage at home on a daily basis. A total of 17 patients started self-dilation because of TRBES. Before starting self-dilation, patients underwent a median of 17 (IQR 11-27) endoscopic procedures. From the start of self-dilation, the median follow-up period was 12 (IQR 8-29) months. Sixteen (94%) patients were able to learn and perform self-dilation at home on a daily basis and one patient was not motivated to learn and continue self-dilation. Ten (59%) patients required a median of 2 (range 1-12) endoscopic dilations to facilitate self-bougienage and 6 (35%) patients could upsize the bougie diameter without endoscopic support. At end of follow-up, 16 (94%) patients reached a stable self-dilation frequency by which they could tolerate solid food (Ogilvie score ≤ 1). The median final bougie diameter was 14 mm (IQR 13-14 mm). Once a stable situation was reached, only 4 (24%) patients required additional endoscopic dilation (range 1-6 procedures). One patient had a transient bleed from a small cardiac mucosal laceration. Conclusions: In this small cohort series, self-bougienage was found to be successful in the majority of patients when conducted under strict guidance. The majority of patients achieved a stable situation where they could tolerate solid food without the need for endoscopic dilation. The results of this retrospective analysis have led to a prospective registration of clinical and patient-reported outcomes, as well as a patient self-dilation education program. This work was supported by the Dutch Digestive Foundation Grant I 16-04.

Surveillance of premalignant gastric lesions – a multi-center prospective cohort study from low incidence regions

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Background and study aims: Patients with atrophy and metaplasia of the gastric mucosa are at risk for progression to gastric cancer. International guidelines therefore recommend endoscopic surveillance of premalignant gastric lesions. However, the diagnostic yield and preventive effect of surveillance require further study. We therefore aimed to assess the incidence of neoplastic progression in patients from a low-risk area and to assess discriminative tests to identify patients most at risk for progression. Patients and methods: Patients with a previous diagnosis of atrophic gastritis (AG), intestinal metaplasia (IM), or dysplasia from six hospitals throughout the Netherlands and one in Norway were offered endoscopic surveillance according to European guidelines. All histological specimens were assessed according to the updated Sydney classification and the operative link for gastric intestinal metaplasia (OLGIM) system. In addition, we measured serum pepsinogens I and II, and gastrin-17 obtained before surveillance endoscopy. Results: Two-hundred-and-eighty-four (mean age 57.8 year SD 11.4, M/F 142/142) patients were included. In 279 (98%) patients at least one surveillance endoscopy was performed. The mean follow-up time was 57 months (SD 36) with a total of 1,312 patient-years follow-up. Four subjects (1.4%) were diagnosed with high grade dysplasia or gastric cancer during follow-up. This occurred in 3 (2.2%) of 134 patients with OLGIM stage 0-II disease at baseline, versus 1 (1.9%) of 54 patients with stage III-IV (p=0.87). Two of these patients were successfully treated with endoscopic submucosal dissection, while the other two underwent a total gastrectomy. Patients with normal serology markers and limited disease did not develop gastric cancer during follow-up (p=0.41). Conclusions: In a low gastric cancer incidence area, a surveillance program for premalignant gastric lesions can detect gastric cancer at an early curable stage with an overall risk of neoplastic progression of 0.3% per year. Use of serologic markers in endoscopic surveillance programs improves risk stratification. These data strengthens international guidelines in their recommendations on surveillance of premalignant gastric lesions.

Safety and effectiveness of colorectal endoscopic full-thickness resection using a new, flat-based over-the-scope clip: a prospective study

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Colorectal surgery is associated with significant morbidity and mortality rates. It is therefore of high importance to explore alternative minimal invasive treatment methods for situations where standard polypectomy techniques are unsuccessful or inadequate. Endoscopic full-thickness resection (eFTR) using over-the-scope clips is a new, promising, minimally invasive technique. We aimed to evaluate the safety and effectiveness of a new, flat-based over-the-scope clip (Padlock Clip™) for colorectal eFTR. In this prospective study, patients ≥ 18 years with an indication for eFTR were included. Patients with lesions >20 mm were excluded. Histological diagnosis was performed by an expert gastro-intestinal pathologist. Telephone follow-up was performed to assess adverse events and to evaluate pain perception on a Numeric Rating Scale (0 – 10). Twenty-three patients were included with a median lesion size of 10 mm (IQR 6 – 10; range 4 - 20). Lesions were located in the proximal colon (N=10), distal colon (N=8) and rectum (N=5). eFTR was performed on scar tissue in 18 cases (recurrent non-lifting adenoma (N=8); scar tissue of a malignant polyp with Rx/R1-resection margins (N=10)), and on naïve polyps in 5 cases (non-lifting malignant polyp (N-4); adenoma in diverticulum (N=1)). Technical success rate and full-thickness resection rate were 100% (23/23; 95%CI 86-100%) and 91% (21/23; 95%CI 73-98%) respectively. Median procedural time was 40 minutes (IQR 25 – 55) with a median cap time of 8 minutes (IQR 4 – 15). Complication rate was 13% (3/23; 5-32%), with one complication (1/23; 4.3%) scored as severe (cecal perforation). eFTR of scar tissue showed a trend towards a smaller specimen volume as compared to resection of naïve polyps (median 1.1 cm^3; IQR 0.6 – 1.8 vs 1.6 cm^3; IQR 1.2 – 2.2, p=0.09). In patients in whom re-resection was performed on the scar of a low-risk malignant polyp with Rx/R1-resection margins (N=10), lateral margins were positive for scar tissue in all but 2 cases resulting in remaining uncertainty on the radicality of resection. The two successful cases concerned eFTRs of scar tissue of a polyp with an original size <20 mm. Patients' pain score declined from a median of 3 (range 0-7) on the first day, to 1 (range 0-5) on day 7 and 0 (range 0-1) on day 30. In conclusion, colorectal eFTR with the Padlock Clip is safe and feasible. The technique seems promising for naive lesions deemed unsuitable for conventional endoscopic resection, and for resection of recurrent adenoma in a non-lifting scar. However, re-resection of scar tissue of low-risk malignant polyps ≥20 mm did not provide a high certainty on the radicality of the resection.

Endoscopic full-thickness resection: a prospective case series from a large clinical teaching hospital in The Netherlands

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Summary Endoscopic full-thickness resection (eFTR) is an alternative to surgery for non-lifting or difficult-to-reach colorectal lesions in which other endoscopic techniques are not successful. In eFTR a clip is placed below the lesion prior to removing a circular transmural specimen.This allows en-bloc resection and determination of depth-of-invasion, without the risk of fecal spill. We aim to present our experiences with this device and evaluate eFTR indication, efficacy and safety. From July 2015 until December 2016 two gastroenterologists, specialized in advanced endoscopic techniques, performed 37 procedures (in 36 patients) using a Full Thickness Resection Device. Mean age was 67 years. Indications were resection of non-lifting adenomas (n=14), residual adenoma in a diverticulum (n=1), submucosal tumor (n=2), primary resection of malignant lesion (n=2) and resection of scar tissue after irradical endoscopically treated low-risk T1-carcinoma (n=18). Two lesions were treated by combining Endoscopic Mucosal Resection and eFTR in a single session. Lesions were located in both the left and right hemi-colon (including distal rectum) and were reached in all cases. Technical success (macroscopic complete and en-bloc resection) was accomplished in 34 (92%) and R0-resection in 27 (73%) cases. Peri-procedural bleeding occurred in four cases (one required a blood transfusion). In one case a primary perforation, due to clip dysfunction, was treated endoscopically with an over-the-scope clip. No emergency surgery was necessary. In all cases a single dose of broad spectrum antibiotics was given. Mean duration of hospitalization was 1.39 nights. Five patients needed elective additional surgery because of a high-risk adenocarcinoma. Planned procedure time in right and left sided interventions was 90 and 60 minutes respectively. Mean largest specimen diameter was 22 mm. Mean time to surveillance endoscopy (n=20) was 143 days (range 78-358), two clips were still in place at 78 and 130 days respectively. Conclusions: eFTR appears to be a safe technique for both benign and malignant colorectal lesions, that may be performed under conscious sedation. It reduces the need for surgery in selected cases. Specimen diameter varies with colonic wall thickness and mobility. Prospective studies are necessary to clarify the role of eFTR in the treatment of low-risk T1-colorectal cancer, weighing the risk of residual lymph node metastases after eFTR against morbidity and mortality of colorectal surgery. Furthermore, the necessity of antibiotic prophylaxis in a procedure without fecal spill and the need for post-eFTR hospitalization have yet to be determined.

Inhibition of the BMP pathway prevents development of Barrett's associated adenocarcinoma in a surgical rat model

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Patients with Barrett's Esophagus (BE) have an increased risk for developing esophageal adenocarcinoma (EAC), which presents with very poor prognosis. Our group previously demonstrated that BMP4, a member of the TGF- beta family, is one of the key players in the process of the metaplastic transformation of the esophagus. Further, BMP4 and its downstream targets have also been shown to be upregulated in EAC and are thought to play a major role in the malignant progression of BE to EAC as well as subsequent metastatic spread of EAC.

Although our preliminary in vitro studies have shown that the effect of BMP4 can be inhibited by its natural antagonist Noggin, it is still uncertain if Noggin could also result in inhibition of the malignant progression of BE in vivo. The best available physiological BE animal model to date is the surgical rat model. This BE rat model is characterized by the cascade of inflammation and injury of the esophageal mucosa caused by reflux of bile and acids and is eventually followed by progression to EAC.

The current study was therefore designed to investigate whether in vivo inhibition of the BMP4 pathway could prevent formation or induce regression of BE and/or EAC in a surgical rat BE model. As expected, the BMP activity (as measured by phosphorylation of the BMP target gene SMAD1/5/8) in the esophagus was decreased after Noggin treatment. Although, at sacrifice there was no difference in macroscopic length or severity of esophagitis when comparing Noggin with control group, there was a significant difference in inflammation score (i.e. severity of inflammation) between both Noggin and the control group. Although not significant, there were also differences in the type of Barrett's epithelium in the Noggin treated group, as they appeared to be more of the mixed type (intestinal metaplasia and squamous epithelium interspersed). Most importantly, we did observe significantly less EAC in the Noggin treated group (50%) as compared to the control group (73%) ($p < 0.05$).

Concluding, we show that Noggin as administered in this study is not capable of inducing regression of advanced Barrett's esophagus/in a surgical BE rat model. However since we observed an effect of Noggin in the earlier stages of the transformation to intestinal metaplasia, Noggin might still be effective as an preventative agent for EAC development.

BMP signalling leads to stem cell loss and epithelial differentiation in the mouse intestine: a next generation sequencing-based approach

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The crypt-villus architecture in the intestine is tightly regulated by morphogens, including the Bone Morphogenetic Proteins (BMPs). Loss of BMP signalling, either by loss of critical signalling components or transgenic overexpression of BMP-antagonists in mice causes intestinal polyposis mimicking hereditary polyposis syndromes. Abrogated BMP signalling enhances Wnt signalling and intestinal stem cell (ISC) renewal, eventually leading to tumourigenesis. This might be partly due to enhanced PTEN activity, which in turn represses Akt activity, necessary for full activation of Wnt signalling in ISCs. However, it is likely that BMP signalling also influences stemness and differentiation through several other, undescribed pathways. This study aims to identify how BMP signalling acts on ISCs and epithelial differentiation by using a Next Generation RNA Sequencing approach. Mice with a constitutively active BMP receptor type 1A (caBMPR1a) were injected with β-naphthoflavone (BNF) to induce recombination specifically in the intestinal epithelium (Cyp1a1-Cre*caBMPR1a*Rosa(YFP)). Mice lacking the caBMPR1a construct were injected with BNF and served as controls. The mice were sacrificed at 1, 3 and 5 days post induction and the small intestine was used for further analyses. Immuno-histochemistry was performed to study morphological changes, recombination efficiency and changes in signalling pathways. Total mRNA from the small intestine at day 3 was sequenced to study differential gene expression. Gene Set Enrichment Analysis (GSEA) was used to study gene sets enriched in the expression data. Constitutive activation of BMP signalling in the intestinal epithelium led to rapid disruption of the crypt-villus architecture with loss of the stem cell marker OLFM4, increased proliferation (Ki67, BrdU) and increased differentiation at 3 days after induction. GSEA at 72h post induction revealed that the “differentiation” gene set was up regulated in the BMP-overexpression group, whereas the “proliferation” gene set and “stem cell” gene set were down regulated. Among the top differentially expressed genes are several genes important for correct positioning of cells in the crypt-villus axis (e.g. WNT5B), drivers of proliferation (e.g. EPHB4) and regulators of epithelial-to-mesenchymal transition (e.g. TM4SF4).
Taken together our data indicate that constitutive activation of BMP signalling in the intestinal epithelium leads to up- and down regulation of several genes/gene sets important for epithelial homeostasis and differentiation. Further studies are ongoing to explore how BMP signalling acts on these signalling pathways, both *in vivo* and using *in vitro* organoid models.

Fibrostenotic phenotype of fibroblasts in Crohn's disease is dependent on tissue stiffness and reversed by LOX inhibition

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Background&aim: In Crohn's disease (CD), intestinal inflammation often leads to fibrosis, characterized by excess extracellular matrix (ECM) deposition, increased tissue stiffness and stricture formation. ECM modulation is mainly mediated through activity of fibroblasts which both deposit and degrade ECM components. To evaluate the role of fibroblasts in intestinal fibrosis in CD, we compared phenotype and function of fibroblasts obtained from normal, inflamed and stenotic regions of the ileum. Methods: Fibroblasts were isolated from resection specimens of normal, inflamed and stenotic ileum within the same CD patients and analyzed for gene expression profile. Fibroblasts were cultured in matrigel/collagen mix to measure ECM contraction in vitro. Matrix metalloproteinase (MMP) activity was measured upon culture in both soft and stiff matrices, mimicking normal and stenotic tissue conditions. Results: Transcriptional analysis showed that fibroblasts from stenotic ileum were distinct from both inflamed and normal fibroblasts with respect to genes involved in ECM organization and collagen production. In accordance with transcriptional data, stenotic fibroblasts showed an unexpected high activity of MMPs compared to normal and inflamed fibroblasts when cultured in the absence of ECM. This was counterintuitive, since MMP activity would be expected to be decreased in stenosis. However, when cultured in ECM with compliance of their native stiff environment, stenotic fibroblasts displayed decreased MMP3 activity. This activity increased when cultured in soft environment. In sharp contrast, fibroblasts isolated from normal ileal regions had increased MMP3 activity upon stiffening of the ECM, suggesting a regulatory function to maintain tissue homeostasis. Functionally, stenotic fibroblasts induced significantly more ECM contraction than both normal and inflamed fibroblasts, consistent with tissue contraction in vivo. In addition, stenotic fibroblasts expressed increased levels of the collagen crosslinking enzyme lysyl oxidase (LOX), further contributing to tissue stiffness. Inhibition of LOX restored MMP3 activity of stenotic fibroblasts in a stiff ECM to the MMP3 activity level of normal fibroblasts. Consequently, LOX inhibition prevented ECM contraction induced by stenotic fibroblasts. In normal fibroblasts LOX inhibition did not affect ECM contraction. Conclusion: Stenotic fibroblasts display inherent alterations in gene expression and exhibit an aberrant response to tissue stiffness, contributing to ECM deposition and fibrosis. Altering the microenvironment by LOX inhibition corrects this phenotype, suggesting this as a potential anti-fibrotic agent in CD.

Oral Tyrosine Kinase 2 inhibitor ameliorates T cell transfer colitis

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Several Janus Kinase (JAK) inhibitors selectively targeting one JAK-family member are currently under development for the treatment of inflammatory bowel diseases (IBD). Tyrosine Kinase 2, one of the JAK family members, mediates signalling of pro-inflammatory cytokines involved in the pathogenesis of IBD including IL6, IL12, IL23 and interferon gamma (IFNγ). The aim of this study was to investigate the potency of an oral TYK2 inhibitor (TYK2i) in vivo in a murine colitis model. T cell transfer colitis was induced by adoptive transfer of wild type CD45RB^{high} T lymphocytes into RAG1KO mice. After onset of endoscopic disease (day 36), animals were administered with placebo or TYK2i (10, 30, 70 mg/kg/day) daily by oral gavage. Upon sacrifice, colon weight, colon length and disease activity index (DAI, consisting of diarrhoea, oedema and occult blood, score 0-7) were recorded. Colon tissue was analysed by histology (score 0-12) and protein and transcriptional analyses of various cytokines were performed. In the T cell transfer colitis model, daily administration of TYK2i prevented loss of bodyweight at all doses tested. Both endoscopic and clinical disease activity were decreased by TYK2i in a dose-dependent manner, with animals receiving 70mg/kg displaying disease activity comparable to healthy controls (median activity 0, 1.75 and 0 for healthy controls, placebo and 70mg/kg respectively). Histologically, animals receiving 70 mg/kg showed significantly decreased colitis when compared to placebo treated animals, although some residual inflammation was apparent (median score 1, 5.25 and 1.5 for healthy controls, placebo and 70mg/kg respectively). Analysis of the affected colon revealed decreased expression of IFNγ and IL6 both at the mRNA and protein level, as well as decreased protein expression of TNFα. Our results show that oral administration of a TYK2 inhibitor ameliorates the course of T cell transfer colitis, suggesting TYK2 as a potential therapeutic target in the treatment of IBD.

Disrupting IL-10 receptor signaling on CD11c^{+} myeloid cells causes a gluten-dependent small intestinal inflammation

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Celiac disease (CD) is a chronic, small intestinal, T-cell driven inflammatory disease depending on dietary gluten. The initial events leading to the breach of tolerance to gluten in CD patients still remain elusive. We recently showed that in mice, IL-10 producing Tr1-like cells maintain gluten tolerance. Moreover, we and others have previously shown that IL-10 is essential to maintain small and large intestinal homeostasis by regulating CD11c^{+} myeloid cells. Altogether, this led us to hypothesize that dietary gluten would trigger a small intestinal inflammatory response in mice with disrupted IL-10 regulation of CD11c^{+} myeloid cells. Indeed, in Cd11c^{cre}Il10ra$^{fl/fl}$ mice lacking IL-10 receptor alpha signaling in CD11c^{+} myeloid cells, dietary gluten drove a CD-like small intestinal enteropathy characterized by crypt hyperplasia and accumulation of intraepithelial lymphocytes (IEL). In particular, Cd11c^{cre}Il10ra$^{fl/fl}$ mice displayed increased frequencies of small intestinal αβTCR CD4^{pos}CD8αα^{pos} and CD4^{pos}CD8α^{neg} IEL. The CD4^{pos}CD8αα^{pos} IEL had a cytotoxic CD4 lymphocyte (CD4 CTL) phenotype characterized by a low expression level of Thpok and positivity for 2B4, granzyme B and CD103. Moreover, the CD4^{pos}CD8αα^{pos} IEL population predominantly expressed Ifng while the CD4^{pos}CD8α^{neg} IEL population predominantly expressed Il17. In agreement with its known role in the recruitment and activation of IEL, the small intestinal epithelium of Cd11c^{cre}Il10ra$^{fl/fl}$ mice upregulated MHCII on its surface and showed increased expression of T23, a gene encoding the non-classical MHCI molecule Qa-1^{b} able to activate cytolytic IEL. Crucially, a gluten-free diet prevented the small intestinal epithelium activation and completely abolished the increase in CD4^{pos}CD8αα^{pos} CTL, CD4^{pos}CD8α^{neg} IEL, Il17 and Ifng. Altogether, our data indicate that disrupting IL-10 regulation of CD11c^{+} myeloid cells causes a gluten-dependent small intestinal inflammation with features typically associated with CD.

Reduced frequencies of regulatory TIGIT-expressing mucosal T cells in the circulation are characteristic for ongoing intestinal disease

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Currently, monitoring ongoing intestinal T-cell responses in inflammatory bowel disease (IBD) patients is difficult. We have previously shown that in human peripheral blood the $CD62L^{neg}CD38^{+}CD4^{+}$ T-cell population is highly enriched for T cells of mucosal origin, while circulating non-mucosal ($CD62L^{neg}CD38^{neg}CD4^{+}$) T cells contain cells homing to other tissues such as skin. We hypothesize that the composition and activational state of the circulating mucosal ($CD62L^{neg}CD38^{+}CD4^{+}$) T-cell population reflects ongoing intestinal immune responses, which are preferentially regulatory in healthy controls (HC) and inflammatory in IBD patients. During active disease but not during clinical remission, IBD patients exhibited increased frequencies of activated $CD25^{+}$ mucosal T cells and antigen-experienced $CD45RA^{neg}$ mucosal T cells in peripheral blood when compared to age-matched HC. Increased frequencies correlated with high serum C-reactive protein and were not detectable when analyzing the circulating $CD4^{+}$ T-cell population as a whole. Conversely, in adult HC circulating mucosal T cells had a strong non-inflammatory phenotype as evidenced by lower frequencies of interferon-g (IFNg) secreting-, but higher frequencies of interleukin-10 (IL-10) secreting T cells when compared to non-mucosal T cells. To identify surface proteins that account for this non-inflammatory phenotype and that are suitable for disease monitoring, we performed RNA sequencing on mucosal and non-mucosal T cells from adult HC. Mucosal T cells were enriched in transcripts associated with immune regulation, proliferation and gut homing. In particular, the regulatory molecules IL-10 and T-cell immunoglobulin and ITIM domain receptor (TIGIT) were increased. Flow cytometric analysis showed that the mucosal T-cell population contained 40% $TIGIT^{+}$ cells versus only 20% in the non-mucosal population. In agreement with its inhibitory function, $TIGIT^{+}$ mucosal T cells expressed high IL-10 mRNA at base and secreted less IFNg compared to $TIGIT^{neg}$ mucosal T cells upon stimulation. Moreover, TIGIT expression remained stable after in vitro activation rendering it a putative marker for monitoring the non-inflammatory component of the mucosal T-cell population. Strikingly, significantly reduced frequencies of $TIGIT^{+}$ mucosal T cells, but not $TIGIT^{+}$ non-mucosal T cells, were observed in peripheral blood of pediatric IBD patients with active disease. In conclusion, we show that compositional changes of the circulating mucosal T-cell population, in particular increased frequencies of CD25+CD45RAneg and decreased frequencies of TIGIT+ cells, allow to monitor active intestinal disease.

Anti-TNF immune complexes inhibit mucosal IL-12 and IL-23 production via Fc engagement on pro-inflammatory macrophages

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Introduction Infliximab is a full monoclonal IgG1 antibody that induces mucosal healing in a substantial proportion of IBD patients. In contrast, only 4% of patients achieved endoscopic remission with certolizumab, a TNF blocking Fab' fragment. Therefore, TNF blockade alone appears insufficient to resolve intestinal inflammation, indeed we previously showed that the Fc region of anti-TNF mediates therapeutic efficacy in vivo. We also showed that the Fc-region of anti-TNF skews monocytes towards a regulatory phenotype. However, in the inflamed intestine of patients with IBD monocytes have already differentiated into pro-inflammatory macrophages, therefore we investigated the effects of different anti-TNF compounds on the phenotype of pro-inflammatory macrophages. Methods Monocytes from healthy donors were cultured for 7 days with IFNγ then stimulated with LPS 100 ng/ml and different anti-TNF compounds (10 ug/ml for 48 hours). Cytokines were measured by ELISA. We collected mucosal biopsy specimens from IBD patients before and during anti-TNF treatment and performed qPCR for IL-12B and GAPDH. Results Infliximab but not certolizumab affected the cytokine profile of pro-inflammatory macrophages by increasing IL-10 and repressing IL-12 and IL-23 production. Fcγ-receptors have been shown to signal via spleen tyrosine kinase (SYK). Indeed, the effects of infliximab were mediated via SYK. In with previous reports, infliximab was able to form large immune complexes with soluble TNF. Combining certolizumab with non-specific IgG1 immune complexes resulted in a cytokine profile equal to infliximab treated macrophages. Etanercept, a soluble TNF receptor fused to an Fc region which has failed to show clinical efficacy in IBD, was not able to form immune complexes. Indeed, despite the presence of an Fc region, etanercept could not supress IL-12/IL-23p40 or increase IL-10 production by pro-inflammatory macrophages. Finally, in a cohort of anti-TNF treated IBD patients the gene encoding IL-12-IL23p40 was significantly decreased in the mucosa of endoscopic responders but remained high in non-responders. Conclusion The Fc region of monoclonal anti-TNF inhibits IL-12 and IL-23 production by pro-inflammatory macrophages via the formation of large immune complexes. We provide an explanation for the lack of efficacy of certolizumab and etanercept in IBD, furthermore our data argue that clinically effective anti-TNF interferes with the same pathways as novel therapeutic antibodies targeting IL-12 and IL-23.

Local Administration of Mesenchymal Stromal Cells alleviates Experimental Colitis

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Mesenchymal stromal cells (MSCs) are a new potential therapeutic modality in inflammatory bowel diseases (IBD) because of their immunomodulatory properties and participation in tissue repair processes. However, when injected intraperitoneally or intravenously only a small portion of the cells, if any, reaches the inflamed colon. In the present study we assessed whether endoscopically injected MSCs, as single cells or in spheroids, into the intestinal wall of the inflamed distal colon affect the course of experimental colitis. A total of 2.0 x 10^6 green fluorescent protein (GFP)-positive single MSCs or 2000 GFP-positive MSC spheroids (1000 MSCs/spheroid) were endoscopically injected in every quadrant of the distal colon of mice with established dextran sulphate sodium (DSS)-induced colitis (n=8/group). Body weight was measured daily and disease activity was scored at time of sacrifice (6 days after treatment). Some mice received luciferase expressing MSCs to locate the cells by in vivo bioluminescent imaging (BLI). Differences in mRNA expression profiles of relevant regulatory genes between single MSCs and MSC spheroids in vitro were assessed by quantitative PCR (qPCR). Endoscopically injected MSCs and MSC spheroids both alleviated DSS-induced distal colitis, as shown by a higher relative body weight from day 3 up to day 6 after treatment compared to controls, with significant differences at day 5 (MSCs 88±3%; MSC spheroids 87±2% vs controls 79±2%, both $p<0.05$). Furthermore, mice treated with single MSCs or MSC spheroids had a lower disease score compared to control mice (MSCs 1.8±0.3, $p=0.05$; MSC spheroids 1.4±0.3 vs controls 2.8±0.4, $p=0.01$). Microscopic evaluation of the colons showed a lower microscopic IBD score in MSC-treated mice (MSCs 5.4±0.7, $p<0.05$; MSC spheroids 5.7±0.8, $p<0.07$ vs controls 7.8±0.7). Both single MSCs and MSC spheroids were found in and attached to the bowel wall by BLI and GFP staining after injection. qPCR analysis showed increased expression of transforming growth factor β1, cluster of differentiation 200 and vascular endothelial growth factor in spheroids compared to single MSCs, whereas cyclo-oxygenase-2 and C-C motif chemokine ligand 2 were downregulated. In conclusion, endoscopic injection of MSCs into the inflamed distal colon, as single cells as well as in spheroids, attenuates DSS-induced colitis and these MSCs can be detected within and connected to the bowel wall. Despite differential expression of several genes involved in immune regulation, tissue repair and trafficking, MSCs as single cells or in spheroids had a similar efficacy. These data indicate the beneficial potential of local MSC treatment for distal colitis.

The role of recipient epithelial cells in regeneration after liver transplantation: Different kinetics of chimerism for hepatocytes and bile duct epithelial cells

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Impaired regeneration of the biliary tree after liver transplantation has been linked to post-operative biliary complications and, more specific, to non-anastomotic bile duct strictures (NAS). Ischemic damage of stem cell populations in the graft may impair regenerative processes of both hepatocytes and bile duct epithelial cells (cholangiocytes). It has been hypothesized that recipient-derived (stem) cells may contribute to the restoration of the damaged graft and thereby establishing epithelial chimerism. Therefore, the aim of this study is to determine the extent and kinetics of recipient-derived hepatocytes and cholangiocyte repopulation in transplanted livers after graft explantation due to NAS and other reasons. We retrospectively identified recipients which required a re-transplantation for various indications between 2001 and 2015. Recipient-derived cells in the liver explant were determined using immunohistochemistry for HLA-A2 and X- and Y-chromosome fluorescent in situ hybridization (FISH). Bile ducts were located by cytokeratin 19 staining. Overall, 13 explants for which a re-transplantation was performed were included in this study, of which five for NAS. All were HLA-A2 positive recipient who received a HLA-A2 negative liver graft. Additionally, four grafts were of female donors transplanted in male recipients. Median time until re-transplantation was 167 days. In all grafts, extensive repopulation of hepatocytes and cholangiocytes by recipient cells was observed. These results were confirmed by XY-FISH analysis. The repopulation of hepatocytes was time dependent. A significant difference was observed between early and late re-transplantations (<180 days mean 8.3% ±SD 6.4 vs. 31.8% ±23.5 >365; p=0.03). In contrast, the percentage of recipient derived cholangiocytes in the same grafts was not time-dependent (10.8% ±12.9 vs. 8.5% ±8.5; p=0.75). No clear differences in hepatocyte repopulation was observed between NAS and the non-NAS group (11.8% ±9.6 vs. 26.0% ±27.2; p=0.38) though there was a trend toward more cholangiocyte repopulation in the NAS livers (13.8% ±12.7 vs. 3.5% ±4.4 p=0.054). Conclusion. Extensive epithelial chimerism occurs after liver transplantation. The kinetics of hepatocyte and cholangiocyte chimerism is significantly different, suggesting distinct underlying regenerative mechanisms.

Hepatic LGR5 stem cells contribute to liver carcinogenesis

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Background & Aims: The concept that adult stem cells can accumulate genetic/epigenetic changes and subsequently contribute to tumor initiation and progression has attracted great interest, but remains controversial. Leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) is a recently identified marker for a liver stem cell population. Here we investigate the role of hepatic LGR5-expressing cells in liver carcinogenesis. Methods: A LGR5-promotor driven diphtheria toxin (DT) receptor knock-in mice model with a GFP reporter and a lineage tracing mice model with a membrane-targeted tandem dimer Tomato/green fluorescent protein (mTmG) reporter were used. Carbon tetrachloride (CCl_4) was used to induce chronic liver injury and diethylnitrosamine (DEN) was used to induce primary liver tumor in mice. Results: We observe the absence of a LGR5-expressing compartment in the mouse liver throughout an unchallenged life span, but it is induced upon CCl_4-induced injury. However, this liver LGR5-positive compartment has only limited contribution to tissue repair as observed by lineage tracing. Surprisingly, we find that the carcinogen DEN also induces a liver LGR5-positive stem cell compartment. In thus-induced hepatic tumors, the percentage of LGR5 cells is significantly higher as compared to tumor adjacent tissue (n=28, P<0.0001, 4-fold higher), and this even more apparent when contrasted to tissue of CCl_4-induced chronic injury (n=28, P<0.0001, 66-fold higher). Tumor organoids generated by ex vivo culturing of primary mouse liver cancer contain a LGR5-expressing cell population. Subcutaneous transplantation of these tumor organoids into immunodeficient NOG mice results in solid tumors, which retain a LGR5 positive compartment. Isolation and culturing of single $LGR5^+$ cell from primary mouse tumor initiated tumor organoids, and transplantation of these organoids into NOG mice formed tumor again. Thus, these cells have cancer initiating/stem cell-like properties. Importantly, lineage tracing shows that liver $LGR5^+$ stem cells and their daughters cells contribute to the development of liver tumor.
Conclusion: Hepatic LGR5 stem cells are only induced following liver injury and importantly contribute to DEN-induced liver carcinogenesis but not to tissue repair. Thus targeting LGR5-positive cells appears promising as an anti-cancer strategy in the liver.
Keyword: LGR5, Tumor stem cell, Tumor organoid, Liver tumor.

Pegylated interferon alpha treatment rapidly clears Hepatitis E Virus infections in humanized mice

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Background and aims: Safe and effective antiviral options are needed for ribavirin intolerant, immunocompromised patients with chronic Hepatitis E Virus (HEV) genotype (gt) 3 infections. Pegylated interferon (pegIFN) has been used extensively to treat chronic viral hepatitis infections and baseline intrahepatic IFN-stimulated gene (ISG) expression has been linked to treatment success. We studied the antiviral potency of pegIFN against HEV gt3, HEV gt1 and HBV gtA infections in an immunocompromised small animal model and modelled intrahepatic ISG responses pre- and post-treatment.
METHODS: 62 uPA$^{+/+}$Nod-SCID-IL2Rγ$^{-/-}$ mice were transplanted with one of three human hepatocyte donors. Human liver-chimeric mice were challenged with HEV gt3, HEV gt1 or HBV gtA. Infected mice received either a single or twice weekly injections with pegIFNa-2b for 2 or 4 weeks. Quantification of HEV RNA was performed in liver, bile and feces using RT-qPCR. Human gene expression of human-chimeric mouse livers was analyzed using RT-qPCR and the nanostring nCounter® human-immunology panel for respectively 10 and 578 genes. 5 Non-chimeric mice were used as controls. Human CXCL10 was measured in mouse serum.
RESULTS: HEV gt3 infections were cleared from liver and feces after 8 and 4 pegIFN doses, but relapsed in 2/4 mice after a single pegIFN injection. PegIFN anti-HEV activity was confirmed in HEV gt1 infected mice with complete clearance from liver and feces after 4 injections. In contrast, HBV gtA infected mice showed a <1 log IU/ml drop in serum HBV DNA and had high intrahepatic HBV DNA levels (>6 log IU/gr liver) at the end of a 2 week pegIFN treatment course. Baseline pre-treatment ISG expression was evaluated in 20 HEV gt3 and 10 HEV gt1 infected chimeric-mouse livers and revealed no ISG induction compared to 8 control chimeric mice. An in-depth gene expression array on 14 HEV gt3 infected chimeric-mice confirmed the absence ISG induction, irrespective of time point after inoculation, hepatocyte donor or HEV strain. Post- pegIFN treatment a clear human specific ISG induction was observed in liver (>10-fold *CXCL10* mRNA increase), which led to increased circulating human CXCL10 levels in mouse serum.
Conclusions: HEV gt1 and gt3 infections do not induce innate intrahepatic immune responses and are extremely sensitive to pegIFN in immunocompromised humanized mice. This might inform treatment strategies for ribavirin resistant HEV.

Establishment of malignant organoid model from primary mouse liver tumors

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Background & Aims: Organoid is a 3D organ-bud grown *in vitro* that can be cultured from a single stem cell. Since adult liver stem cells can generate healthy organoids, we here aim to explore whether malignant organoids can be obtained from primary liver tumors for studying tumor-initiating cells/tumor stem cells.
Methods: Diethylnitrosamine (DEN) was used to induce primary liver tumor in mice. The culture of mouse liver tumor organoids was optimized based on the protocol for culturing normal organoids from liver tissues.
Results: We succeeded in culturing organoids from several primary liver tumors from mice. These tumor-derived organoids can be maintained over 5 months as followed up to date, passaged in the ratio of 1:5 and every 4-5 days. Organoids derived from normal liver are mainly maintained in the stem cell stage and the organoids will stop proliferation upon differentiation into mature cell types. Interestingly, these tumor-derived organoids harbored cell types expressing both markers of hepatocyte and cholangiocyte, but proliferated rapidly. In addition, we found that isolated single cells from the tumor organoids can efficiently re-initiate organoids with an efficiency of ~25%, indicating high percentage of potential tumor-initiating cells. Subcutaneous transplantation of these tumor organoids into immunodeficient NOG mice successfully initiated tumor within two weeks, confirming their malignant property. Furthermore, organoids can be re-cultured from those xenograft tumors with increased growth speed and also can be long-term passaged.
Conclusion: We have succeeded in culturing malignant organoids from primary mouse liver tumors. This shall represent as a new model and bear broad implications for studying tumor initiating/stem cells and the process of liver tumor initiation.
Keyword: Tumor organoid, Primary liver tumor, Tumor initiating cells.

Analysis of HLA I peptides presented on human hepatocytes using ultrasensitive mass spectrometry

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Antigen specific immunotherapy is a promising strategy for the treatment of several liver-related diseases including Hepatitis B (HBV) and Hepatocellular carcinoma (HCC). Treatment effect requires both the induction of antigen specific T cells and the presentation of the peptide in HLA on the target cell. Although T cell induction is studied extensively as a measure of response to vaccination, it is less clear how well T cell cognate-peptides are presented in HLA on the target cells. To study HLA-presentation by patient-derived hepatocytes obtained from liver resection or biopsy, we set up a novel method to isolate human hepatocytes from small liver tissue samples, without the need for perfusion. This method allowed isolation of up to $200x10^6$ hepatocytes per gram liver with a viability and purity of over 90% across multiple etiologies, including severe cirrhosis. Using this approach, we now anticipate to analyze HLA-presentation of HBV peptides and tumor antigens in a large number of patient samples to identify the best targets for immunotherapy. We already applied unbiased mass spectrometry (MS) on human hepatocytes and this yielded several hundred HLA-binding peptides from $50x10^6$ cells, a sensitivity similar to the best MS-based HLA-peptidome study reported. In depth analysis revealed that these peptides mostly (>90%) consisted of 9-mers, which is consistent with their HLA-origin. Furthermore, using in silico prediction, the identified peptides were predicted to exclusively bind HLA-alleles expressed on the source material, collectively validating that these peptides truly originated from peptide-HLA complexes. In a second approach based on targeted MS, we searched for immunogenic peptides that may be presented beyond the detection limit of unbiased MS yet at sufficient levels to activate a T cell. As a proof of principle, we were able to detect a well-studied HBV epitope exogenously loaded on as little as $5x10^6$ cultured lymphoblastic cells with an equivalent sensitivity of epitope cognate T cells. This result demonstrates that targeted MS has high potential to analyze the HLA-presentation of specific peptides in small clinical samples.
Conclusion: we have developed methodology to identify novel and/or screen for known HLA-bound peptides on freshly isolated human hepatocytes from small scale clinical liver samples across etiologies including HBV and Hepatocellular carcinoma.

Pancreas and pancreatic tumor protein synthesis rates *in vivo* in cancer patients

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Living tissues are in a constant state of turnover, with a balance between protein synthesis and breakdown rates. Tumor growth should be secondary to a dysbalance between protein synthesis and breakdown. Only few data are available on organ tissue protein synthesis *in vivo* in humans, even less is known regarding tumor protein synthesis rates *in vivo* in cancer patients. In this study, we compare protein synthesis rates of pancreatic tumor tissue with that of the healthy pancreas tissue *in vivo* in human cancer patients.
Eight patients with pancreatic cancer undergoing pancreaticoduodenectomy were included into this study. Primed continuous infusions with L-[ring-$^{13}C_6$]phenylalanine and L-[3,5-$^{2}H_2$]tyrosine were started 2.5 h prior to surgery and continued through the surgical procedures (5-7 h). During surgery, biopsies were taken from the pancreas, the pancreatic tumor, and the *vastus lateralis* muscle. Post-absorptive fractional protein synthesis rates (%/h) were assessed by measuring the incorporation of labeled L-[ring-$^{13}C_6$]phenylalanine in tissue protein with the weighed plasma L-[ring-$^{13}C_6$]phenylalanine enrichments being used as precursor pool. Differences in synthesis rates between pancreas and muscle tissue and between pancreas and pancreatic tumor tissue were compared using the Wilcoxon signed-rank test.
Plasma L-[ring-$^{13}C_6$]phenylalanine enrichments (6-9 MPE) did not change significantly throughout the procedure (p=0.60). In six patients we were able to collect both pancreas and pancreatic tumor tissue. Pancreas protein synthesis rates were 18-fold higher when compared with skeletal muscle protein synthesis rates (0.694±0.228 vs 0.031±0.003 %/h, respectively; p<0.05).Pancreatic tumor protein synthesis rates (0.268±0.053 %/h) were 2.5-fold lower than pancreas protein synthesis rates (0.694±0.228 %/h; p<0.05).
Conclusion: Pancreas protein synthesis rates are several fold higher than skeletal muscle protein synthesis rates. Pancreatic tumor protein synthesis is relatively slow when evaluated in the light of turnover rates of the tissue in which the tumor resides. Therefore, tumor growth may be attributed to even lower protein breakdown rates.

Autophagy regulates Rac1 and RhoA activity in dendritic cells

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The T300A variant of the *ATG16L1* gene that reduces autophagy is one of the few highly prevalent risk factors associated specifically with Crohn's disease, but not with ulcerative colitis. We have previously shown a regulatory role for autophagy during dendritic cell (DC) - T cell interactions, where the T300A allele results in enhanced contact time and T cell hyperactivation. Furthermore, we have recently shown that autophagy^{low} DC have altered cytoskeletal morphology, with an elongated shape, reduced filopodia, enhanced membrane ruffling and impaired migratory capacity. We here further investigated the role of autophagy and RhoGTPases in DC cytoskeletal organization and function .
Methods: Autophagy^{low} DC were generated from small interfering RNA, ATG16L1 siRNA, monocyte-derived dendritic cells carrying at least one WT ATG16L1 allele. Cells were cultured with IL-4/GM-CSF for 6 days, after which ATG16L1 siRNA was added for 2 days. Rac1 and RhoA activity was measured using G-Lisa. Results: The observed morphology with lack of filopodia is consistent with Rac1 overactivation, and indeed Rac1 activity was increased in autophagy^{low} DC. Both morphology and migratory capacity were restored upon Rac1 inhibition. Physiologically, Rac1 and RhoA are in equilibrium and mutually inhibitory. Indeed, there was a reduction in RhoA activity in the autophagy^{low}DC compared to control DC (n=6). Whole protein levels of Rac1 and RhoA were not altered, suggesting a functional regulation rather than protein degradation.
Conclusion: Our results suggest that a defect in autophagy results in dysregulation of Rac1 and RhoA activity, resulting in altered DC migration. As active Rac1 and RhoA form a gradient in moving DC, we are currently investigating the role of autophagy in the locoregional regulation of RhoGTPases.

Immune responses in acute hepatitis B: chronicity versus resolved infection

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An acute hepatitis B virus (AHB) infection is mostly self-limiting but may lead to chronicity in a minority of adult patients. We analysed immune responses during AHB infection in patients who cleared the virus and a unique patient who became chronically infected. Nine patients with AHB infection (n=5 genotype A, n=1 genotype B, D, E and F) were included. Sampling was performed at baseline (BL), week 1, 4, 12 and 24. Eight healthy controls (blood donors) were included for comparison. NK cells were phenotyped by flowcytometry. PBMC from (gt A infected) patients were stimulated with HBV peptide pools, followed by intracellular cytokine staining. At BL, median HBV DNA load was 5.12 log IU/mL (range 3.53-8.23) and median was ALT 2,652 U/mL (range 690-3,970). Of 9 patients, 8 cleared HBsAg within 6 months (6/8 with anti-HBs formation). One patient (genotype A) became chronically infected (i.e. HBsAg and HBV DNA positivity ≥ 6 months after infection). Early time points were associated with an increase in CD56bright NK cells as compared to healthy controls (p=0.0037) and an increase in activated NK cells (CD38, HLA-DR, NKp46, perforin and granzyme B). Similarly, TRAIL expression on CD56bright NK cells was upregulated and normalized in all but the chronically infected patient towards week 24. In patients that cleared HBV, the peak of HBV-specific CD8+ and CD4+ responses was generally seen later in the course of the infection (around week 1 or 4). In the patient that became chronically infected, very low HBV-specific T cell responses were observed at all time points. ConclusionNK cells are activated early in the course of acute HBV infection. In patients who clear acute HBV infection, broad and multi-specific T cell responses are observed. Failure of NK cell normalization as well as narrow T cell responses may lead to chronic infection.

Hepatitis E virus activates signal transducer and activator of transcription 3 to facilitate virus replication

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Although hepatitis E has emerged as a global health issue, there is still no proven medication available and its host-virus interactions remain poorly understood. Signal transducer and activators of transcription 3 (STAT3) plays a key role in regulating host immune and inflammatory responses. This study aims to reveal the interactive dynamics of STAT3 with hepatitis E virus (HEV) and the consequences for viral replication. STAT3 activation requires phosphorylation at tyrosine 705 (Y705). Phosphorylated STAT3 results in dimerization and translocation to the nucleus to exerts its biological function. Thus, to evaluate the role of STAT3 in HEV replication, the statue of STAT3 was detected. In the presence of HEV, the level of STAT3-Y705 phosphorylation was strong induced. However, uninfected Huh7 cells did not show any detectable phosphorylated STAT3. Consequently, HEV-dependent STAT3 phosphorylation corresponded to a concomitant increase in STAT3 transcriptional activity by 50±8%. Importantly, HEV-dependent STAT3 phosphorylation was totally blocked by several JAK inhibitors. A commercial STAT3 inhibitor, S31-201, was used to specifically block STAT3 phosphorylation. S31-201 leads to significant inhibition of HEV replication. Thus, STAT3 serves as a promising target for the development of anti-HEV therapy.

6-thioguanine potently inhibits rotavirus infection through suppression of Rac1 activation

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Rotavirus is one of the major causative agents of gastroenteritis in infants younger than 5 years old. The disease causes 114 million episodes of diarrhea, 2.4 million patient's need to be Admitted into hospital, and an accurate estimated half million deaths annually. Recently it is increasingly clear That rotavirus infection HAS emerged as an Important cause of complications in organ transplantation recipients, and might be associated with inflammatory bowel disease (IBD) as well. 6-thioguanine (6-TG) HAS BEEN used as an immunosuppressive drug and treatment of IBD in the clinic. Hereto, we Aimed to Investigate the effects and mode-of-action of 6-TG on rotavirus. Caco2 cell line 3D model of human primary intestinal organoid, laboratory rotavirus strain (SA11) and patient-derived rotavirus strain were used in this study. We found That treatment or SA11 rotavirus Caco2 cells infected with various Concentrations (0001-10000 ng / ml) or 6-TG resulted in potent inhibition of rotavirus RNA replication and VP4 protein synthesis in a dose-dependent Manner. The IC_{50} value of 6-TG against rotavirus SA11 was 3.0×10^{-4} nM, CC_{50} or 6-TG to Caco2 cells was 9847.6 nM and selectivity index (SI, CC_{50} / IC_{50}) was 3.3×10^{7}. This effect was confirmed in primary Further organoids model with both laboratory and patient-derived strains. Mechanistically, 6-TG was bootable to inhibit active form of Rac1 (Rac1 GTP). L entiviral RNAi mediated loss-of-function assay to silence gene Rac1 resulted in inhibition of rotavirus infection. Rotavirus infection was restricted in Rac1 knockout mouse embryonic fibroblasts (MEFs) Compared with wild-type MEFs. Similar results were observed with the specific Rac1 inhibitor NSC23766. These data Demonstrated That active Rac1 (Rac1 GTP) a supportive role had rotavirus infection, All which is a target for the antiviral effect of 6-TG. Importantly, continuous treatment with 6-TG for 20 passages did not ATTENUATE its antiviral potency, indicating a high barrier to drug resistance development. In combination with the classical antivirals, 6-TG HAS additive effect with interferon-alpha with a synergy volume or -2.8 uM^2 % , but moderate antagonistic effect with ribavirin with a synergy volume or -26.02 uM^2 % .
CONCLUSIONS: We have identified 6-TG as a potent inhibitor of rotavirus infection with a high barrier to resistance development. Thus for transplantation patient's and IBD patients at risk for rotavirus infection, the choice of 6-TG treatment as an Appears rational.

PI3K-Akt-mTOR-4E-BP1 axis sustains rotavirus infection and Represents an anti-viral target

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Rotavirus infection is a major cause of severe dehydrating diarrhea in infants and resul ting in approximate 114 million diarrheal episodes and 453 000 infant deaths annu-ally. Rotavirus infection was found usefull in Particular cases or immunocompromised patient's irrespective to Their Age. Although two licensed vaccines safe named RotaTeq and Rotarix are available. The lack of specific treatment calls for novel avenues to combat this pathogen. Numerous signaling pathways play roles in regulating Important virus infection Either by supporting or defending the infection or viruses. Those among, the PI3K-Akt-mTOR signaling pathway plays a vital role in regulating the infection course of many viruses. We aim to determining Whether and how PI3K-Akt-mTOR signaling pathway Regulates rotavirus infection. In this study, we have dissected the effects of PI3K-Akt-mTOR signaling pathway on rotavirus infection by using pharmaceutic inhibitors of the pathway, I entiviral RNAi mediated loss-of-function assay and 4E-BP1 gene knock-out mouse embryonic fibroblasts (MEFs) cells. Both conventional cell culture models and a 3D model of human primary intestinal organoids were used in the study. We have usefull Investigated impact of a clinical used the mTOR inhibitor, rapamycin, on SA11 and patient-derived rotavirus strains. We found That PI3K-Akt-mTOR signaling is essential in sustaining rotavirus infection. Thus, blocking the key elements of this pathway-including PI3K, mTOR and 4E-BP1, HAS resulted in potent anti-rotavirus activity. Importantly, treatment or 5 or 10 nM rapamycin Significantly inhibited viral genomic RNA by 80.0 ± 0.1% (n = 8; P <0.01) and 79.9 ± 0.1%(N = 9; P <0.01) in Caco2 cells, respectively. This effect was confirmed in primary Further organoids model with both laboratory and patient-derived strains. This effect Involves 4E-BP1 mediated induction of autophagy, All which in turn exerts anti-rotavirus effects, since starvation-induced autophagy and autophagy related Important elements-including LC3II and Beclin1 knockdown resulted in inhibition of rotavirus infection.

Conclusions: These results revealed The Importance of the PI3K-Akt-mTOR signaling in rotavirus-host interactions and provided new avenues for antiviral drug development.

Splanchnic release contributes to the elevated pool of FGF19 in the circulation of patients with obstructive cholestasis

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Patients with obstructive cholestasis (OC) have elevated serum levels of FGF19, a bile salt-induced ileal enterokine that represses bile salt (BS) synthesis. Given the lack of luminal BS in patients with OC we hypothesized that their high systemic FGF19 levels may have an extra-ileal origin. Here we explored venous-arterial (VA) differences (Δ) across major abdominal organs to study the source of circulating FGF19 in OC. Perioperative levels of BS and FGF19 were determined in arterial blood (RA), and portal (PV), hepatic (HV), superior (SMV) and inferior mesenteric (IMV) veins of patients with (n=6) and without (n=14) cholestasis, who underwent pancreatic surgery for various indications. Positive ΔVA indicates release, negative indicates uptake. Data are expressed as median [IQR]. Patients in the OC group had higher levels of bilirubin, ALP (*P*=0.009), γGT (*P*=0.02), ALT (*P*=0.02) and AST (*P*=0.02), confirming cholestasis and hepatobiliary injury. FGF19 levels were higher in all blood vessels of OC patients (PV: 1.08 [0.57-20.0] vs. 0.11 [0.03-0.17] ng/mL, *P*=0.0002; RA: 3.4 [0.56-12.3] vs. 0.08 [0.02-0.15] ng/mL, *P*<0.001; HV: 3.6 [0.62-3.5] vs. 0.06 [0.03-0.16] ng/mL, *P*=0.0002; SMV: 3.7 [0.57-11.8] vs. 0.09 [0.02-0.14] ng/mL, *P*<0.0001 and IMV: 3.8 [0.55-12.8] vs. 0.09 [0.02-0.15] ng/mL, *P*=0.0001). Similarly, BS levels were increased in all vessels in the OC group, except for the SMV (PV: 39.3 [22-181] vs. 16.7 [7.4-22.3] µmol/L, *P*=0.02; RA: 23.0 [15.7-106] vs. 2.4 [1.1-10.3] µmol/L, *P*=0.003; HV: 31.8 [23.5-138] vs. 5.3 [1.7-42.8] µmol/L, *P*=0.03; SMV: 35.5 [21.9-136] vs. 20.1 [10.6-37.6] µmol/L, *P*=0.5 and IMV: 33.1 [19.7-173] vs. 5.5 [3.4-12.0] µmol/L, *P*=0.0002). In controls, both FGF19 and BS levels were higher in the SMV than in the IMV (0.08 [0.02-0.14] vs. 0.07 [0.02-0.12] ng/mL, *P*=0.0045) and (20.1 [10.6-37.6] vs. 5.5 [3.4 vs.12.0] µmol/L, *P*=0.0046), respectively. These differences were not observed in the OC group. There was no significant release of FGF19 by the small (SMV-RA) or large intestine (IMV-RA), nor significant uptake by the liver (HV-(0.7*PV+0.3*A)), in either group. Nonetheless, splanchnic release (HV-RA) of FGF19 was higher (+0.16 ng/mL, *P*=0.03) in patients with OC, suggesting increased splanchnic production in OC. In controls, but not in patients with OC, BS were released by the small intestine (+10.0 µmol/L, *P*<0.001), but not by the large intestine (*P*=0.24), and taken up by the liver (-3.3 µmol/L , *P*<0.001).
Conclusions: This study reveals that circulating levels of FGF19 across the gut-liver axis are elevated during OC. Whereas FGF19 is released by the splanchnic area during OC, hepatic production is not likely to be the source.

High percentage of visible lesions in patients with Barrett's oesophagus referred with dysplasia in random biopsies

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Endoscopic recognition of dysplasia or early cancer in Barrett's oesophagus (BE) is difficult. Experience in recognition of early neoplastic lesions is thought to increase the detection of visible dysplastic lesions. A previous study reported that endoscopists at community hospitals detect neoplastic lesions at a significant lower rate than referral Centers. The aim of the study was to establish the surplus of lesions found as well as the final outcome of pathology in patients referred with dysplasia or early adenocarcinoma (EAC) in the absence of endoscopically visible lesions. In our tertiary referral Center we retrospectively analysed all patients referred by 19 community hospitals with the diagnosis of BE with dysplasia or EAC between February 2008 and April 2016. All patients underwent a dedicated imaging endoscopy with high-definition endoscopy supplemented with virtual chromoendoscopy and/or acetic acid staining at the discretion of the endoscopist. All procedures were performed by an endoscopist with extensive experience in the detection of early neoplastic lesions in BE. During endoscopy all visible lesions were noted and biopsied and/or removed by endoscopic resection (ER). Patients were included for analysis when the presence of visible lesions was not described in the referral endoscopy report. In total 184 patients were referred with dysplasia or EAC of which 82 patient (80.5% male, age 42-81 years (median (68)) did not show a visible lesion upon referral endoscopy. Referral diagnosis of these 82 patients was LGD (32), HGD (43) and EAC (7). In our tertiary Center in 41/82 patients a significant visible lesion was detected during imaging endoscopy. Four of 32 patients (12.5%) referred with LGD showed a visible lesion during imaging endoscopy and definitive histology after ER showed resection specimens corresponding to LGD (1) and EAC (3). Thirty of 43 patients (69.8%) referred with HGD showed a visible lesion during imaging endoscopy and definitive histology after ER showed HGD (15) and EAC (15). In 7/7 patients (100%) referred with EAC in the biopsies a lesion was identified upon imaging endoscopy. In 18/75 (24%) patients referred with dysplasia (LGD/HGD) the referral diagnosis was thus upstaged to EAC. The presence of any grade of dysplasia in random biopsies in BE screening in community hospitals is a marker for more severe final pathology after endoscopic work-up in tertiary referral Center. The high percentage of missing visible lesions in BE containing EAC underscores current guide to referrer patients with any grade of dysplasia to expert Centers and expresses the need for training in recognition of dysplasia for endoscopists.

Salvage endoscopic resection in patients with oesophageal adenocarcinoma after chemoradiotherapy

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Oesophageal adenocarcinoma is the fastest rising type of cancer in the western world. For early oesophageal adenocarcinoma, endoscopic resection is an accepted curative treatment with an excellent long-term prognosis. For advanced disease, the preferred curative treatment is neoadjuvant chemoradiotherapy (CRT) followed by oesophageal resection. In patients who are unfit for surgery, definitive CRT is an alternative, but local failure after definitive CRT at the primary site remains a significant problem. Currently there is no systematic follow-up protocol for endoscopy in patients with oesophageal adenocarcinoma after definitive CRT not fit for surgery, but fit for endoscopy. Case series from Japan have reported endoscopic resection of residual oesophageal squamous cell carcinoma after chemoradiotherapy. However, to date curative treatment with salvage endoscopic resection in case of residual adenocarcinoma after CRT has not been reported. This is the first report ever describing endoscopic resection of residual oesophageal adenocarcinoma after chemoradiotherapy. Two patients with advanced oesophageal adenocarcinoma (cT2N0M0) had been treated with chemoradiotherapy, because comorbidity precluded oesophageal resection. When residual tumour was observed endoscopically, complete remission was achieved by salvage endoscopic therapy alone or in combination with APC. Endoscopic and radiologic follow-up by means of a CT scan was performed once every 3 months in the first year after endoscopic resection, once every 6 months in the second year, and once a year in the subsequent years. During this subsequent follow-up there were no signs of metastases, and complete remission of cancer and dysplasia sustained for respectively 35 months and 37 months. Both patients died of a non-tumour related cause.
In conclusion, this report suggests that salvage endoscopic resection after CRT could potentially be a curative treatment for residual adenocarcinoma after CRT in selected patients who are not suitable for surgery. Endoscopic follow-up of patients after CRT fit for endoscopy could be considered.

A randomized, controlled trial comparing a simplified and standard regimen for focal radiofrequency ablation treatment of dysplastic Barrett's esophagus

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Radiofrequency ablation (RFA) is highly effective and durable for the treatment of dysplastic Barrett's esophagus (BE). For focal RFA a simplified regimen (3x15J/cm^2-no clean) has proven equally effective as the standard (2x15J/cm^2-clean-2x15J/cm^2) regimen. Advantages of the simplified regimen include less introductions of the endoscope and shorter procedure time. Unfortunately, this simplified regimen was associated with a higher stricture rate. Therefore, we lowered RF-energy to 12J/cm^2 and we now hypothesize that this new simplified regimen (3x12J/cm^2-no clean) is as effective and safe as the standard regimen for the treatment of dysplastic BE. In this ongoing non-inferiority design RCT, patients with dysplastic BE or residual BE after endoscopic resection (ER) of a visible lesion were included and randomly assigned on a 1:1 ratio to either the simplified (3x12J/cm^2-no clean) or the standard (2x15J/cm^2-clean-2x15J/cm^2) regimen. Trimonthly focal RFA treatments (maximum of 3 sessions) were continued until all BE was eradicated. Primary outcome parameter was endoscopic and histological eradication of intestinal metaplasia (IM) and dysplasia (CE-IM and CE-DYS) after 2 focal RFA treatments. Secondary outcome parameters were CE-IM and CE DYS after 3 focal RFA sessions, stricture rate requiring dilation therapy, and procedure time. Calculated sample size was a minimum of 36 patients per group. Seventy-nine patients (median BE C0M2) were included between March 2015 and July 2016. Worst histology was LGD in 23 (29%), HGD in 39 (49%) and early cancer in 17 (22%). Thirty-four (43%) patients underwent primary circumferential RFA prior to inclusion in the study. To date, 66 patients completed the study; in 13 patients RFA treatment is still ongoing. After two focal RFA sessions, CE-IM and CE-DYS was reached in 31/37 (84%) patients in the simplified arm, compared to 24/29 (83%) patients in the standard arm (p=ns). After 3 focal RFA sessions, eradication rates in both arms increased to 34/37 (92%) and 26/29 (90%) (p=ns), respectively. Among patients treated with the simple regimen, strictures requiring dilation were observed in 3/37 (8%), compared with 3/29 (10%) patients following the standard regimen (p=0.54). Procedure time included a median of 13 (IQR 10-16) minutes for the simplified regimen, compared to 19 (IQR 15-22) minutes for the standard regimen (p=<0.001). Conclusion: The simplified regimen (3x12J/cm^2-no clean) for focal RFA treatment is non-inferior to the standard regimen (2x15J/cm^2-clean-2x15J/cm^2), and is associated with a significantly shorter procedure time, making it favorable to use.

Seven-year prospective follow-up results of radiofrequency ablation for Barrett's esophagus with high-grade dysplasia and early cancer

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Radiofrequency ablation (RFA) of Barrett's esophagus (BE), with or without prior endoscopic resection (ER) of focal lesions, results in complete eradication of intestinal metaplasia (CE-IM) and complete eradication of neoplasia (CE-neo) in 93-100 % and 96-100%, respectively. The aim of this study was to assess if these excellent results after successful RFA for BE with high-grade dysplasia (HGD) or early cancer (EC) are sustained on the long term. We screened all patients treated with RFA, and ER in case of visible lesions, for BE with histologically proven HGD/EC, who were previously enrolled in 5 consecutive cohort studies in a Dutch tertiary referral center. All patients who had reached endoscopic and histologically confirmed CE-neo and CE-IM after RFA were included for evaluation of long-term follow-up (FU). Primary outcome: recurrence of HGD/EC; recurrence of endoscopically visible BE. Secondary outcomes: Buried Barrett's (BB); IM distal to a normal appearing neo-SCJ; need for retreatment; sustained CE-IM and CE-neo at last FU. Sixty-eight patients were included (55 men, median 64 yrs, median BE C5M6). In 53/68 patients ER was performed (worst pathology: low-grade dysplasia (LGD) (n=3), HGD (n=23), EC (n=27)). Worst pathology pre-RFA (after any ER): non-dysplastic IM (n=9), LGD (n=27), HGD (n=32). Median FU was 85 mo (IQR 58-96) with median 7 FU endoscopies per patient. Recurrence of HGD/EC was found in 2 patients (3%): one patient with T1m2 cancer 3cm above the neo-SCJ after 44 mo and one patient had a visible lesion at the neo-SCJ with HGD after 22 mo, both were treated successfully with ER. Recurrence of endoscopically visible BE was seen in 22 patients (32%) after median 20 mo: small Barrett island (n=10), BE tongue (≤1cm n=9, ≤2cm n=1), circumferential BE ≤2cm (n=2). In 3 patients BB were detected (overall 3/448 FU endoscopies, 0.7%). IM in the neo-SCJ was found in 19 patients (28%), this was not reproduced in 84%. In 2 patients LGD without IM was found in the neo-SCJ. Eleven patients required retreatment: APC for small areas of visible BE (n=5), 6 patients had additional ER (1x T1m2, 1x HGD, 2x LGD, 2x Barrett island), RFA for LGD without IM in the neo-SCJ (n=1) . CE-neo and CE-IM (excluding IM in the neo-z-line) at last FU was seen in 96% and 100% respectively. Conclusions: With 7-years of follow-up, this study presents the longest published follow-up data on RFA for BE with HGD/EC to date. Our long-term outcomes show that after successful RFA recurrence of HGD/EC is rare (3%). Recurrence of endoscopically visible BE was found in 32% of patients, however it was confined to small islands or tongues ≤1cm in the vast majority of patients.

Routine use of endoscopic ultrasound in patients with suspected common bile duct stones prevents unnecessary ERCP's

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Background: Endoscopic ultrasound (EUS) has been proven safe and accurate in the diagnosis of common bile duct stones (CBDS). Routine use of EUS in the work up of CBDS can prevent unnecessary endoscopic retrograde cholangiography's (ERCP's) with its potential severe complications. Since EUS is not widely available, therapeutic strategy is often based on other clinical parameters. The aim of this retrospective study was to investigate the accuracy of EUS and its clinical impact on the use of ERCP in patients with suspected CBDS. Methods: In a single-center observational study, all consecutive patients who underwent an ERCP and/or EUS for CBDS from 2012-2014 were identified. In addition, all patients with suspected CBDS who underwent EUS from 2014 until 2015, were enrolled in a database. Demographic data, clinical presentation, laboratory test results, imaging studies (abdominal ultrasound, EUS, ERCP) and clinical manifestations during follow up were recorded and analyzed. Patients were categorized in low, intermediate and high probability of CBDS, according to the ASGE guidelines. In patients with a positive EUS, ERCP was considered the gold standard. In patients with a negative EUS, biliary events related to CBDS during one year follow up were considered as false negative. Results: From 2012 until 2015, the increase in EUS examinations was significantly associated with a decrease in ERCP's ($P<0.001$). In total, 304 patients were enrolled in the database: 41(13%) were classified as low, 136 (45%) as intermediate and 127(42%) as high probability for CBDS. Positive EUS findings were confirmed by ERCP in 115 out of 127 patients (sensitivity 91%). From the patients with negative EUS (N=177), eleven had a biliary complication (specificity 94%). Four (10%) patients with low risk at CBDS, 35 (26%) with intermediate risk and 76 (60%) with high risk had confirmed CBDS. Conclusion: Since the introduction of EUS in our hospital there has been a significant decrease in ERCP interventions for suspected CBDS. EUS is accurate in determining the presence or absence of CBDS. We suggest that routine use of EUS in the diagnosis of CBDS should be implemented in the Dutch guideline.

Expert and construct validity of a novel mechanical ERCP simulator

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Simulator-based training has become an important pillar in competence based medicine, especially in training novice endoscopists. Several simulators have been validated and it has been demonstrated that the use of simulators in gastrointestinal endoscopy accelerates the early learning curve of trainees. ERCP simulator-based training seems an ideal platform in training of novices. Surprisingly, limited data are available on simulators in ERCP training, only 6 simulators have been described. However, despite their seemingly obvious training potential, the applicability of each of these simulators as a training tool has not been demonstrated. We aimed to determine the expert and construct validity of the Boškoski-Costamagna mechanical ERCP Trainer, and to assess its didactic value, as judged by experts. Participants were divided into four groups based on ERCP lifetime experience: novices (<100 ERCPs), intermediate (100-600 ERCPs), experienced (601-2500 ERCPs), and experts (>2500 ERCPs). Participants performed several standardized assignments on the simulator, including cannulation of both ducts, stent placement, and stone extraction. Outcome parameters included times to complete the procedure, ability to cannulate both ducts, successful stent placement, and stone extraction; number of attempts to cannulate the bile ducts. Participants were instructed to perform the assignments to the best of their ability without a competitive element. All experts filled out a questionnaire on the simulator's realism and didactic value. A total of 46 participants were included. Novices (N=11) completed the total procedure in 21:09 (min:sec), intermediates (N=5) in 10:58, experienced (N=8) in 06:42 and experts (N=22) in 06:05. Experts were significantly faster than novices (Kruskal-Wallis test $p<0.000$).There were no statistical differences between novices and experts in number of attempts ($p=0.985$). Experts rated the realism of the simulator 7.12 on a ten-point Likert scale. The realism of the various ERCP therapeutic procedures scored 7.99 for biliary plastic stent placement, pancreatic plastic stent placement 7.8, and CBD stone extraction 7.42. The potential as a training tool of the simulator in training novices was rated 3.91 on a four-point Likert scale, and there was a high agreement among experts to include the simulator in the training of novice endoscopists (3.86 on a four-point scale). Conclusion: The novel Boškoski-Costamagna ERCP simulator demonstrates excellent expert and construct validity. ERCP experts highly agree on the didactic value and added value of this simulator in the training curriculum of novice endoscopists.

Differences in colonoscopy associated costs between primary colonoscopy and colonoscopy after positive FIT in colorectal cancer screening

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In colorectal cancer (CRC) screening programs, variable screening tests are being used, including primary colonoscopy and fecal immunochemical testing (FIT). Screenees with a positive FIT have a higher prevalence of advanced neoplasia than screenees undergoing a primary colonoscopy without preselection. Nonetheless, cost-effectiveness analyses comparing these differential screening programs consistently use equal colonoscopy costs. We aimed to compare colonoscopy differences affecting colonoscopy costs between CRC screening programs based on FIT and primary colonoscopy. We prospectively collected data of 2,107 Dutch average risk individuals, aged 50-75 years, who underwent a colonoscopy after a positive FIT or a primary screening colonoscopy. In the FIT-based CRC screening program, cut-offs used for colonoscopy referral were 15 or 47 µg hemoglobin/g feces. In both screening programs, colonoscopists were instructed to remove any screen-detected polyp. Costs in Euros (€) were based on 2013 cost prices of a Dutch tertiary hospital, excluding taxes. Multivariate analyses of covariance were used to determine if colonoscopy duration and mean number of polyps per patients differed between FIT-based colonoscopies and primary colonoscopies corrected for potential confounders, including gender and age. In total, 1,413 screenees underwent a primary colonoscopy and 694 underwent a colonoscopy after a positive FIT. In case polypectomy was needed, additional fixed costs of materials used were €95.73 and additional variable costs were €8.46 per polyp removed. Mean primary colonoscopy duration was 23 min (standard deviation (SD) ±12 min) versus 30 min (SD±16 min) for a colonoscopy after a positive FIT, $p<0.001$. Mean number of polyps removed per patient were 2.5 (SD ± 2.2) and 3.7 (SD ± 3.0), respectively, $p<0.001$. Multivariate analyses of covariance showed that both mean colonoscopy duration ($p<0.001$) and number of polyps per patient ($p<0.001$) were significantly higher in FIT-based colonoscopies compared to primary colonoscopies when corrected for confounders. Conclusion In CRC screening programs, colonoscopy duration and number of polyps detected are significantly higher in colonoscopies performed following a positive FIT compared to primary screening colonoscopies. These differences affect colonoscopy resources and costs and should be taken into account in cost-effectiveness analyses and implementation programs of CRC screening.

Feasibility, safety and accuracy of the Extra Wide Angle View (EWAVE) Colonoscope for the detection of colorectal lesions

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Colonoscopy is the reference standard for the detection and removal of colorectal polyps and adenomas, but is associated with significant adenoma miss rates. In order to improve the detection of adenomas, a new Extra Wide Angle View (EWAVE) colonoscope was developed (Olympus Medical Systems). This EWAVE colonoscope is a prototype that offers a 235-degree view obtained from a forward-viewing as well as a lateral backward-viewing lens, both incorporated into one image. We conducted a prospective multiCenter cohort study assessing the feasibility, safety and accuracy of the EWAVE-colonoscope for the detection of colorectal adenomas. This study was performed in five, both regional and tertiary endoscopy centers in Europe. We included patients with a personal history of colorectal neoplasms, a positive family history for CRC, and those having symptoms, and were scheduled for colonoscopy between November 2015 and June 2016. Consenting patients underwent a colonoscopy with the EWAVE-colonoscope performed by an experienced and EWAVE-trained endoscopist (≥500 colonoscopies, ≥10 with the EWAVE system). Two hundred patients were included, of which 193 (96.5%) underwent EWAVE colonoscopy. Six patients withdrew informed consent and for one case an EWAVE-trained endoscopist was not available at the time of colonoscopy. Cecal intubation rate was 97.4% with a median cecal intubation time of 4 minutes (IQR 2:00-7:00). Median net withdrawal time was 14:49 minutes (IQR 12:00-19:00). EWAVE colonoscopy had a polyp detection rate (PDR) of 61.1% with an overall detection of 260 polyps in 118 patients. Median polyp size was 4.0 millimeters (IQR 3.0-5.0). In 51.8% (100/193) of the patients at least one non-pedunculated (Paris Classification Is or IIa) polyp was detected and the detection rate of right-sided polyps was 37.3% (72/193). The adenoma detection rate (ADR) was 39.9% (77/193) and the advanced ADR (adenomas with a villous component, high-grade dysplasia or a lesion size ≥10 millimeter) was 13.5% (26/193). In 4 patients colorectal cancer was detected. There were no adverse events.
Conclusion: EWAVE colonoscopy is feasible and safe and achieved an ADR of 39.9%, which seems superior to the ADRs (25.8-31.8%) of conventional colonoscopy in similar patient populations. For the future a randomized comparison with conventional colonoscopy is needed to further elucidate the additional benefits of this wide-angle view colonoscope.

Feasibility of the use of virtual reality glasses to relieve pain and discomfort in patients during colonoscopy

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Background Colonoscopy is an invasive procedure which may cause pain and discomfort to the patient. To enhance comfort and relieve pain, patients routinely receive sedatives and analgesics. However, sedatives and analgesics may cause adverse events. Virtual reality (VR) offers immersive, three-dimensional experiences that may offer an additive analgesic effect by distracting the attention of the patient. AIM We performed a pilot study to investigate the feasibility of VR distraction during colonoscopy.
Methods Adults with any indication of colonoscopy were considered for participation. Patients were randomized into two groups: with and without VR glasses. Main outcome was feasibility of colonoscopy in terms of communication and length of procedure. We assessed patient comfort, pain and anxiety before, during and after the procedure, using patient questionnaires and qualitative assessment by the investigators.
Results We included 19 patients, and 10/19 wore VR glasses. Base characteristics and procedural characteristics of both groups were similar. No significant differences were observed in patient comfort, pain, and anxiety in relation to the procedure, between the two groups. All patients in the intervention group have completed the procedure wearing VR glasses. Patients in the intervention group described a pleasant distracting effect using VR glasses. Endoscopists did not experience any disadvantages of the VR glasses in terms of communication with the patient, change of position of the patient or lengthening of the procedure.
Conclusion It is feasible to implement VR distraction in colonoscopy. Patients reported the experience as pleasant and distracting.

Visualizing hepatocellular amino acid kinetics through mass spectrometry imaging of stable isotopes

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Background and Aims Mass Spectrometry Imaging (MSI) is a high-performance analytical tool that can be used to simultaneously explore the distribution of numerous molecules throughout tissues. Currently, the major limitation is that it provides a static snapshot of what are inherently highly dynamic systems where new molecules are constantly synthesized and consumed. Here we developed new and innovative MSI methodologies that overcome this limitation and simultaneously view the dynamic molecular-level changes occurring within biological tissues by measuring dilution and hydroxylation of stable isotopes. We evaluated the method specifically on hepatocellular metabolism of the essential amino acid L-phenylalanine. Stable isotopes of phenylalanine are commonly used in clinical studies to measure protein turnover. In liver, phenylalanine is hydroxylated into L-tyrosine, and altered levels are related to NASH, NAFLD, cirrhosis and several cancer types. We investigated reproducibility of the measurement of phenylalanine kinetics in liver and correlated kinetics with tissue morphology and other amino acids. Methods A bolus injection of $^{13}C_6$ phenylalanine was administered via the tail vein of immune-compromised Nu-Fox1nu/nu mice (n=16). The mice were sacrificed at 10, 30 or 60 minutes after injection. Liver sections were covered with TAHS for on-tissue derivatization and DHB as a matrix for high resolution MALDI-MSI in positive mode. A novel MATLAB algorithm was developed to visualize spatial tracer kinetics. After MSI analysis, liver sections were stained with hematoxylin and eosin, reviewed for tissue morphology, and co-registered with the Mass Spectrometry images. Results and discussion We have optimized a method for on tissue derivatization of amino acids and other compounds containing an amine group, facilitating the spatial and dynamic measurement of liver metabolism. We detected and identified ~50 amino metabolites at each pixel. In addition, tracer-tracee ratios and de novo hydroxylation were visualized at a spatial resolution of 25 µm. We validated and complemented our results using conventional GC-C-IRMS facilitating quantitative measurement of phenylalanine and tyrosine enrichment of free amino acids and proteins in tissues and blood. We present a novel and reproducible method to explore the spatial distribution and dynamics of hepatocellular amino acid metabolism, allowing for the first time, visualization of co-localization of phenylalanine and amino acid kinetics in liver.

Reducing PPI and H2RA prescriptions in pediatrics

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Prescribing acid-suppressant medication for children has increased substantially over the past two decades, despite (inter)national guide recommendations to prescribe prudently. This medication is often not effective in reducing symptoms of gastro-esophageal reflux disease (GERD) and can lead to side effects. Therefore, a national campaign was launched (Choosing Wisely) to reduce unnecessary prescriptions. Our study aim was to reduce the number of prescriptions of acid-suppressant medication for GERD in children aged 0 – 18 years through active implementation of the Dutch guide recommendations (Wise Choices). Active implementation consisted of two parts: pediatricians and residents in a Dutch academic pediatric hospital, received information on appropriate prescribing of acid-suppressant medication. They received a link to an app and a pocket-sized summary card with evidence-based recommendations (Wise Choices). Additionally, clinicians who prescribed acid-suppressant medication were contacted by e-mail/telephone to provide individual feedback which consisted of discussing the indication for prescribing and their knowledge of the national guide and Wise Choices. Data on prescriptions of acid-suppressant medication were collected electronically before (January 2014–August 2015), during (September 2015–February 2016) and after the intervention (March–April 2016). Interrupted time series analysis was used to assess the effect of the intervention on the number of prescriptions for acid-suppressant medication. In total 4053 prescriptions for PPI (93.1%, n = 3776) and H2RA (6.9%, n = 279) were registered between January 2014 and April 2016. The number of prescriptions ranged from 99 to 195/month (mean 145, SD 20.0). Of the 78 clinicians that were contacted in the intervention period, 76 (97%) responded. Upon first contact 61.5% of respondents was familiar with the guideline, another 23.1% had heard of the guide but was unfamiliar with the content. Similarly, 43.6% of respondents was familiar with the Wise Choices upon first contact and 24.4% had heard of the campaign but was unfamiliar with the content. Two months post-intervention, a decrease of 43.6 prescriptions per month was measured (95% CI 1.2 to 86.1). This study shows the majority of clinicians was familiar with the national guide-line, less than half of the clinicians were familiar with the Wise Choices. A non-significant reduction of acid-suppressant medication prescriptions on the short term was observed. Since this was measured after a short follow-up period, repeated measurements after a longer follow-up period are necessary to evaluate the long-term implementation effect.

The effect of specific refluxate components on bile receptor signaling and development of metaplastic Barrett-like glands in mice

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Chronic reflux, a risk factor for the development of Barrett's esophagus (BE), causes damage to the normal squamous epithelium of the esophagus. The effect of different bile acids (BAs) in the refluxates, which play a role in BE development, has been poorly studied with respect to the pathogenesis of BE. Insights in the effects of the bile components can help provide more efficacious targets for preventing the development of metaplasia and the progression from BE to EAC. BAs not only have detergent properties, but can also act as signaling molecules by activating the farnesoid X receptor (FXR) and G-protein coupled bile acid receptor (TGR5). Both receptors are upregulated in BE and EAC compared to normal squamous mucosa, suggesting a possible role in the progression of BE (De Gottardi 2006; Hong 2010). The aim of the study was to analyze refluxates of BE patients and evaluate the effect of the different bile components on metaplastic gland development and bile receptor activation. Determination of the bile composition in refluxate of BE patients by HLPC showed the presence of both glyco-conjugated (67.6±8.8%) and tauro-conjugated BAs (31.5±9.15). Although deoxycholic acid (DCA), formed through deconjugation by microbial enzymes present in the colon, was almost absent in our refluxates (0.5±0.4%), others have shown their presence in reflux (Nehra 1999) possibly due to pH increase caused by PPI use resulting in gastric bacterial overgrowth and deconjugation of BAs. Each of the six conjugated bile components [glyco-, glycodeoxy-, glycochenodeoxy-, tauro-, taurodeoxy- and tauro-chenodeoxy cholic acid] and DCA were tested individually in vivo for 16 weeks at 10mM. All mice developed multi-layered glands at the SCJ (36/36). Overall, mice treated with glyco-conjugated BAs developed more glands compared to DCA or tauro-conjugated BAs. Also alcian blue expression, representing mucin production, was higher compared to DCA treated or tauro-conjugated BAs treated group. To investigate which bile components are able to activate bile receptors we transfected primary mouse esophageal keratinocytes with either TGR5 or FXR and treated the cells with different BAs. Activation of the receptors result in conformational changes, which can be detected by measuring fluorescence resonance energy transfer (FRET). Both DCA and all conjugated BAs were able to activate the membrane bound TGR5 receptor, as shown by a change in signal. DCA was able to activate FXR, while the addition of all conjugated BAs did not result in a signal change. The possibility of DCA to activate the FXR may result in the onset of different genes, which might result in the progression from BE to EAC.

Increased frequency of Barrett's esophagus in patients with MUTYH associated polyposis

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Aim Barrett's Esophagus (BE) is driven by inflammation that is thought to be triggered by gastro-esophageal reflux (GERD). This chronic state of systemic and localized inflamemation promotes DNA damage, DNA replication stress and genomic instability, which increases the risk of developing clones containing genomic alterations, eventually leading to adenocarcinoma. Here, we investigate in patients with an impaired DNA repair system, the prevalence of BE and esophageal adenocarcinoma. Methods Patients with clinically and genetically confirmed diagnosis of attenuated familial adenomatous polyposis ((A)FAP) or MUTYH associated polyposis (MAP) were retrospectively identified via the database of the Dept of medical genetics of one academic hospital and the Dutch Hereditary Cancer Registry. Upper gastrointestinal examination reports, associated pathologic charts of upper gastrointestinal biopsies and PALGA data were reviewed to determine the prevalence of BE and EAC in these patients. The available coupes of the Barrett biopsies were revised by two expert GI pathologists. Results We identified 378 patients with A(FAP), of which 4 patients (1,1%) had a BE. Of the 95 patients with MAP, BE was found in 7 (7,4%). Two of those patients with BE developed an EAC. The average age at the first diagnosis of BE in MAP patients was 53,5 years (range 44-65). Conclusion Based on these results, we recommend that surveillance of patients with MAP should not only be focused on duodenal adenomas but also on the presence of Barrett's esophagus. The prevalence of BE with patients with MAP seems to be increased and possibly the progression of the metaplasia-dysplasia-carcinoma sequence is accelerated. From a biological point of view this observation could make sense, due to the impaired MUTYH protein function that plays a pivotal role in the DNA damage repair caused by oxidative stress for example by gastro-esophageal reflux disease.

Detection of sepsis in preterm infants by fecal volatile organic compounds analysis: a proof of principle study

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Objectives Several studies associated altered gut microbiota composition in preterm infants with late-onset sepsis (LOS), up to days prior to clinical onset of sepsis. However, microbiota analysis as early diagnostic biomarker is in clinical practice currently not feasible because of logistic aspects and high costs. Therefore, we hypothesized that analysis of fecal volatile organic compounds (VOC) may serve as non-invasive biomarker to predict LOS at a preclinical stage, since VOC reflect the composition and activity of intestinal microbial communities. Methods In a prospective multicenter study, fecal samples were collected daily from infants with a gestational age of <30 weeks. VOC signatures of fecal samples from infants with LOS, collected up to five days before diagnosis, were analyzed by means of an electronic nose technology (Cyranose 320®) and compared to matched controls. Results Fecal VOC profiles of infants with LOS (n=36) could be discriminated from controls (n=40) at three days (AUC [± 95%CI], p-value, sensitivity, specificity; 70.2 [52.2-88.3], 0.033, 57.1%, 61.5%), two days (77.7 [62.7-92.7], 0.050, 75.0%, 70.8%) and one day (70.4 [49.6-91.3], 0.037, 64.3%, 64.3%) before the onset of LOS. Conclusions Fecal VOC profiles of preterm infants with LOS could be discriminated from matched controls, up to three days before clinical onset of the disease, underlining the hypothesis that intestinal microbiota may play an etiological role in LOS. Notably, VOC profiling is clinically feasible and the potential of this technique in the early detection of LOS needs to be confirmed in future studies.

Filgotinib, a selective JAK1 inhibitor, induces clinical remission in patients with moderate-to-severe Crohn's disease: results from the Phase II FITZROY study

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Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor, which demonstrated efficacy in patients with rheumatoid arthritis. This Phase II study evaluated efficacy and safety of filgotinib in patients with active Crohn's disease (CD). 174 patients with moderate-to-severely active CD [CDAI: 220 to 450) and ulcerations confirmed by centrally read endoscopy were randomized (3:1) to receive 200mg filgotinib (FIL) or placebo (PBO) once daily for 10 weeks. Thereafter, patients continued to receive filgotinib (200mg or 100mg once daily) or placebo for another 10 weeks. Anti-TNF-naïves (42%) and anti-TNF non-responders (58%) were included. Immunosuppressive agents had to be discontinued, but steroids were kept stable until Week 10. Efficacy and safety data from the 10-week induction period are presented, including the primary endpoint of clinical remission (CDAI < 150) at Week 10. Base characteristics were comparable in the filgotinib and placebo group, including mean disease duration (8.3 years), mean CDAI score (293), mean SES-CD score (14.6), mean CRP (15.6 mg/L, 41% > 10mg/L) and oral corticosteroids use (51%, mean daily dose 20.8 mg/day). Filgotinib induced clinical remission in 47% of patients, compared to 23% with placebo (p=0.0077) at Week 10. Significantly more filgotinib-patients showed a clinical response (CDAI improvement ≥ 100 points) (FIL: 59%, PBO: 41%, p=0.0453) and improved quality of life (PRO2 mean change from base FIL: -21.9; PBO: -15.6; p=0.0321; IBDQ mean changes from base (FIL: 33.8, PBO: 17.6; p=0.0046)) compared to placebo. This was evident in all IBDQ subcomponents: bowel symptoms (FIL: 10.0; PBO: 5.6; p=0.0040), systemic symptoms (FIL: 5.7; PBO: 2.9; p=0.0044), emotional status (FIL: 12.1; PBO: 6.1; p=0.0094), and social functioning (FIL: 6.2; PBO: 2.9; p=0.0202). Numerically more patients on filgotinib had their CRP normalized (FIL: 27%, PBO: 14%) and showed at least 50% improvement in SES-CD score (FIL: 25%, PBO: 14%). Histopathology scores on biopsies taken at Week 10 decreased significantly more with filgotinib versus placebo (FIL: -3.5, PBO: -0.6; p=0.0359). Filgotinib was safe and well tolerated. Similar incidences in early discontinuations, SAEs and AEs including infections were observed, with the majority of SAEs related to worsening of CD. Filgotinib is the first JAK inhibitor showing efficacy in moderate-to-severe CD, as demonstrated by induction of clinical remission and response, and improved quality of life. A global Phase III program is ongoing with filgotinib to confirm these data in Crohn's disease (DIVERSITY), as well as in ulcerative colitis patients (Phase IIB/III SELECTION study).

Long-term follow-up in Dutch autoimmune hepatitis patiënts

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Autoimmune hepatitis (AIH) is a severe immune-mediated inflammation of the liver, requiring lifelong immunosuppressive therapy. Little is known about the disease course of AIH in patients being treated with immunosuppressive therapy for multiple decades. In this study we aimed to assess the long-term outcomes of a large nationwide cohort of patients with AIH. Patients included into the Dutch national AIH database in 2008 were selected if they had a probable/definite AIH diagnostic score. Medical charts were retrospectively reviewed from diagnosis until September 2016. Parameters included time to remission, relapses, base and follow-up histological and biochemical assessment, steroid and thiopurine related side-effects and liver transplantations. Biochemical remission was defined as complete normalization of ALT <45 U/L and IgG < 16 g/L, relapses as ALT> 3x upper limit of normal or an IgG >20 g/L. Survival was prospectively assessed from June 2008 to September 2016. Records from 381 patients (294 females, 77%) were retrieved from 5 academic and 4 general hospitals. The median age at diagnosis was 43 years (IQR 25-56). The median follow-up (FU) was 13 years (IQR 10-18) with a total of 5140 person years at risk. Base liver histology of 298 biopsies showed fibrosis in 159 (42%) and cirrhosis in 58 (15%) patients. There was a significant progression of cirrhosis staging ($p<.001$) in the FU compared with the base biopsy. At 12 months of therapy 83% of patients achieved biochemical remission. Relapse occurred in 54% of AIH patients. Dual-energy X-ray absorptiometry was performed in 221 patients, radiologists reported osteoporosis in 44 and osteopenia in 92 patients. Steroid-induced diabetes occurred in 39 (10%) of patients. Cataract was reported in 35 (9%) of patients during FU. During the prospective 8 year FU period, 43 (12%) patients died, 18 (5%) of whom died due to AIH related causes. The mean age at death was 71 years (range 33-94; SD 15 years). Liver transplantation was performed in 18 (5%) patients and indicated in another 9 patients (2%). The median time from diagnosis to transplantation was 41 months (IQR 12 to 121). This is the first study in which the outcome of AIH including treatment related adverse events is assessed systematically over a long follow-up period. Long-term AIH is characterized by numerous events. Besides a significant progression to fibrosis and cirrhosis, patients experienced considerable side-effects during the disease course. The 8-year survival in this cohort was 88%, which is similar to other cohort studies in AIH.

Diagnostic yield of upper gastrointestinal endoscopy in young adults (18 - 40 years); the referral guide ("NHG maagklachten") tested in daily practice

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Gastroscopy is a commonly used procedure to diagnose abnormalities of the upper part of the GI tract. However, its yield is low in the absence of alarm symptoms, as functional disorders are most prevalent in this group. At the background of rising healthcare costs, we were interested whether our open access endoscopy unit functions effectively for young adult patients referred for upper endoscopy. This is also a topic in the research out of the NVMDL (Kennisagenda). We reviewed the indications and results of gastroscopy in patients between 18 and 40 years old in the period 2010-2014. We checked whether the indication for endoscopy was in accordance with the NHG guideline. Alarm symptoms that justify endoscopy are: hematemesis, melena, persistent vomiting, disorders or pain associated with food passage, unintentional weight loss, anemia and a suddenly changed dyspepsia in a patient with a gastric band. Examples of indications that are not in with the guide are pyrosis, reflux and dyspepsia. We defined a gastroscopy effective if it resulted in a change of treatment, or if it assessed a premalignant or malignant lesion. Treatment with proton pump inhibiters was not considered as a change of treatment policy, since the guidelines recommend starting empirically in absence of alarm features. Neither Helicobacter pylori eradication, as its presence can be diagnosed in a much cheaper and less invasive way. Examples of significant findings are cancer, Barrett, Candida- and eosinophilic esophagitis, ulcers, corpus alienum. Examples of findings that did not change treatment regimen are gastritis, hiatal hernia, and reflux esophagitis. Results: Between 2010 and 2014, 1661 upper endoscopies were performed in our institution in patients between 18 en 40 years old (of 10690 total upper endoscopies performed, 15.5%). Mean age was 30,9 years. Of these 1661, 1060 referrals (63,8%) were not in with the NHG standard. Only 30 significant findings were assessed in this group (2,8%). When the referral for gastroscopy was in with the NHG guideline, yield was much higher (155 significant findings in 601 referrals, 25,8%). When divided by referrer: of the 712 patients without alarm features who were referred by the general practioner, only 12 had significant findings, resulting in a yield of 1,7%.
In conclusion, the yield of gastroscopy in young adult patients without alarm features is low. This group represents a significant portion of the workload in non-academic practice and a potential for reducing health care costs when better selection is made who to refer or to accept for endoscopy.

Cholestatic liver injury during critical illness: disturbed enterohepatic bile salt signaling in patients with diarrhea

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Aim of the current study was to explore the hypothesis that diarrhea during critical illness disrupts normal enterohepatic signaling of bile salts through intestinal malabsorption of bile salts. This disruption could play a role in critical illness associated liver injury, for which the presence of diarrhea (>350mg/day) is a risk factor. We investigated plasma levels of bile salts, FGF19 (a bile salt-induced enterokine controlling bile salt synthesis) and C4 (a serum marker reflecting bile salt synthesis) in critically ill patients. The study population consisted of enterally fed, mechanically ventilated patients admitted to our intensive care unit (ICU). Patients with a primary hepato-biliary diagnosis (i.e. biliary obstruction or cholangitis) or admitted after elective surgery were excluded. After inclusion, allocation to the diarrhea group (N=12) or no diarrhea group (N=18) was based on 24 hour fecal production ≥ 350 ml. There were no significant differences in demographic characteristics and ICU length of stay between the two groups. Data were tested for normality by visual inspection of histograms, Q-Q plots and a Shapiro-Wilk's test and are presented as median [interquartile range] or mean ± standard deviation. Mann-Whitney or t-tests were used as appropriate. Decreased FGF-19 levels were observed in the diarrhea group (0.20 ± 0.12 vs. 0.29 ± 0.10 ng/mL, p=0.03) indicating disturbed enterohepatic signaling. Plasma bile salt levels were increased in patients with diarrhea compared to patients without diarrhea (9.8 [5.0-23.9] vs. 4.5 [2.9-7.4] µmol/L, p=0.01]). C4 levels were not different between the two groups (6.8 ± 4.0 vs. 6.4 ± 3.6 ng/ml, p=0.77). Bilirubin, alka phosphatase (ALP) and gamma-GT levels also were not different between the two groups. In conclusion, diarrhea in critical illness disturbs the normal enterohepatic circulation of bile salts, as evidenced by reduced plasma levels of FGF-19. This lowering was not accompanied by an anticipated elevation of systemic C4 levels, and suggesting that hepatic bile salt synthesis is not increased in patients with diarrhea. Furthermore, increased systemic bile salt levels suggest that hepatic uptake is affected in critically ill patients with diarrhea. The consequences of these disturbances in bile salt homeostasis and their relation with critical illness-associated liver injury require further investigation.

The effect of low FODMAP diet on long term global health outcomes in IBS patients

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Aims Low FODMAP diet has proven efficacy in the management of IBS symptoms. However, there are no long-term studies reporting the effect on quality of life (QoL) in IBS patients. We aimed to determine the effect of the low FODMAP diet on QoL and other non-gastrointestinal (GI) symptoms in IBS patients. Methods A prospective observational study of IBS patients referred for low FODMAP dietary advice was performed. Patients completed on questionnaires (IBS-QoL, GSRS, State-trait Personality Inventory, Fatigue Impact Scale, Karolinska Sleep Questionnaire, Subjective Vitality Scale and the Happiness Measures); at baseline, six weeks (T6) and six months (T26) with the primary outcome of improvement in QoL at 6 months. The secondary outcomes were improvement of (non) GI symptoms. FODMAP adherence and diet satisfaction were also measured at T26. Results 102 patients were recruited (median age 43 years (range 16-74), 83 women). To date, 68 (67%) and 20 (20%) participants had completed the T6 and T26 assessments, respectively. There were significant improvements in QoL from base at T6 (63.6-71.7, $p<0.013$, N=68) and T26 (53.7-66.6, $p<0.011$, N=20). GI symptom reduction was seen at T6 (3.05-2.52, $p<0.01$, N=68) and at T26 (3.3-2.7, $p<0.018$, N=20). There was a significant reduction in fatigue at T6 (43.1-18.9, $p<0.0001$, N=65) and T26 (52.6-42.1, $p<0.02$, N=20). Low FODMAP diet was not associated with significant changes in vitality, sleep, happiness, depression or anxiety. There was a significant correlation between GI symptom response and QoL ($r=-0.784$, $p<0.001$, N=14) and fatique ($r=0.931$, $p<0.001$, N=14). There was no significant correlation between low FODMAP diet adherence and improvement of (non) gastroenterological outcomes. Additionally, no significant correlation between adherence and satisfaction was seen.
Conclusion Low FODMAP diet was associated with improved long-term QoL, reduction in fatique, and improvement of GI symptoms. These data support a wider range of benefits for IBS patients consuming a low FODMAP diet.

Comparison of taste and texture of Metamucil®, Volcolon® and psyllium orange generic: a randomized double-blinded study

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Chronic idiopathic constipation is a frequently reported disorder and reduces patients' quality of life. In patients who do not respond to dietary changes and behaviour modification, prescription of laxatives is often considered as the next step. Fibre supplements are one of the most widely used laxatives, although adherence to treatment remains challenging. A pleasant taste and texture of a medicine improves patient compliance and adherence. There are several different formulas of fibre supplements, however, there are hardly any studies investigating which supplement is preferred. A switch to the most favoured supplement might increase patients' long-term adherence. Therefore, the aim of this study was to compare the taste and texture of the three most prescribed psyllium fibre supplements in The Netherlands: Metamucil orange®, Volcolon sugarfree® and psyllium orange generic. The design of the study was randomized and double-blinded. Healthy volunteers between 18-70 years were recruited by advertisement. A 5-point hedonic scale (extremely poor [1] to extremely good [5]) was used to score both the taste and palatability of the 3 fibre supplements. A one-way repeated measured analysis of variance (ANOVA) was conducted to evaluate if there was a difference between the fibre supplements. Bonferroni correction was used for pairwise comparisons. One-hundred healthy volunteers (76 females; mean age 29 years, range 18-62) were recruited. Mean hedonic scores for taste were statistically different for all pairwise comparisons ($p < 0.0001$): Metamucil orange® = 3.81 (std. deviation 0.76), Volcolon sugarfree® = 2.05 (std. deviation 0.81) and psyllium orange generic = 3.14 (std. deviation 0.78). Mean hedonic scores for palatability were also statistically different for all pairwise comparisons ($p < 0.0001$): Metamucil orange® = 3.60 (std. deviation 0.80), Volcolon sugarfree® = 2.27 (std. deviation 0.93) and psyllium orange generic = 2.79 (std. deviation 0.88). There were no statistically differences between females and males in scores of taste or palatability of all 3 fibre supplements.
Conclusions: Metamucil orange® was the most tasteful and palatable psyllium fibre supplement compared to Volcolon sugarfree® and psyllium orange generic. Prescription of this supplement in particular is proposed in patients with chronic idiopathic constipation.

Prevalence and effects of paediatric home tube feeding in the Netherlands

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Tube feeding ensures growth in children who are unable to eat or drink by themselves, but may also have negative effects on health (side-effects, complications, a difficult transition to oral feeding) and psychosocial functioning (parental distress, impaired interaction between parents and child). It is a financial burden as well. We aimed to assess the prevalence and possible side-effects of home tube feeding in Dutch children since there are no data available in the Netherlands so far. The prevalence of paediatric home tube feeding was calculated using data of both the Medicines and Devices Information Project of the National Health Care Institute[1], and the Statistics Netherlands[2] (2010-2014). A cross-sectional parental on questionnaire was used to obtain data regarding demographics, history, tube feeding and side-effects. Dutch children (<18 years old) with tube feeding ≥2 weeks were included. During 2010-2014 the prevalence of home tube feeding varied between 83 and 92 : 100,000/year. In 2014, n=2853 children received tube feeding (51.5% male)[1]. The prevalence of home tube feeding decreased with increasing age (from 234: 100,000 in the 1 year olds to 50: 100,000 in the age category 10-17 years. A total of 279 children (53% male) were included in our survey; age category 0 (8.6%), 1 (15.8%), 2 (14.7%), 3 (11.8%), 4 (10.4%), 5-9 (22.2%), and 10-17 (16.5%) years of age. 60% (n=168) had a gastrostomy tube and 33% (n=93) a nasogastric tube. 31% (n=68) were tube fed since birth and 88% (n=244) had ≥1 medical diagnosis (most common were congenital abnormalities (42%), perinatal problems (38%), neurologic disorders (16%)). Parents of 74% reported ≥1 side-effects: vomiting (37%), lack of appetite (29%), and gagging (29%). Neither gagging nor vomiting were associated with type of tube (p=0.092 and p=0.191 respectively) or diet (p=0.435 and p=0.627 respectively). The nasogastric tube was replaced by home care (81%), hospital (35%) or parents (22%), and resulted in negative experiences in 94% of the patients.
Conclusion: The prevalence of paediatric home tube feeding in the Netherlands is 83-92 : 100,000/year. Parents do report frequent side-effects and negative experiences of tube replacement or the tube itself. These results may lead to a more careful monitoring of tube feeding, but more prospective research is necessary. [1] GIP / National Health Care Institute the Netherlands, April 2016 [2] http://statline.cbs.nl/Statweb/ May 2016

Men are more prone to present with an atypical clinical subtype of celiac disease than women

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Celiac disease (CeD) is a common immune mediated gluten induced enteropathy and is characterized by a considerable clinical heterogeneity. In our previously published case record study we describe that males are diagnosed at a significantly higher age compared to adult females. To get insights in this finding, we performed a questionnaire study focusing on the duration, type and frequency of complaints in this biopsy proven celiac cohort from the north-eastern part of the Netherlands. 193 questionnaires were filled out by adult CeD patients (Marsh≥2). Diarrhoea, abdominal pain, fatigue and weight loss are defined as "classical symptoms". Statistical analyses were performed using the Mann Whitney U and chi-squared test. 35% of patients are not followed up annually by a medical specialist. Additionally, five percent of patients reported a non-adherence to the gluten free diet. Before the diagnosis of CeD, 10% (20/193) of the patients reported no complaints at all. In addition, 15% (26/173) of the patient did not suffer from any of the classical complaints. These 26 patients were also diagnosed at a higher age (compared to those with classical complaints before diagnosis of CeD (59.7 years (51.7-64.5) vs 38.0 years (23.0-51.5), $P=3.8*10^{-06}$). Within the group of patients with complaints at diagnosis (n=173) men were diagnosed at a higher age (49.8 (33.3-60.2), $P=1.7*10^{-2}$) compared to women (36.8 (25.0-52.3)), reported less symptoms ($P=2.6*10^{-3}$) and less classical complaints ($P=7.8*10^{-3}$). After multiple linear regression analysis, having classical symptoms was identified as an independent predictor of lower age of diagnosis ($P= 7.9*10^{-06}$). Before diagnosis, 40% displayed a symptoms duration of less than one year, 26% one to three years and 34% more than three years. The duration of symptoms was not influenced by sex (P=0.6), having classical complaints versus no classical complaints (P=0.2) or age of diagnosis (P=0.7). Conclusions: Males are diagnosed at a higher age compared to females and present less frequently with the classical symptoms for celiac disease, although they suffer from the same duration of symptoms before diagnosis. Either having classical or no classical symptoms did not influence disease duration. Males seem to be diagnosed at higher age because they are more prone to have another, more atypical, clinical subtype of CeD that presents later in life, and not through an influence of having non-classical symptoms on disease duration.Our findings suggest the need for more awareness for an atypical presentation of celiac disease in aged men and suggest the need for more adherence to published guidelines regarding follow up.

The effects of four weeks pectin intake on intestinal permeability in young adults and elderly

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It has been suggested that intestinal permeability is increased in in aged populations, but the underlying evidence is very limited. A decrease in intestinal barrier function may lead to permeation of noxious luminal substances into the intestinal mucosa, inducing immune activation and damage to the intestinal mucosa. Dietary fibers, such as pectin, may improve intestinal barrier function. Our aims were to assess the effect of aging on intestinal permeability, and to investigate the effects of four weeks pectin supplementation on intestinal permeability in young adults and elderly. In this double-blind, placebo-controlled trial, 52 healthy young adults (22 male; age 23.1±4.3 years; BMI 22.9±2.7 kg/m^2) and 48 healthy elderly (27 male; mean age 69.7±2.8; BMI 25.8±2.7 kg/m^2) were randomly assigned to receive 15g/day pectin or placebo for four weeks. Site specific permeability was assessed at base and after intervention. Urinary excretion of sucrose, lactulose/mannitol (L/M) and sucralose/erythritol (S/E) ratio reflect gastroduodenal, small intestinal and colon permeability, respectively. Sigmoid biopsies were obtained in a subgroup after intervention. Six biopsies were used for Ussing chamber experiments, and exposed to mast cell degranulator C48/80 (1 µg/ml) or control medium at the serosal side. Transepithelial electrical resistance (TEER) and permeation of fluorescein (1 mg/ml, 375 DA) were measured at base and every 30 min for 120 min. One biopsy was snap frozen for gene transcription analysis of tight- and adherens junctions. GAPDH was used as reference gene. The effect of age and of pectin in biopsies were compared using independent-samples T Tests. The effects of pectin on urinary sugar excretions were analyzed using linear mixed models. Sucrose, L/M and S/E ratio, as well as TEER and fluorescein levels did not differ between age groups, nor between the interventions. Mucosal cadherin (1.15±0.014 vs 1.17±0.017, p=0.047) was significantly higher expressed in elderly compared with young adults, and catenin (1.14±0.019 vs 1.12±0.014, p=0.017) and occludin (1.20±0.016 vs 1.18±0.020, p=0.039) were significantly increased by pectin intake compared with placebo. No difference was found for claudin-2, claudin-3, claudin-4, myosin light-chain kinase and zonula occludens-1. None of the observed differences in gene transcription remained significant after correction for multiple testing. Our findings show that the functional capacity of the intestinal barrier is maintained in healthy elderly. Furthermore, four weeks pectin intake did not reinforce paracellular intestinal permeability as determined by multiple parameters in vivo and ex vivo.

The role of phase angle by bioelectrical impedance analysis in the assessment of nutritional status and disease severity in adult patients with mitochondrial disorders caused by the m.3243A>G mutation

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Phase angle (PA), a parameter obtained by a non-invasive bedside technique, bio-electrical impedance analysis (BIA), that has already proven its role in the monitoring of the nutritional status and disease severity in numerous diseases with altered metabolism. In patients with mitochondrial disease (MD) caused by the m.3243A>G mutation data are available of Nutritional Assessment and disease severity based on the Newcastle Mitochondrial Disease Adult Scale (NMDAS). These results show that patients are frequently malnourished, with unfavorable body composition exemplified by low fat free mass index (FFMI) and high fat mass (FM). It is known that disease severity is associated with a presence of malnutrition in MD patients. However, the role of the BIA-derived PA in MD has not been established yet. This study aimed to determine whether the PA that is measured by BIA presents a reliable indication of the nutritional status and/or disease severity of MD patients that could be easily implemented in clinical trials. Nutritional assessment was performed in 44 MD patients (age 47 ± 12 years, 36 (82%) females) including single frequency BIA at 50 kHz with calculation of the PA, anthropometrics, handgrip strength (HGS) and the Patient Generated Subjective Global Assessment questionnaire (PG-SGA). In all patients, NMDAS was performed to measure disease severity. Correlation analysis was performed of PA and NMDAS (sub scores) as well as of nutritional assessment variables, with Bonferroni correction for multiple testing. One sample T test was used to compare the PA of MD patients and healthy references of Bosy-Westphal (2006). PA was significantly lower in MD patients when compared with healthy subjects ($p<0.01$). PA was inversely correlated with total NMDAS (Pearson $r=-0.440$, $p=0.003$) and NMDAS myopathy (Spearman $r=-0.427$, $p=0.004$) and positively correlated with FFMI (Pearson $r=0.481$, $p=0.001$). PA didn't correlate significantly with PGSGA (Spearman $r=0.181$, $p=0.239$) and HGS (Pearson $r=0.333$, $p=0.027$). Conclusion:The PA calculated by BIA is moderately related to disease severity, myopathy and body composition (FFMI) in adult MD patients. These results are in with findings in other diseases. Therefore, BIA-derived PA holds promise as a non-invasive tool for clinical and research purposes in these patients.

Risk estimation for lymphoma and gastrointestinal carcinoma after diagnosis of celiac disease based on a nationwide population-based case-control study

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Celiac disease (CD) usually runs a benign course, but patients are likely at increased risk to develop various malignancies. To support evidence-based follow-up programs in CD patients, we performed a large population-based study to assess the subsequent risk for malignant lymphoma and GI carcinoma after a confirmed diagnosis of CD . All patients with lymphoma or GI carcinoma diagnosed in the Netherlands between 1994 and 2014 were retrieved through the Dutch nationwide population-based pathology database (PALGA). Within this series, all cases with histologically confirmed CD before or within 3 months after the diagnosis of malignancy were identified. For risk estimates, odds ratios were determined using binary logistic regression analysis with corrections for age and gender in comparison to a control group of patients with basal cell carcinoma or melanoma. Of 349,193 patients with lymphoma or GI carcinoma (cases) and 577,254 controls, respectively 349 (0.1%) and 282 (0.05%), were diagnosed with CD. Of 160 CD patients with GI adenocarcinoma, 65% was localized in the colon or rectum, 19% in the small bowel, 8% in the stomach and 8% in the esophagus. As compared with the non-CD group, small bowel localization was highly preferential in CD patients (19% versus 2%). Of 18 squamous cell carcinoma (SCC) in CD, the far majority was seen in the esophagus (89% versus 71% in the non-CD group). T-cell lymphomas were most frequent (131 of all 169 lymphomas in the CD group), of which 101 were diagnosed as EATL. Of these, 76% were located in the small bowel, 8% other GI localizations and 16% outside the GI-tract. B-cell lymphomas were relatively rare (21%), in reverse to the distribution in non-CD patients. Preliminary data showed an adjusted OR for prior CD diagnosis with small bowel adenocarcinoma of 11.9 [95% CI, 8.2-17.2], with esophageal SCC of 3.5 [95% CI 2.1-5.8] and with lymphoma (all subtypes) of 4.8 [95% CI 4.0-5.8] with subdivision analysis pending. Adenocarcinoma of the colon, esophagus and stomach and SCC of the anus were not associated with CD history. Conclusion This large population-based study describes the characteristic distribution of lymphoma and GI carcinoma in CD patients and determines an increased risk for developing lymphoma (OR 4.8), SCC of the esophagus (OR 3.5) and distal and proximal small bowel adenocarcinoma (OR 11.9) after CD diagnosis. No increased risk for GI tract adenocarcinoma at other sites was noted. This may have important consequences for follow-up advice in newly diagnosed CD patients.

Development and first experiences of the Netherlands Donor Feces Bank

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Background Since 2013, many stool banks have been developed following publications reporting on clinical success of Fecal Microbiota Transfer (FMT) for recurrent Clostridium difficile infections (CDI). Protocols for donor screening, fecal preparation, and transfer of the fecal suspension, however, differ between various countries and institutions. In 2015, the Netherlands Donor Feces Bank (NDFB) was founded with the primary aim to provide a standardized product for the treatment of patients with recurrent CDI in the Netherlands. Material/methods In 2015, support of a national ZonMW grant was used to develop standard operation procedures for donor recruitment, donor selection, donor screening, and production of frozen fecal suspensions for FMT. A business case was also developed to calculate the costs per FMT product and treated patient. Furthermore an overview of the currently existing donor feces banks worldwide was made, and donor screening protocols were compared. In May 2016 the first FMT was performed using the NDFB facility. Results Between March 2016 and November 2016, 148 of 239 initial donor responders completed a questionnaire; 16 of 148 registered volunteers were invited for laboratory screening test of which six passed the screening. Two donors failed second screening after two months and their fecal suspensions were discarded. One donor was lost to follow up. Finally, three (2.0%) of the 148 screened responders were enrolled as a qualified feces donor. Between March 2016 and November 2016, 16 patients with microbiological confirmed recurrent CDI were treated with FMT in 11 different Dutch hospitals. Thirteen (81.2%) of the patients were successfully treated by FMT. Three of the 16 patients (18.8%) suffered a CDI relapse after FMT of which two could possibly be explained by antibiotic use within one month after treatment. One serious adverse event (SAE) has been reported from a patient who vomited a part of donor feces suspension three hours after FMT. The patient did not aspirate and was cured of CDI. Preliminary results of the business case revealed that the costs of an FMT product issued by NDFB per patient are approximately € 910. This is based on an annual production of at least 100 FMT suspensions and assuming an average patient needs 1.1 FMT suspensions. Conclusions A national organization to support FMT is preferred above local initiatives, since many thresholds have to be taken. Only 2% of all screened donors delivered qualified feces samples after screening. The success rate of FMT for recurrent CDI was 81.2%, similar as the reported experiences in the literature. The accompanied costs are approximately € 910 per patient.

Helicobacter pylori colonization is not associated with Non-Alcoholic Fatty Liver Disease (NAFLD) in the general population

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NAFLD pathogenesis is incompletely understood, but emerging data under an important role for the gut microbiome. Helicobacter pylori (HP) is amongst the most well-known gut pathogens. Recently, Mediterranean and Asian studies suggested that HP infection is associated with NAFLD, but results are conflicting. Therefore, the aim of this study was to examine the association of HP colonization and NAFLD in a large well-characterized Caucasian population study. This was a cross-sectional analysis of The Rotterdam Study, an ongoing prospective population-based cohort of inhabitants of Ommoord, a suburb of Rotterdam. Participants of 55 years and older underwent an extensive clinical work-up, including elaborate blood sampling. Anti-HP IgG-serology was considered positive at ≥20 U/ml (HP+). NAFLD was defined as having a fatty liver index (FLI, composed of waist circumference, triglycerides, BMI and GGT) of ≥60 in absence of excessive alcohol consumption, viral hepatitis and steatogenic drugs. Multivariable logistic regression analyses correcting for metabolic and lifestyle traits were performed. The robustness of our data was tested by performing sensitivity analyses: 1) in a HP+ subgroup relating continuous IgG-titer (as proxy for active HP infection) with NAFLD and, 2) using the hepatic steatosis index (HSI) and NAFLD-Liver Fat Score (NAFLD-LFS) as alternative biomarkers of NAFLD. Data were available for 1588 participants. Median age was 62 (59-69), 55% was female and 97.5% was Caucasian. HP+ was found in 727 (45.8%) and NAFLD in 566 (35.6%) participants. No difference was found in the proportion of HP+ among participants with and without NAFLD (46.3% vs. 45.5%; OR 1.03; P=0.79). HP was associated with lower education, HDL and alcohol consumption, older age, higher waist circumference and hypertension. Multivariable logistic regression modelling with adjustment for age, gender, ethnicity and education showed no association between HP and NAFLD (OR 0.93; 95%CI 0.74-1.17; P=0.56), neither did additional adjustment for BMI, insulin resistance, hypertension, HDL, alcohol, smoking and ALT. Additionally, IgG-titer was not related to NAFLD in a subgroup of HP+ participants (OR 1.00 per 50 U/ml increase; 95%CI 0.97-1.03; P=0.84). Finally, using HSI and NAFLD-LFS did not alter our results. Conclusions: In this large and only North-European population study we found no association between Helicobacter pylori colonization and presence of NAFLD. High IgG-titer, as surrogate for active disease, was not associated with NALFD either, but this needs to be further investigated using more robust measures of active infection.

Validation of a Score Chart to Predict the Risk of Chronic Mesenteric Ischemia: a Discriminative and Useful Tool in Clinical Decision-Making

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Chronic Mesenteric Ischemia (CMI) is the result of insufficient gastrointestinal mucosal perfusion, mostly caused by atherosclerotic stenosis of mesenteric arteries. Other causes of CMI are vasculitis, median arcuate ligament syndrome or non-occlusive ischemia (NOMI). The diagnosis of CMI remains challenging as chronic abdominal pain is common and mesenteric artery stenoses are prevalent in the general population. Harki et al. (J Clin Gastroenterol, 2016) designed a score chart to predict the risk of CMI based on a cohort of CMI suspected patients. This score chart consists of patient characteristics (female 1 pt, weight loss 1 pt, cardio-vascular disease 1 pt) and radiologic evaluation (50-70% celiac artery (CA) stenosis 1 pt, >70% CA stenosis 4 pts, 50-70% superior mesenteric artery (SMA) stenosis 1 pt and >70% SMA stenosis 3 pts). A total score of 0-2 pts predicts an absolute risk of CMI of 0-21%, 3-6 pts a 22-46% risk and ≥7 pts a risk of >79%. We aim to validate this prediction model in a new prospective cohort. Patients suspected of CMI referred to two Dutch specialized CMI centers were included consecutively from January 2014 to March 2016. After diagnostic work-up of medical history taking, mesenteric CT- or MR-angiography and a mucosal ischemia test (visible light spectroscopy or tonometry), all patients were discussed in a specialized CMI multidisciplinary meeting resulting in an expert based consensus diagnosis. All patients with a CMI consensus diagnosis were planned for treatment (revascularization for occlusive disease and medication for NOMI). A definitive diagnosis of CMI was made if successful treatment resulted in durable symptom relief. The score chart to predict the risk of CMI was computed for each patient. The multidisciplinary team was blinded for the score. A total of 165 patients were included and consensus diagnosis of CMI was made in 72 (44%) patients, which resulted in 66 (40%) patients with a definitive diagnosis of CMI after therapy. A definitive diagnosis of CMI was made in 10% of the patients with low risk, in 42% of the patients with intermediate risk and in 97% of the patients with high risk of CMI according to the score chart, respectively. The discriminative ability of the score chart was strong (C-Statistic 0.89). Conclusion: The score chart for CMI is a reliable tool for clinicians to discriminate the risk of CMI, which can be used to help in clinical decision-making, for example a wait-and-see policy in patients with low risk and immediate vascular intervention in patients with high risk of CMI. This may result in less diagnostics, prompt treatment and decreasing health costs and patient-burden in the future.

Sustained Symptom Relief after Revascularization of Single Mesenteric Artery Stenosis in Patients with Chronic Mesenteric Ischemia

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An isolated stenosis of the celiac artery (CA) or the superior mesenteric artery (SMA) is not uncommonly detected in patients with abdominal complaints. These patients may suffer from chronic mesenteric ischemia (CMI) causing nonspecific abdominal complaints as postprandial pain, nausea or diarrhea. However, the existence of single artery mesenteric ischemia is a topic of continuous clinical debate and reports on the effectiveness of single mesenteric artery revascularization are scarce. Therefore, we evaluated the long-term clinical success rates for single mesenteric revascularization of a stenosis of either CA or SMA in patients with gastrointestinal symptoms and confirmed mucosal ischemia. Data from all consecutive patients referred to the outpatient clinic of a Dutch tertiary referral center between January 2006 and October 2010 for analysis of CMI based on a single mesenteric artery stenosis were collected. All patients underwent a standardized diagnostic work-up at base consisting of medical history taking and physical examination, imaging of the gastrointestinal arteries with either CT- or MR-angiography and/or conventional catheter angiography, and a functional test for detecting mucosal ischemia using either tonometry or visible light spectroscopy. All cases were discussed in a multidisciplinary meeting attended by a vascular surgeon, interventional radiologist and gastroenterologist, all specialized in CMI, leading to an expert based consensus diagnosis. Patients with a consensus diagnosis of CMI were treated with either surgical or endovascular revascularization. The primary outcome was the clinical response to revascularization defined as relief of presenting symptoms as experienced by the patient. A consensus diagnosis of CMI was obtained in 65/97 patients and all consensus patients were revascularized. The etiology was in 58/65 patients stenosis of the CA (89%) (33/58 based on vascular disease (57%), 25/58 based on median arcuate ligament syndrome (MALS) (43%)) and in 7 patients a stenosis of the SMA based on atherosclerosis. After a mean follow-up of 5.5 ± 3.0 years (median 6.7, IQR 1.9-7.8 years) after treatment, 42/65 patients (65%) experienced sustained symptom relief with no significant difference in lesion localization (CA 64% versus SMA 71%, p=0.690) or lesion etiology (MALS 60% versus vascular disease 68%, p=0.538). Conclusion: This study shows that revascularization of the CA or SMA provides sustained relief of abdominal pain in 65% of patients diagnosed with CMI due to single mesenteric artery stenosis. This provides the opportunity to help patients with otherwise unexplained, refractory abdominal complaints.

Capsule endoscopy over the years in a large tertiary center cohort: the diagnostic yield in patients with obscure gastrointestinal bleeding

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Capsule endoscopy (CE) allows non-invasive visualisation of the mucosa of the entire small intestine, and is therefore a preferred modality in the exploration of small bowel diseases. Main indication for CE is obscure gastrointestinal bleeding (OGIB). The aim of this study was to describe the findings of CE using a structured terminology and determine the diagnostic yield of CE, overall and more specific-in patients with OGIB, in a large cohort from a single tertiary referral center. In this study data of 2057 CEs performed between 2003 and 2016 in a single tertiary referral center were analysed using the Capsule Endoscopy Structural Terminology. This number of patients has not been examined in a single center before. Three different types of capsules were used over time; from 2003-2016 PillCam SB® (Given Imaging, Yogneam, Israel) and MiroCam® (Seoul, South Korea) were used. Since 2011 PillCam Colon® (Given Imaging, Yogneam, Israel) was also used. Diagnostic yield was defined as the percentage of detection of definite and probable explanations for the bleeding indication. 2057 CEs were included (PillCam SB n=1273, PillCam Colon n=405, MiroCam n=350). Of all patients (n=1914), 143 underwent a second CE over the years (6.4%). Mean age was 57.9 years (SD 17.9; range 1-94), 51% female. 77% of CEs has been performed in patients with OGIB, divided in overt gastrointestinal bleeding (overt OGIB, 26.4%) and occult gastrointestinal bleeding (occult OGIB, 73.6%). The main findings of CE were angiectasia (17.7%), erosions (12.3%) and visible blood (11.1%). In patients with overt OGIB a diagnostic yield of 40.6% was established. In patients with occult OGIB the diagnostic yield was 29.7%. Overall, this leads to a diagnostic yield of 33.3% for obscure gastrointestinal bleeding. Interestingly, the diagnostic yield improved with 17% when a second CE was performed (from 36% to 53%). Furthermore, no difference in diagnostic yield was found between PillCam SB and PillCam Colon capsules during the period both capsules were used.
Conclusions: Capsule endoscopy has a diagnostic yield of 33.3% for obscure gastrointestinal bleeding. As expected, the yield for overt gastrointestinal bleeding is higher than for occult ($P<0,05$). The efficacy of a dual camera capsule compared to a single camera needs to be further evaluated.

Work ability in rectal cancer patients during the first year of treatment

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Introduction: Rectal cancer treatment is associated with substantial morbidity and decreased quality of life. The impact of treatment on workability has however hardly been studied. We evaluated workability in rectal cancer patients during the first year of treatment. Methods: All working-aged rectal cancer patients (<67 years) within a prospective colorectal cancer cohort referred for radiotherapy were selected. Workability was assessed with the Work Ability Index (WAI) questionnaire before start of treatment and at 3, 6 and 12 months. The WAI score, ranging from 7 to 49, was calculated for patients with paid employment at time of assessment and who completed at least one questionnaire. Workability was categorized in poor (7-27), moderate (28-36), good (37-43) and excellent (44-49). Results were stratified for treatment strategies and compared with scores of the age-matched Dutch reference population. Results: Of 156 eligible patients, 133 (85.3%) responded to at least one questionnaires. Non-responders did not return the questionnaires (8.3%) or had missing values in the questionnaire (6.4%). Of the responders, 107 patients (80.5%) had paid employment. These patients had a mean age of 56.2 years and 73.8% were male. All patients underwent neoadjuvant therapy of which 64.5% chemoradiation, 30.8% short-course radiation and 4.7% other regimes. Surgery was performed in 89.7%, mostly by low anterior (50.5%) or abdominoperineal resection (33.6%). At baseline, the mean WAI score was 32.3, which was substantially lower than the reference population score of 40.9. Workability was poor in 27.5% of the patients, and moderate, good and excellent in resp. 34.1%, 34.1% and 4.4%. Corresponding scores of the Dutch reference population were 2.8%, 14.2%, 47.2% and 35,8% resp. Workability was limited by illness in 82.4% of the patients, and 23.1% completely stopped working. At 3 months, the mean WAI score decreased significantly to 27.1 ($p<.001$) and was poor in 54.7% of the patients. Here after, at 6 and 12 months, the mean WAI score increased to resp. 29.1 and 34.6. At 12 months, 55.3% of the patients reported absenteeism of 100-365 days as result of health problems in the past year compared to 2.3% in the reference population. Only 14.9% of the patients reported no absenteeism. Stratification by neoadjuvant regimen and surgical procedure did not modify the results. Conclusion: Workability in patients with rectal cancer is negatively affected by treatment but seems to recover to base levels at 12 months after diagnosis. Compared to the Dutch population, rectal cancer patients report a much lower workability and a higher level of absenteeism.

Association of Chromosomal Instability, Microsatellite Instability and CpG Island Methylator Phenotype with Postcolonoscopy Colorectal Cancer in a retrospective cohort study

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Over 50% of the postcolonoscopy colorectal cancers (PCCRCs) (CRC diagnosed after a colonoscopy that excluded cancer) originate from missed precursor lesions, in particular the subtle appearing non-polypoid adenomas and sessile serrated lesions. The biologic pathway of these lesions is unclear. We hypothesized that PCCRCs and subtle appearing precursors may share molecular features. In a retrospective cohort study, we examined the occurrence of chromosomal instability (CIN), mutations, microsatellite instability (MSI) and CpG island methylator phenotype (CIMP) in PCCRCs and prevalent CRCs. We identified all PCCRCs diagnosed from 2001 to 2010 in a large gastroenterology practice from the Netherlands. PCCRCs were defined as cancers occurring within 5 years after complete colonoscopy, which excluded CRC. We applied a clinical algorithm to assign the most likely explanation of PCCRC (incomplete colonoscopy/ insufficient bowel preparation, missed lesion, incompletely resected lesion or new cancer). PCCRCs attributable to technical factors (insufficient bowel preparation/ incomplete colonoscopy or incomplete resection) were excluded. We reviewed clinical and pathological records. Whole genome DNA copy number changes and mutation status of genes commonly affected in CRC (APC, KRAS, BRAF, FBXW7, PIK3CA, NRAS, SMAD4 and TP53) were examined by shallow whole-genome sequencing and targeted sequencing respectively, using Illumina next generation sequencing platforms. MSI and CIMP status were examined using the pentaplex marker panel from Promega and the Weisenberger CIMP panel using methylation-specific PCR, resp. In total, 87 PCCRCs and 99 prevalent CRCs were examined. Regarding clinicopathological features, PCCRCs are more often located proximally in the colon ($p<0.001$), non-polypoid appearing ($p=0.001$), early stage tumors ($p=0.006$) and poorly differentiated ($p=0.001$) compared to prevalent CRCs. Regarding DNA copy number alterations, PCCRCs contain less often 18q ($p=0.001$) deletions and 13q ($p=0.01$) gains than prevalent CRCs. Furthermore, PCCRCs contain less frequently APC ($p=0.04$), NRAS ($p=0.03$), and TP53 mutations ($p=0.03$) than prevalent CRCs. In contrast, MSI ($p=0.01$) and CIMP ($p=0.02$) are more frequent in PCCRCs than prevalent CRCs. Conclusion: Both CIN and MSI pathways are associated with the occurrence of PCCRC. PCCRCs contain less often deletions of chromosome 18q, gains of chromosome 13q, APC, NRAS and TP53 mutations and more often MSI and CIMP than prevalent cancers. Such molecular profiles are similar to those previously described in non-polypoid adenomas and sessile serrated lesions, supporting the hypothesis that these lesions are in the origin of PCCRCs.

Symptomatic patients participating in colorectal cancer screening: cancer risk and tumor location

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Colorectal cancer (CRC) screening with fecal immunochemical tests (FIT) reduces CRC-related mortality up to 22%, yet when used in symptomatic invitees it may lead to diagnostic and treatment delay because of suboptimal sensitivity in detecting advanced neoplasia (AN). Invitees at high risk, such as those with CRC-related symptoms, are therefore advised not to participate in FIT-screening but instead directly consult their general practitioner (GP). Nevertheless, we regularly noticed symptomatic FIT-positive screening participants. Our objectives were to estimate the proportion of FIT-positive participants in screening with CRC-related symptoms, to evaluate whether the presence of these symptoms was associated with the presence of CRC or AN, and, if so, with the location of the tumor. We analyzed data of all FIT-positive participants (>47 µg Hb/g feces) in the national Dutch CRC-screening program who were seen in two certified colonoscopy centers in 2014-2016. Colonoscopy and clinical data were retrieved using a structured reporting system, enabling prospective data collection and automatic quality assessment. CRC-related symptoms were weight loss, visible rectal blood loss in stool/on stool/on toilet paper, change in bowel habit and tenesmus in the last 3 months. AN was defined as CRC or advanced adenoma (size ≥10mm, villous histology ≥25% or high-grade dysplasia). CRC location was categorized as either proximal or distal to the splenic flexure. We calculate single and conditional odds ratios using multivariable logistic regression to express the strength of the associations. We included 527 participants, of whom 313 had AN and 41 had CRC as most relevant finding. In total, 206 of 527 reported having at least one CRC-related symptom (39%). Odds ratio for all symptoms exceeded unity, but only change in bowel habit (OR 2.86; 95%CI 1.23 to 6.62) and visible blood in stool (OR 8.65; 95%CI 2.34 to 32.0) were significantly associated with detected CRC. None of the symptoms were significantly associated with detected AN. All participants with CRC and either change in bowel habit (n=8), or tenesmus (n=4), or weight loss (n=2), had a distal tumor.

Conclusion A disturbingly large proportion of FIT-positive screening participants in the Netherlands report CRC-related symptoms. Additional initiatives should be undertaken to increase awareness of CRC-related symptoms, and specifically for symptomatic screening invitees, to consult their GP immediately instead of performing FIT.

Vedolizumab prevents T-cell re-entry to intestinal and skin graft and ameliorates rejection: a case report

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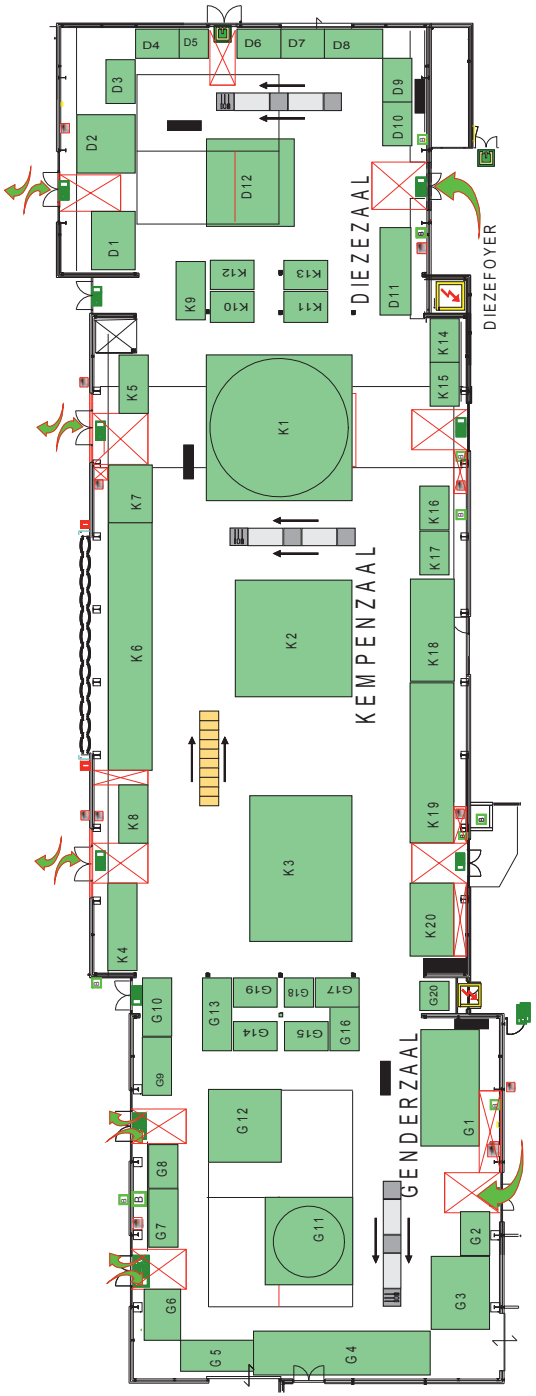
A woman with a history of a severe case of pancolitis underwent initially a subtotal colectomy and ileostomy. After several episodes of infections and a deterioration of her general clinical status with kidney and liver disorders, a gastroduodenostomy with necrotomy of the abdominal wall fascia was performed, followed by an skin autograft placement and the start of total parenteral nutrition (TPN). During the following two years, she suffered from several episodes of TPN infection, infection of the abdominal wall opening, and is admitted to the intestinal transplant waiting list. The patient underwent an intestinal (I) and abdominal wall (AW) transplantation in March, 2015. Initial immuno-suppression therapy consisted of mycophenolic acid (MMF), prednisolone and tacrolimus. There were signs of rejection since day 6 post-transplant (I) and from day 21 (AW). Mid April, the patient suffers from leukopenia so MMF is stopped definitely. On day 47, ITx shows rejection grade 2 which was temporarily resolved with metilprednisolone. On day 68 she was diagnosed with rejection grade 1 (I), and because of the antecedent of leukopenia, treatment with vedolizumab was approved on weeks 0, 2, 6 and every 8 weeks thereafter. During treatment, the patient suffered from several infectious episodes that did not affect the efficacy of their treatment, even though she was under this immunosuppressive therapy. Nonetheless, six months into treatment, it was temporarily suspended because of a long-lasting infection with NORO virus. Vedolizumab is an α4β7 antibody which inhibits various immunological cell types from entering the intestinal graft via the binding of this integrin with its receptor MAdCAM-1 in the endothelial cells. It is a gut-homing inhibitor that has been recently approved for use in inflammatory bowel diseases. This case report focuses on the effect of vedolizumab on rejection of the I and AW grafts, by showcasing the immunological cell kinetics throughout the time that the patient underwent treatment with said drug. Intestinal graft biopsies were stained and scored for vedolizumab and caspase-3. Skin from AW was biopsied and stained and scored for CD-3 and CD-8. This study shows that the definite disappearance of rejection signs were accompanied by a decrease in the number of vedolizumab-stained cells in I and a decrease in T-cell population in AW after start of vedolizumab therapy. We suggest the use of vedolizumab as part of the primary immunosuppressive therapy after intestinal transplantation as way to decrease rejection rates, and suggest an additional mechanism of action of vedolizumab that is not gut-specific.

Lijst van standhouders, Digestive Disease Days NVGE, 23 en 24 maart 2017 te Veldhoven

G = Genderzaal, D = Diezezaal, K = Kempenzaal	*Standnummer*
AbbVie	K 1
Allergan BV	D 1
Aquilant Nederland	G 16
B.Braun Medical BV	K 17
Bayer BV, HealthCare Costumer Care	D 3
Biogen	K 20
Boston Scientific Nederland BV	G 11
Bristol Myers Squibb BV	G 10
Cablon Medical BV	G 7
Cobra Medical BV	D 11
Cook Nederland BV	D 2
Crohn en Colitis Ulcerosea Vereniging Nederland	G 13
Dr. Falk Pharma Benelux BV	G 1
Endotechniek	D 8
Erbe	K 4
Ferring BV	K 19
FMH Medical BV	G 4
Fresenius Kabi Nederland BV	D 6
GE Healthcare BV	K 12
Gilead Sciences Nederland BV	G 12
Hallyard Health	K 8
Ingeborg Kuys Healthcare Communications	G 14
Intercept Pharma Nederland BV	D 4
Janssen - Cilag BV	G 3
Johnson & Johnson Medical BV	K 5
Lamepro BV	K 14
Mediplast	K 16
Meditec BV	K 11
Medivators BV	D 7
Medix Publisher	K 15
Medtronic Trading NL BV	K 9
Mermaid Medical	K 13
MSD	K 3
Norgine	K 18
Olympus Nederland BV	K 6
Olympus Surgical	K 7
Pentax Nederland BV / Hitachi Medical systems BV	D 12
Pfizer PFE BV	G 5
Prion Medical BV	K 10
R-Biopharm AG	G 20
RVC BV	G 9
Sananet Care BV	D 5
Scholings commissie MDL	G 19
Selinion Medical	G 2
Stichting Opsporing Erfelijke Tumoren	G 18
Surgical Technologies	G 17
Takeda Nederland BV	K 2
Teva Nederland	D 9
Tramedico BV	G 8
V&VN MDL	G 15
Winclove BV	G 6
Zambon Nederland BV	D 10



Genderzaal

G 1	Dr . Falk Pharma Benelux BV
G2	Selinion Medical
G3	Janssen - Cilag BV
G4	FMH Medical BV
G5	Pfizer PFE BV
G6	Winclove BV
G7	Cablon Medical BV
G8	Tramedico BV
G9	RVC BV
G 10	Bristol Myers Squibb BV
G 11	Boston Scientific Nederland BV
G 12	Gilead Sciences Nederland BV
G 13	Crohn en Colitis Ulcerosea Vereniging Nederland
G 14	Ingeborg Kuys Healthcare Communications
G 15	V&VN MDL
G 16	Aquilant Nederland
G 17	Surgical Technologies
G 18	Stichting Opsporing Erfelijke Tumoren
G 19	Scholings commissie MDL
G20	R-Biopharm AG

Kempenzaal

K 1	AbbVie
K 2	Takeda Nederland BV
K 3	MSD
K 4	Erbe
K 5	Johnson & Johnson Medical BV
K 6	Olympus Nederland BV
K 7	Olympus Surgical
K 8	Hallyard Health
K 9	Medtronic Trading NL BV
K 10	Prion Medical BV
K 11	Meditec BV
K 12	GE Healthcare BV
K 13	Mermaid Medical
K 14	Lamepro BV
K 15	Medix Publisher
K 16	Mediplast
K 17	B.Braun Medical BV
K 18	Norgine
K 19	Ferring BV
K 20	Biogen

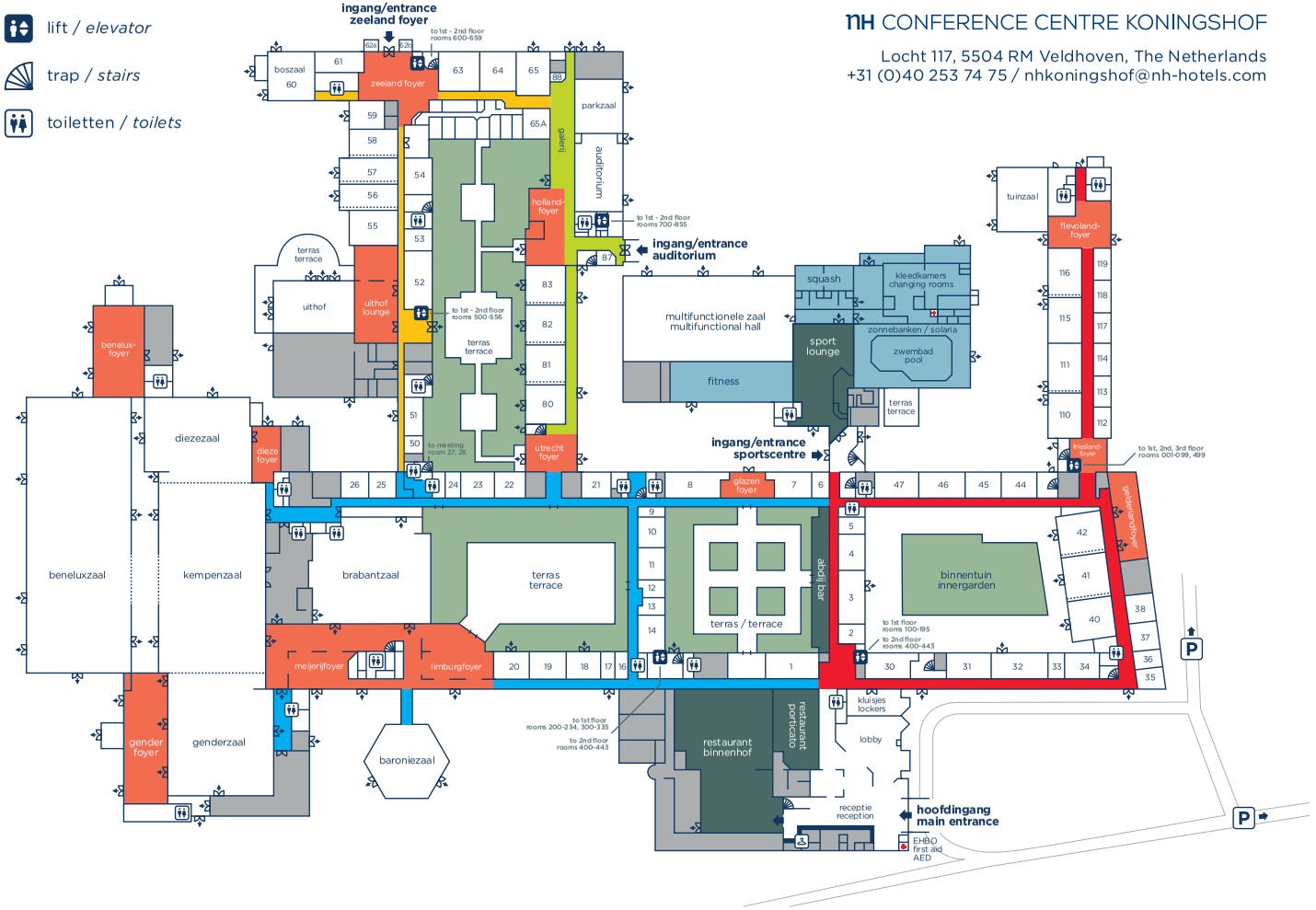
Diezezaal

D 1	Allergan BV
D 2	Cook Nederland BV
D 3	Bayer BV , HealthCare Costumer Care
D 4	Intercept Pharma Nederland BV
D 5	Sananet Care BV
D 6	Fresenius Kabi Nederland BV
D 7	Medivators BV
D 8	Endotechniek
D 9	Teva Nederland
D 10	Zambon Nederland BV
D 11	Cobra Medical BV
D 12	Pentax Nederland BV / Hitachi Medical systems BV

lift / *elevator*

trap / *stairs*

toiletten / *toilets*



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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			
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Toezending verenigingspost aan huis- / werkadres			

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□ Sectie Gastrointestinale Endoscopie
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□ Sectie Inflammatoire Darmziekten
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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:

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Datum en handtekening:

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Dit ondertekende formulier per fax (023 – 5513087) of e-mail (secretariaat@nvge.nl) 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			
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** Doorhalen wat niet van toepassing is.*

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

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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 *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. *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-glycoproteinetransporter (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, 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 patiënten met gelijktijdige infectie met hiv of HBV. De werkzaamheid van Daklinza als onderdeel van een herbehandelregime 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: 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 *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. De klinische gegevens die het gebruik van Daklinza en sofosbuvir ondersteunen bij patiënten die zijn geïnfecteerd met HCV genotype 4 en 6 zijn beperkt. Er zijn geen klinische gegevens bij patiënten met genotype 5. Patiënten met Child-Pugh C leverziekte: De veiligheid en werkzaamheid van Daklinza voor de behandeling van HCV-infectie bij patiënten met Child-Pugh C leverziekte is vastgesteld in het ALLY-1 (AI444215, Daklinza + sofosbuvir + ribavirine gedurende 12 weken) klinische onderzoek; de SVR-percentages waren echter lager dan in patiënten met Child-Pugh A en B. Daarom wordt een conservatief behandelregime van Daklinza + sofosbuvir +/- ribavirine gedurende 24 weken voorgesteld voor patiënten met Child-Pugh C. Ribavirine kan worden toegevoegd op basis van een klinische beoordeling van een individuele patiënt. Zwangerschap en anticonceptieverweiren: 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. 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-intoleratie, 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. Bijwerkingen van graad 3 werden bij minder dan 1% van de patiënten gemeld en er waren geen patiënten met een graad 4 bijwerking. Vier patiënten zijn met het Daklinza behandelregime gestopt wegens bijwerkingen, waarvan maar één als gerelateerd aan de onderzoeksbehandeling werd 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 + ribavirine* werden de volgende bijwerkingen zeer vaak gemeld: anemie, hoofdpijn, nausea en vermoeidheid. Vaak werden gemeld: verminderde eetlust, insomnia, prikkelbaarheid, duizeligheid, migraine, opvlieger, dyspneu, inspanningskortademigheid, hoesten, neusverstopping, diarree, braken, buikpijn, gastro-oesofageale refluxziekte, constipatie, droge mond, flatulentie, rash, alopecia, pruritus, 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 Januari 2016.

Referenties

1. Nelson DR, et al. Hepatology 015;61:1127-35.
2. Wyles DL et al. Daclatasvir plus Sofosbuvir for HCV in Patients
3. Daklinza® Summary of Product Characteristics.
4. HCV richtsnoer www.hcvrichtsnoer.nl update mei 2016.
5. EASL guidelines: Journal of Hepatology 2015 vol. 63, 199–236, EASL Clinical Practice Guidelines: Management of hepatitis C virus infection European Association for the Study of the Liver.

Daklinza®
(daclatasvir)

Bristol-Myers Squibb

1392NL16PR10817

Verkorte SPC-tekst **Salofalk® 500 mg Granu-Stix®, Salofalk® 1000 mg Granu-Stix®, Salofalk® 1,5 g Granu-Stix® en Salofalk® 3 g Granu-Stix®.**

Kwalitatieve en kwantitatieve samenstelling: Maagsapresistent granulaat met verlengde afgifte, resp. 500 mg, 1000 mg, 1,5 g en 3 g mesalazine per sachet. **Therapeutische indicaties:** voor de behandeling van colitis ulcerosa, zowel in de acute fase als ter voorkoming van recidieven hiervan. **Dosering:** ter behandeling van acute episodes van colitis ulcerosa: eenmaal daags 1 sachet Salofalk® 3 g Granu-Stix®, 1 of 2 sachets Salofalk® 1,5 g Granu-Stix® of 3 sachets Salofalk® 500 mg Granu-Stix® of 3 sachets Salofalk® 1000 mg Granu-Stix® (1,5 - 3,0 g mesalazine per dag), bij voorkeur 's ochtends, op geleide van de klinische behoefte van de individuele patiënt. Het is ook mogelijk om de voorgeschreven dagelijkse hoeveelheid in te nemen in verdeelde doses (1 sachet Salofalk® 500 mg Granu-Stix® driemaal daags of 1 sachet Salofalk® 1000 mg Granu-Stix® driemaal daags), indien dit prettiger is voor de patiënt. Als onderhoudsbehandeling ter voorkoming van recidieven van colitis ulcerosa: de standaard behandeling is 0,5 g mesalazine driemaal daags overeenkomend met een totale dosis van 1,5 g mesalazine per dag. Voor patiënten met een verhoogd risico op recidief, om medische redenen of omwille van problemen om zich te houden aan een driemaal daagse dosis, kan het doseerschema aangepast worden naar 3,0 g mesalazine eenmaal daags bij voorkeur in de ochtend. Kinderen vanaf 6 jaar: acute episodes: 30-50 mg mesalazine/kg/dag in verdeelde doses, maximale dosering 75 mg mesalazine/kg/dag. De totale dosering dient niet de maximale dosering voor volwassenen te overschrijden. Als onderhoudsbehandeling kan 15-30 mg mesalazine/kg/dag worden gegeven in verdeelde doses. De totale dosering dient niet de aanbevolen dosering voor volwassenen te overschrijden. In het algemeen wordt aanbevolen om de helft van een dosering voor volwassenen te geven aan kinderen met een lichaamsgewicht tot 40 kg; boven 40 kg kan de normale dosering voor volwassenen gegeven worden. **Wijze van toediening:** oraal. De inhoud van Salofalk® Granu-Stix® sachets mag niet worden gekauwd. De granules moeten op de tong worden geplaatst en zonder kauwen met veel vloeistof worden doorgeslikt. Zowel bij de behandeling van acute ontstekingsverschijnselen als tijdens een langdurige behandeling dient Salofalk® Granu-Stix® regelmatig en consequent te worden gebruikt om het gewenste therapeutische effect te bereiken. De duur van de behandeling wordt bepaald door de arts. **Contra-indicaties:** bekende overgevoeligheid voor salicylaten of voor één van de hulpstoffen, ernstige lever- en nierfunctiestoornis. **Waarschuwingen:** voorafgaand aan en tijdens de behandeling dient een controle van het bloed (differentiaal bloedtelling; leverfunctieparameters zoals ALT of AST, serum creatinine) en de urine (dip sticks) te worden verricht, indien de behandelend arts dit noodzakelijk acht. Wanneer er andere verschijnselen optreden, dient er onmiddellijk een controle plaats te vinden. Voorzichtigheid is geboden bij patiënten met een leverfunctiestoornis. Gebruik van Salofalk® Granu-Stix® dient niet te worden gebruikt bij patiënten met een nierfunctiestoornis. Er moet rekening worden gehouden met mesalazine-geïnduceerde niertoxiciteit wanneer de nierfunctie achteruit gaat tijdens de behandeling. Patiënten met een longziekte, met name astma, dienen zeer zorgvuldig te worden gecontroleerd tijdens een behandelingskuur met Salofalk® Granu-Stix®. Patiënten met een voorgeschiedenis van overgevoeligheid voor preparaten die sulfasalazine bevatten dienen zorgvuldig te worden bewaakt bij het begin van een behandelingskuur met Salofalk® Granu-Stix®. Bij het optreden van onverdraagzaamheidsreacties, zoals krampen, acute buikpijn, koorts, hevige hoofdpijn en rash, dient de behandeling onmiddellijk te worden gestaakt. Bij patiënten met fenylketonurie dient men er rekening mee te houden dat Salofalk® Granu-Stix® aspartaam als zoetstof bevatten, overeenkomend met 0,56 mg (Salofalk® 500 mg Granu-Stix®), 1,12 mg (Salofalk® 1000 mg Granu-Stix®), 1,68 mg (Salofalk® 1,5 g Granu-Stix®) en 3,36 mg (Salofalk® 3 g Granu-Stix®) fenylalanine. **Bijwerkingen:** bloed- en lymfestelselaandoeningen: afwijkingen van het bloedbeeld (aplastische anemie, agranulocytose, pancytopenie, neutropenie, leukopenie, trombocytopenie) (zeer zelden, <1/10.000). Zenuwstelselaandoeningen: hoofdpijn, duizeligheid (zelden, ≥1/10.000; <1/1.000). Perifere neuropathie (zeer zelden, <1/10.000). Maagdarmstelselaandoeningen: buikpijn, diarree, flatulentie, misselijkheid, braken (zelden, ≥1/10.000; <1/1.000). Acute pancreatitis (zeer zelden, <1/10.000). Hartaandoeningen: myocarditis, pericarditis (zelden, ≥1/10.000; <1/1.000). Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen: allergische en fibrotische longreactie (inclusief dyspneu, hoest, bronchospasmen, alveolitis, pulmonaire eosinofilie, long infiltratie, pneumonitis) (zeer zelden, <1/10.000). Nier- en urinewegaandoeningen: vermindering van de nierfunctie, waaronder acute en chronische interstitiële nefritis en nierinsufficiëntie (zeer zelden, <1/10.000). Huid- en onderhuidaandoeningen: alopecia (zeer zelden, <1/10.000). Skeletspierstelsel- en bindweefselaandoeningen: myalgie, artralgie (zeer zelden, <1/10.000). Immuunsysteemaandoeningen: overgevoeligheidsreacties zoals allergisch exantheem, farmacogene koorts, lupus erythematodes, pancolitis (zeer zelden, <1/10.000). Lever- en galaandoeningen: afwijkingen van parameters van de leverfunctie (verhoogde concentratie transaminasen en parameters van cholestasis), hepatitis en cholestatische hepatitis (zeer zelden, <1/10.000). Voortplantingsstelsel- en borstaandoeningen: oligospermie (reversibel) (zeer zelden, <1/10.000). **Verpakking:** doos met 60 sachets (Salofalk® 1,5 g Granu-Stix® en Salofalk® 3 g Granu-Stix®) of 100 sachets (Salofalk® 500 mg Granu-Stix® en Salofalk® 1000 mg Granu-Stix®). **Afleverstatus en vergoeding:** U.R. en volledig vergoed. RVG 28130, RVG 28131, RVG 100059 en RVG 107302. **Registratiehouder:** Dr. Falk Pharma GmbH, Leinenweberstrasse 5, D-79108 Freiburg, Duitsland. **Voor informatie:** Dr. Falk Pharma Benelux B.V., Breda, 076-5244200, of raadpleeg de volledige SPC. **Versie verkorte SPC-tekst:** 20140729.

Referenties:

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2. Leifeld L et al. Aliment Pharmacol Ther 2011; 34: 1115-22.
3. Kruis W et al. Gut 2009; 58: 233-40.
4. Kruis W et al. Aliment Pharmacol Ther 2011; 33: 313-22.

Focus op perfectie

Dr. Falk

DATUM GOEDKEURING NOVEMBER 2015 / 19-2015-NL

Verkorte samenvatting van de productkenmerken

Naam van het geneesmiddel: Cortiment 9 mg. Kwalitatieve en kwantitatieve samenstelling: Een tablet bevat 9 mg budesonide. Farmaceutische vorm: tabletten met verlengde afgifte. Therapeutische indicaties: Inductie van remissie bij lichte tot matig ernstige actieve colitis ulcerosa). Contra-indicaties: Overgevoeligheid voor het werkzame bestanddeel of voor één van de hulpstoffen. Cortiment bevat o.a. sojaolie. Bijzondere waarschuwingen en voorzorgen bij gebruik: Gebruik met voorzichtigheid bij patiënten met een infectie, hypertensie, diabetes mellitus, osteoporose, ulcus pepticum, glaucoom of cataract, of wanneer diabetes of glaucoom in de familie voorkomt, of met een andere aandoening waarbij het gebruik van glucocorticoïden ongewenste effecten kan hebben. Het overstappen vanaf een andere steroïdenbehandeling kan resulteren in symptomen die samenhangen met veranderingen in de systemische steroïdenwaarden zoals: allergieën, goedaardige intracraniale hypertensie. Het verlagen van de dosis systemische steroïde moet in dat geval met de nodige voorzichtigheid plaatsvinden. Door suppressie van de ontstekingsreactie en het immuunsysteem neemt de vatbaarheid voor en de ernst van infecties toe. De klinische presentatie kan atypisch zijn, en ernstige infecties, zoals sepsis en tuberculose, kunnen worden gemaskeerd, waardoor ze een vergevorderd stadium kunnen bereiken voordat ze worden herkend. Als patiënten zijn geïnfecteerd of wanneer verdenking op infectie bestaat, overweeg dan om de behandeling met glucocorticoïden te verminderen of te staken. Glucocorticoïden kunnen suppressie van de HPA-as veroorzaken en de stressrespons verminderen. Wanneer patiënten een operatie of andere stressvolle situaties ondergaan, wordt aanvullende behandeling met systemische glucocorticoïden aanbevolen. Een verminderde leverfunctie kan invloed hebben op de eliminatie van glucocorticoïden. Het risico van systemische bijwerkingen neemt toe bij patiënten met een ernstige leverfunctiestoornis (bijv. levercirrose). Wanneer de behandeling wordt gestaakt kan het nuttig zijn om de dosis geleidelijk aan te verlagen. Bijzondere zorg is noodzakelijk wanneer het gebruik van systemische corticosteroïden wordt overwogen bij patiënten met bestaande of eerdere ernstige affectiviteitsstoornissen of wanneer deze voorkomen bij familieleden in de eerste graad. Er kunnen systemische effecten van steroïden optreden, met name wanneer deze worden voorgeschreven in hoge doses of gedurende langere tijd. De Cortiment tabletten bevatten lactosemonohydraat en mogen daarom niet worden ingenomen door patiënten met zeldzame erfelijke aandoeningen als galactose-intolerantie, Lapp lactasedeficiëntie of glucose-galactose malabsorptie. Wees voorzichtig met gelijktijdig gebruik van Cortiment met ketoconazol of met grote hoeveelheden grapefruitsap. Omdat bekend is dat corticosteroïden een immunologisch effect hebben, is het waarschijnlijk dat gelijktijdige toediening van Cortiment tabletten de immuunreactie op vaccins vermindert. Bijwerkingen: vaak komt voor: misselijkheid, pijn in de bovenbuik, hoofdpijn, slapeloosheid, stemmingswijziging, daling cortisolwaarde in bloed, influenza, virusinfectie van de bovenste luchtwegen. Registratiehouder: Ferring B.V., Polarisavenue 130, 2132 JX, Hoofddorp. Afleverstatus: U.R. Datum tekst: september 2013

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VERKORTE PRODUCTINFORMATIE HARVONI*▼

▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring.

SAMENSTELLING: 90 mg ledipasvir en 400 mg sofosbuvir. **FARMACEUTISCHE VORM:** filmomhulde tablet **INDICATIES:** 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. **DOSERING:** 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 met krachtige P-gp inductoren. **BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN 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 matige P-gp inductoren:*** matige inductoren van P-glycoproteïne (P-gp) in de darm (bijv. oxcarbazepine), kunnen leiden tot een daling van de plasmaconcentraties van ledipasvir en sofosbuvir, wat resulteert in een verminderd therapeutisch effect van Harvoni. Gelijktijdige toediening van dergelijke geneesmiddelen wordt niet aanbevolen. ***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. Vaak: huiduitslag ***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 oktober 2016. HAR/NL/16-04/PM/1439a. Voor de volledige productinformatie zie de geregisteerde Samenvatting van de Productkenmerken.

HAR/NL/16-04/PM/1439

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GILEAD

STELARA (ustekinumab) – Verkorte productinformatie: Productinformatie bij advertentie elders in dit blad

NAAM VAN HET GENEESMIDDEL: STELARA 45 mg oplossing voor injectie; STELARA 90 mg oplossing voor injectie; STELARA 45 mg oplossing voor injectie in voorgevulde spuit; STELARA 90 mg oplossing voor injectie in voorgevulde spuit. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING:** STELARA 45 mg oplossing voor injectie: Elke injectieflacon bevat 45 mg ustekinumab in 0,5 ml. STELARA 90 mg oplossing voor injectie: Elke injectieflacon bevat 90 mg ustekinumab in 1 ml. STELARA 45 mg oplossing voor injectie in voorgevulde spuit: Elke voorgevulde spuit bevat 45 mg ustekinumab in 0,5 ml. STELARA 90 mg oplossing voor injectie in voorgevulde spuit: Elke voorgevulde spuit bevat 90 mg ustekinumab in 1 ml. Ustekinumab is een geheel humaan IgG1κ-monoklonaal antilichaam tegen interleukine (IL)-12/23, geproduceerd in een muizen-myeloomcellijn met behulp van recombinant-DNA-technologie. **FARMACEUTISCHE VORM:** STELARA 45 mg oplossing voor injectie: Oplossing voor injectie. STELARA 90 mg oplossing voor injectie: Oplossing voor injectie. STELARA 45 mg oplossing voor injectie in voorgevulde spuit: Oplossing voor injectie. STELARA 90 mg oplossing voor injectie in voorgevulde spuit: Oplossing voor injectie. De oplossing is helder tot licht opaalachtig, kleurloos tot lichtgeel. **Therapeutische indicaties:** Plaque psoriasis: STELARA is aangewezen voor de behandeling van matige tot ernstige plaque psoriasis bij volwassenen met onvoldoende respons op, of een contra-indicatie of een intolerantie voor andere systemische therapieën waaronder ciclosporine, methotrexaat (MTX) of PUVA (psoraleen en ultraviolet A). Plaque psoriasis bij pediatrische patiënten: STELARA is aangewezen voor de behandeling van matige tot ernstige plaque psoriasis bij adolescente patiënten van 12 jaar en ouder, bij wie andere systemische therapieën of fototherapieën geen adequate controle geven, of die daarvoor een intolerantie hebben. Arthritis psoriatica (PsA): STELARA is, alleen of in combinatie met MTX, aangewezen voor de behandeling van actieve arthritis psoriatica bij volwassen patiënten bij wie de respons op eerdere niet-biologische *disease-modifying anti-rheumatic drug* (DMARD) therapie inadequaat is gebleken. Ziekte van Crohn: STELARA is geïndiceerd voor de behandeling van volwassen patiënten met matig tot ernstig actieve ziekte van Crohn die onvoldoende of niet meer reageren op ofwel conventionele therapie ofwel een TNFα-remmer of deze behandelingen niet verdragen of er medische contra-indicaties voor hebben. **Dosering en wijze van toediening:** STELARA is bedoeld voor gebruik onder begeleiding en supervisie van artsen met ervaring in het diagnosticeren en behandelen van de aandoeningen waarvoor STELARA is geïndiceerd. Dosering: Plaque psoriasis: De aanbevolen dosering van STELARA is een aanvangsdosis van 45 mg subcutaan toegediend, gevolgd door een dosis van 45 mg na 4 weken en vervolgens iedere 12 weken. Bij patiënten die geen respons hebben vertoond op een behandeling tot 28 weken dient men te overwegen om de behandeling te stoppen. *Patiënten met een lichaamsgewicht van > 100 kg:* Voor patiënten met een lichaamsgewicht van > 100 kg is de aanvangsdosis 90 mg, subcutaan toegediend, gevolgd door een dosis van 90 mg na 4 weken en vervolgens iedere 12 weken. Bij deze patiënten is 45 mg ook effectief gebleken. 90 mg resulteerde echter in grotere werkzaamheid. Arthritis psoriatica (PsA): De aanbevolen dosering van STELARA is een aanvangsdosis van 45 mg, subcutaan toegediend, gevolgd door een dosis van 45 mg na 4 weken en vervolgens iedere 12 weken. Als alternatief kan 90 mg gebruikt worden bij patiënten met een lichaamsgewicht van > 100 kg. Bij patiënten die geen respons hebben vertoond na 28 weken behandeling dient men te overwegen om de behandeling te stoppen. *Ouderen (≥ 65 jaar):* Er is geen aanpassing van de dosis nodig bij oudere patiënten. *Nier- en leverinsufficiëntie:* STELARA is niet bij deze patiëntenpopulaties onderzocht. Er kunnen geen aanbevelingen worden gedaan omtrent de dosering. *Pediatrische patiënten:* De veiligheid en werkzaamheid van STELARA bij kinderen met psoriasis jonger dan 12 jaar of bij kinderen met arthritis psoriatica jonger dan 18 jaar zijn nog niet vastgesteld. Plaque psoriasis bij pediatrische patiënten (12 jaar en ouder): De aanbevolen dosis STELARA op basis van het lichaamsgewicht is hieronder weergegeven (tabel 1 en 2). STELARA dient te worden toegediend in de weken 0 en 4, en vervolgens iedere 12 weken. *Tabel 1: Aanbevolen dosis van STELARA voor psoriasis bij pediatrische patiënten:* **Lichaamsgewicht op het moment van toediening:** Aanbevolen dosis. **< 60 kg:** 0,75 mg/kg[a]. **≥ 60–≤ 100 kg:** 45 mg. **> 100 kg:** 90 mg. [a] Gebruik de volgende formule om het injectievolume (ml) voor patiënten van < 60 kg te berekenen: lichaamsgewicht (kg) x 0,0083 (ml/kg) of raadpleeg tabel 2. Het berekende volume dient te worden afgerond op de dichtstbijzijnde 0,01 ml en worden toegediend met een gegradueerde 1 ml-spuit. Voor pediatrische patiënten die met een lagere dosis moeten worden behandeld dan de volledige dosis van 45 mg is er een 45 mg-injectieflacon verkrijgbaar. *Tabel 2: Injectievolumes van STELARA bij pediatrische psoriasispatiënten < 60 kg:* **Lichaamsgewicht op het moment van toediening (kg):** *Dosis (mg)*: Injectievolume (ml). **30:** *22,5*: 0,25 – **31:** *23,3*: 0,26 – **32:** *24,0*: 0,27 – **33:** *24,8*: 0,27 – **34:** *25,5*: 0,28 – **35:** *26,3*: 0,29 – **36:** *27,0*: 0,30 – **37:** *27,8*: 0,31 – **38:** *28,5*: 0,32 – **39:** *29,3*: 0,32 – **40:** *30,0*: 0,33 – **41:** *30,8*: 0,34 – **42:** *31,5*: 0,35 – **43:** *32,3*: 0,36 – **44:** *33,0*: 0,37 – **45:** *33,8*: 0,37 – **46:** *34,5*: 0,38 – **47:** *35,3*: 0,39 – **48:** *36,0*: 0,40 – **49:** *36,8*: 0,41 – **50:** *37,5*: 0,42 – **51:** *38,3*: 0,42 – **52:** *39,0*: 0,43 – **53:** *39,8*: 0,44 – **54:** *40,5*: 0,45 – **55:** *41,3*: 0,46 – **56:** *42,0*: 0,46 – **57:** *42,8*: 0,47 – **58:** *43,5*: 0,48 – **59:** *44,3*: 0,49. Bij patiënten die geen respons hebben vertoond op een behandeling tot 28 weken dient men te overwegen om de behandeling te stoppen. Ziekte van Crohn: Volgens het behandelingsschema wordt de eerste dosis STELARA intraveneus toegediend. Voor de dosering bij het intraveneuze doseringsschema, zie "Dosering en wijze van toediening" van de SmPC voor STELARA 130 mg concentraat voor oplossing voor infusie. De eerste subcutane toediening van 90 mg STELARA dient 8 weken na de intraveneuze dosis plaats te vinden. Vervolgens wordt toediening om de 12 weken aanbevolen. Patiënten die 8 weken na de eerste subcutane dosis niet voldoende respons hebben vertoond, mogen op dit tijdstip een tweede dosis ontvangen. Patiënten bij wie de respons bij toediening om de 12 weken verdwijnt, kunnen baat hebben bij een verhoging van de toedieningsfrequentie naar om de 8 weken. Patiënten kunnen vervolgens om de 8 weken of om de 12 weken een dosis ontvangen, op basis van klinische beoordeling. Bij patiënten die na 16 weken of 16 weken na overschakeling op de 8-wekelijkse dosis geen baat blijken te hebben bij de behandeling dient te worden overwogen om met de behandeling te stoppen. Behandeling met immunomodulatoren en/of corticosteroïden kan worden voortgezet tijdens de behandeling met STELARA. Bij patiënten die naar tevredenheid reageren op de behandeling met STELARA kan de dosering van corticosteroïden, in overeenstemming met de zorgstandaard, worden verlaagd of gestopt. Bij onderbreking van de behandeling is hervatting van de behandeling met subcutane toediening om de 8 weken veilig en effectief. *Ouderen (≥ 65 jaar):* Er is geen aanpassing van de dosis nodig bij oudere patiënten. *Nier- en leverinsufficiëntie:* STELARA is bij deze patiëntenpopulaties niet onderzocht. Er kan geen doseringsadvies worden gegeven. *Pediatrische patiënten:* De veiligheid en werkzaamheid van STELARA voor de behandeling van de ziekte van Crohn bij kinderen jonger dan 18 jaar zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. Wijze van toediening: STELARA 45 mg en 90 mg injectieflacons of voorgevulde spuiten zijn uitsluitend bedoeld voor subcutane injectie. Indien mogelijk dienen huidzones met tekenen van psoriasis te worden vermeden als injectieplaats. Na een adequate training in de techniek van het subcutaan injecteren mogen patiënten of hun verzorgers STELARA injecteren als een arts beslist dat dit aangewezen is. De arts dient echter te zorgen voor een adequate opvolging van de patiënten. Patiënten of hun verzorgers dienen geïnstrueerd te worden de voorgeschreven hoeveelheid STELARA te injecteren, overeenkomstig de aanwijzingen in de bijsluiter. In de bijsluiter worden uitgebreide instructies voor de toediening gegeven. **Contra-indicaties:** Overgevoeligheid voor de werkzame stof of voor een van de hulpstof(fen). Klinisch belangrijke, actieve infectie (bijv. actieve tuberculose). **Bijwerkingen:** Samenvatting van het veiligheidsprofiel: De meest voorkomende bijwerkingen (> 5%) in gecontroleerde perioden van de klinische studies met ustekinumab bij psoriasis, arthritis psoriatica en de ziekte van Crohn bij volwassenen waren nasofaryngitis en hoofdpijn. De meeste werden beschouwd als mild en noodzaakten geen stopzetting van de studiebehandeling. De meest ernstige bijwerking van STELARA die gemeld is, zijn ernstige overgevoeligheidsreacties met anafylaxie. Het algemene veiligheidsprofiel van patiënten met psoriasis, arthritis psoriatica en de ziekte van Crohn. Bijwerkingen in tabelvorm: De veiligheidsgegevens die hieronder worden beschreven, zijn gebaseerd op blootstelling van volwassenen aan ustekinumab in 12 fase 2- en fase 3-studies bij 5.884 patiënten (4.135 met psoriasis en/of arthritis psoriatica en 1.749 met de ziekte van Crohn). Het gaat daarbij om blootstelling aan STELARA in de gecontroleerde en niet-gecontroleerde perioden van de klinische studies gedurende minstens 6 maanden of 1 jaar (respectievelijk 4.105 en 2.846 patiënten met psoriasis, arthritis psoriatica of de ziekte van Crohn) en om blootstelling gedurende ten minste 4 of 5 jaar (respectievelijk 1.482 en 838 patiënten met psoriasis). Tabel 3 geeft een lijst van bijwerkingen weer uit de klinische studies bij volwassenen met psoriasis, arthritis psoriatica en de ziekte van Crohn en van bijwerkingen gemeld tijdens post-marketinggebruik. De bijwerkingen zijn ingedeeld volgens systeem/orgaanklassen en geordend naar frequentie, met de volgende definities: Zeer vaak (≥ 1/10), Vaak (≥ 1/100 tot < 1/10), Soms (≥ 1/1.000 tot < 1/100), Zelden (≥ 1/10.000 tot < 1/1.000), Zeer zelden (< 1/10.000), niet bekend (kan met de beschikbare gegevens niet worden bepaald). Binnen iedere frequentiegroep worden bijwerkingen gerangschikt in volgorde van afnemende ernst. *Tabel 3: Lijst van bijwerkingen:* **Systeem/orgaanklasse:** *Frequentie*: Bijwerking. **Infecties en parasitaire aandoeningen:** *Vaak*: Bovensteluchtweginfectie, nasofaryngitis. *Soms*: Cellulitis, gebitsinfecties, herpes zoster, virale bovensteluchtweginfectie, vulvovaginale schimmelinfectie. **Immuunsysteemaandoeningen:** *Soms*: Overgevoeligheidsreacties (waaronder rash, urticaria). *Zelden*: Ernstige overgevoeligheidsreacties (waaronder anafylaxie en angio-oedeem). **Psychische stoornissen:** *Soms*: Depressie. **Zenuwstelselaandoeningen:** *Vaak*: Duizeligheid, hoofdpijn. *Soms*: Facialisverlamming. **Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen:** *Vaak*: Orofaryngeale pijn. *Soms*: Neusverstopping. **Maag-darmstelselaandoeningen:** *Vaak*: Diarree, nausea, braken. **Huid- en onderhuidaandoeningen:** *Vaak*: Pruritus. *Soms*: Pustulaire psoriasis, huidexfoliatie, acne. *Zelden*: Exfoliatieve dermatitis. **Skeletspierstelsel- en bindweefselaandoeningen:** *Vaak*: Rugpijn, spierpijn, artralgie. **Algemene aandoeningen en toedieningsplaatsstoornissen:** *Vaak*: Vermoeidheid, erytheem op de injectieplaats, pijn op de injectieplaats. *Soms*: Reacties op de injectieplaats (waaronder hemorragie, hematoom, induratie, zwelling en pruritus), asthenie. Beschrijving van geselecteerde bijwerkingen: Infecties: In de placebogecontroleerde studies bij patiënten met psoriasis, arthritis psoriatica en de ziekte van Crohn waren de percentages infecties of ernstige infecties bij patiënten behandeld met ustekinumab en degenen behandeld met placebo vergelijkbaar. In de placebogecontroleerde periode van de klinische studies bij patiënten met psoriasis, patiënten met arthritis psoriatica en patiënten met de ziekte van Crohn was het infectiecijfer 1,38 per patiëntjaar in *follow-up* bij patiënten behandeld met ustekinumab, en 1,35 bij patiënten behandeld met placebo. De incidentie van ernstige infecties was 0,03 per patiëntjaar in *follow-up* bij patiënten behandeld met ustekinumab (27 ernstige infecties in 829 patiëntjaren in *follow-up*) en 0,03 bij patiënten behandeld met placebo (11 ernstige infecties in 385 patiëntjaren in *follow-up*). In de gecontroleerde en niet-gecontroleerde perioden van klinische studies bij psoriasis, arthritis psoriatica en de ziekte van Crohn, met gegevens van blootstelling van 10.953 patiëntjaren bij 5.884 patiënten, was de mediane *follow-up* 0,99 jaar: 3,2 jaar voor studies bij psoriasis, 1,0 jaar voor studies bij arthritis psoriatica en 0,6 jaar voor studies bij de ziekte van Crohn. Het infectiecijfer was 0,91 per patiëntjaar in *follow-up* bij patiënten behandeld met ustekinumab, en het cijfer van ernstige infecties was 0,02 per patiëntjaar in *follow-up* bij patiënten behandeld met ustekinumab (178 ernstige infecties in 10.953 patiëntjaren in *follow-up*). De gemelde ernstige infecties waren anaal abces, cellulitis, pneumonie, diverticulitis, gastro-enteritis en virale infecties. In klinische studies ontwikkelden patiënten met latente tuberculose die tegelijkertijd werden behandeld met isoniazide geen tuberculose. Maligniteiten: In de placebogecontroleerde periode van de klinische studies bij psoriasis, arthritis psoriatica en de ziekte van Crohn was de incidentie van maligniteiten (uitgezonderd niet-melanome huidkanker) 0,12 per 100 patiëntjaren in *follow-up* voor patiënten behandeld met ustekinumab (1 patiënt in 829 patiëntjaren in *follow-up*), in vergelijking met 0,26 voor patiënten behandeld met placebo (1 patiënt in 385 patiëntjaren in *follow-up*). De incidentie van niet-melanome huidkanker was 0,48 per 100 patiëntjaren in *follow-up* voor patiënten behandeld met ustekinumab (4 patiënten in 829 patiëntjaren in *follow-up*) in vergelijking met 0,52 voor patiënten behandeld met placebo (2 patiënten in 385 patiëntjaren in *follow-up*). In de gecontroleerde en niet-gecontroleerde perioden van klinische studies bij psoriasis, arthritis psoriatica en de ziekte van Crohn, met gegevens van blootstelling van 10.935 patiëntjaren bij 5.884 patiënten, was de mediane *follow-up* 1,0 jaar: 3,2 jaar voor studies bij psoriasis, 1,0 jaar voor studies bij arthritis psoriatica en 0,6 jaar voor studies bij de ziekte van Crohn. Maligniteiten, uitgezonderd niet-melanome huidkankers, werden gemeld bij 58 patiënten in 10.935 patiëntjaren in *follow-up* (incidentie bij de patiënten behandeld met ustekinumab: 0,53 per 100 patiëntjaren in *follow-up*. De incidentie van maligniteiten gemeld bij patiënten behandeld met ustekinumab was vergelijkbaar met de incidentie verwacht in de algemene bevolking (gestandaardiseerde incidentieratio = 0,87 [95%-betrouwbaarheidsinterval: 0,66, 1,14], aangepast voor leeftijd, geslacht en ras). De maligniteiten die het vaakst werden waargenomen, anders dan niet-melanome huidkanker, waren prostaat-, melanoma-, coloректaal- en borstkankers. De incidentie van niet-melanome huidkanker was voor patiënten behandeld met ustekinumab 0,49 per 100 patiëntjaren in *follow-up* (53 patiënten in 10.919 patiëntjaren in *follow-up*). De verhouding van patiënten met basaalcelhuidkankers ten opzichte van patiënten met plaveiselcelhuidkankers (4:1) is vergelijkbaar met de verhouding die verwacht kan worden bij de algemene bevolking. Overgevoeligheidsreacties: Tijdens de gecontroleerde periodes van klinische studies met ustekinumab bij psoriasis en arthritis psoriatica zijn rash en urticaria elk waargenomen bij < 1% van de patiënten. Immunogeniciteit: Minder dan 8% van de patiënten behandeld met ustekinumab in klinische studies bij psoriasis en arthritis psoriatica ontwikkelde antilichamen tegen ustekinumab. In klinische studies bij de ziekte van Crohn ontwikkelden zich bij minder dan 3% van de patiënten die met ustekinumab werden behandeld antilichamen tegen ustekinumab. Er werd geen duidelijke associatie waargenomen tussen de ontwikkeling van antilichamen tegen ustekinumab en de ontwikkeling van reacties op de plaats van de injectie. De meerderheid van de patiënten die positief waren voor antilichamen tegen ustekinumab hadden neutraliserende antilichamen. Er was een tendens tot een lagere effectiviteit bij patiënten positief voor antilichamen tegen ustekinumab; positiviteit voor antilichamen sloot een klinische respons echter niet uit. *Pediatrische patiënten:* Bijwerkingen bij pediatrische patiënten van 12 jaar en ouder met plaque psoriasis. De veiligheid van ustekinumab is onderzocht in een fase 3-studie tot 60 weken bij 110 patiënten van 12 tot 17 jaar. In deze studie waren de gerapporteerde bijwerkingen vergelijkbaar met de bijwerkingen die in eerdere studies werden gezien bij volwassenen met plaque psoriasis. Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via : **België:** Federaal agentschap voor geneesmiddelen en gezondheidsproducten (www.fagg.be). **Nederland:** Nederlands Bijwerkingen Centrum Lareb Website: www.lareb.nl. **Aard en inhoud van de verpakking:** STELARA 45 mg oplossing voor injectie: 0,5 ml oplossing in een type 1-glazen injectieflacon van 2 ml, afgesloten met een van coating voorziene butylrubberen stop. 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Referenties: 1. SmPC Stelara **2.** EPAR rapport Stelara ziekte van Crohn **3.** Feagan B.G. et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease, N Engl J Med 2016;375:1946-60

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▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan Teva snel nieuwe veiligheidsinformatie vaststellen. Beroepsbeoefenaren in de gezondheidszorg worden verzocht alle vermoedelijke bijwerkingen te melden via dso.nl@tevanederland.com. **Handelsnaam:** Thiosix, tabletten **Kwalitatieve & kwantitatieve samenstelling:** Thiosix 10 mg bevat 10 mg tioguanine per tablet. Thiosix 20 mg bevat 20 mg tioguanine per tablet. **Indicaties:** onderhoudsbehandeling van inflammatoire darmziekten (ziekte van Crohn of ulceratieve colitis), bij volwassen patiënten die onvoldoende reageren op of intolerant zijn voor standaard tiopurine behandeling (azathioprine, mercaptopurine). **Contra-indicaties:** Overgevoeligheid voor een van de stoffen. Vrouwen die borstvoeding geven. **Belangrijkste waarschuwingen/voorzorgen:** Tioguanine is een actief cytotoxisch middel en mag alleen onder supervisie van een arts met ervaring gebruikt worden. Er is een verhoogd risico op levertoxiciteit met vasculaire endotheel beschadiging. Behandeling met tioguanine dient gestaakt te worden bij bewezen levertoxiciteit, omdat bij tijdig staken de levertoxiciteit meestal omkeerbaar is. Routinematige controles, zoals omschreven in de volledige SPC, worden ten sterkte aanbevolen. Patiënten met erfelijke deficiëntie van het enzym tiopurinemethyltransferase (TPMT) kunnen ongewoon gevoelig zijn voor het myelosuppressieve effect van tioguanine en snel neigen tot beenmergsuppressie na de start van de behandeling. Patiënten dienen tijdens de tioguanine therapie onder zorgvuldige controle te staan met bloedcel tellingen. Vaccinatie met levende vaccins wordt ontraden. Gebruik van tioguanine bij patiënten die het enzym hypoxanthineguaninefosforibosyltransferase missen, zoals in het geval van Lesch-Nyhan syndroom, wordt ontraden. **Belangrijkste bijwerkingen:** De hierna beschreven bijwerkingen en bijbehorende frequenties zijn geobserveerd in leukemie patiënten die behandeld werden met hogere doseringen. Gewoonlijk wordt tioguanine bij deze patiënten in combinatie met andere cytotoxische middelen toegepast. Hierdoor is het niet altijd mogelijk om bijwerkingen aan één specifiek geneesmiddel toe te schrijven. Dezelfde bijwerkingen, mogelijk met andere frequenties, zijn geobserveerd in patiënten met inflammatoire darmziekten die behandeld werden met 20-80 mg tioguanine per dag. Beenmergsuppressie komt zeer vaak voor. Stomatitis, gastro-intestinale intolerantie en levertoxiciteit met vasculaire endotheelbeschadiging komen vaak voor. De volgende ernstige bijwerkingen komen zelden voor: intestinale necrose en perforatie en centrilobulaire hepatisch necrose is beschreven bij patiënten met combinatietherapie, orale contraceptiva, hoge dosering van tioguanine en alcohol. **Afleverstatus:** UR. **Registratiehouder:** Teva Nederland BV, Swensweg 5, 2031 GA Haarlem, Nederland. **Datum laatste herziening SPC:** 10 april 2015.

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