Bootcongres 2012

wetenschappelijke voorjaarsvergadering

Nederlandse Transplantatie Vereniging

27 en 28 maart 2012

georganiseerd i.s.m.

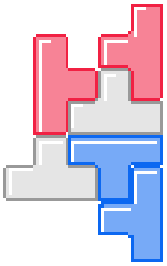
Maastricht UMC+

academisch ziekenhuis Maastricht azM | Maastricht University

Locatie:

MECC - Maastricht

Inhoudsopgave



In het programma vindt u achter de titel van de voordracht een verwijzing naar de pagina waar u het betreffende abstract kunt vinden.

Welkom op het 24ste Bootcongres!

Maastricht, de zuidelijkste stad van Nederland en voor velen al een beetje buitenland , is deze dagen de pleisterplaats van 'Orgaantransplantatie Nederland'.

Tweeduizendentwaalf is voor 'Maastricht' een bijzonder jaar: in 1982 werd in het Ziekenhuis Annadal de eerste niertransplantatie verricht en wij bestaan dit jaar dus 30 jaar als transplantatiecentrum. Wij zijn blij om in zo'n jaar het Bootcongres te mogen organiseren .
Het congres vindt plaats in het moderne MECC, terwijl als contrast het avond-programma juist plaatsvindt op millennium-oude gesteente, op de oude zeebodem.

Het programma is een Odyssee door de Nederlandse transplantatiewereld met 87 voordrachten en 28 posters uit de ingezonden abstracts, waarin de Nederlandse transplantatiewereld U in plenaire en parallelle sessies onder-houdt met nieuwe inzichten in al haar diversiteiten aan onderwerpen (klinisch, basaal, verpleegkundig en donatie) en gebruikte methodes/technieken. Daarnaast vinden er beide dagen interessante lezingen plaats met onderwerpen die voor de transplantatiewereld een eye-opener kunnen betekenen dan wel een verfrissende uitstapje zijn die U mee terug neemt naar huis. Tijdens de lunchpauze op de eerste congresdag vindt de inmiddels beroemde onderwijs-sessie plaats. Tijdens de middagpauze op de tweede dag zijn guided poster-sessies gepland. Dit biedt U de mogelijkheid om informeel en interactief met de onderzoekers van gedachten te wisselen. De posters zijn natuurlijk ook tijdens het gehele congres te bestuderen.

Ook dit jaar zijn er weer prijzen in overvloed: Prof. Jon van Rood heeft toe-gezegd de naar hem genoemde prijs voor het beste proefschrift van de afgelopen twee jaar in de basale transplantatiewetenschappen te overhandigen. Ook worden de prijzen voor het beste gepubliceerde Nederlandse artikel (basaal en klinisch) uitgereikt en de aanmoedigingsprijs voor translationeel transplantatie onderzoek. Daarnaast zijn de prijzen voor de beste presentatie per sessie niet meer weg te denken van dit congres, nadat wij er een 7-tal jaren geleden mee zijn begonnen. Deze worden uitgereikt door de voorzitters van iedere sessie (ook van de postersessies) . Deze voorzitters hebben een dubbelrol: zij zijn ook de jury en staan helemaal vrij in hun (subjectief) oordeel. Op de woensdag is er tijdens de ledenvergadering weer de gelegenheid om met het bestuur van de NTV in discussie te gaan over het gevoerde/te voeren beleid.

De eerste en tweede congresdag gaan dinsdagavond vlekkeloos in elkaar over tijdens de feestavond. Hiervoor hebben wij een unieke Limburgse locatie gekozen: Waar vroeger een zee was, staan wij nu op vaste bodem in een mergelgrot "La Caverne de Geulhem". Na het diner barst daar het feest los.
U wordt om 18.00 uur met bussen vanaf MECC naar deze feestlocatie gebracht en tussen 23.00 uur en 01.15 uur gaan de bussen terug naar de diverse congreshotels. Let op: de grot is verwarmd, dus kleed U zich niet te warm aan.
U en wij zorgen voor het 'vuur'.
Als U na de 2 congresdagen uw terugreis maakt, hopen wij dat U lichamelijk vermoeid maar geestelijk verkwikt bent!

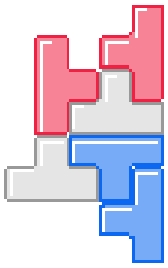
Maarten Christiaans
Voorzitter locaal organisatiecomité MUMC+

Organisatiecommissie Bootcongres 2012

Maarten Christiaans
Ernst van Heurn
Marloes Homberg
Wim de Jongh
Marcel Tilanus
Joris Vanderlocht

Vanuit het secretariaat NTV te Haarlem
Jeanine Gies
Marie José van Gijtenbeek
Marja Weber

Accreditatie is aangevraagd* / toegekend door de volgende verenigingen:



Nederlandse Vereniging voor Heelkunde	12 punten*
Nederlandse Vereniging voor Immunologie	12 punten
Nederlandse Vereniging van Maag-Darm-Leverartsen	12 punten
Nederlandse Internisten Vereniging	12 punten
Nederlandse Vereniging voor Kindergeneeskunde	11 punten*

V&VN, kwaliteitsregister, deskundigheidsgebied Dialyse

V &VN, verpleegkundig specialisten register

Op individuele basis kan accreditatie worden aangevraagd bij:

Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose

Nederlandse Vereniging voor Cardiologie

MECC Maastricht
Forum 100, 6229 GV Maastricht

MECC Maastricht beschikt over ruime parkeerfaciliteiten rondom het gebouw. Uw parkeerkaartje koopt u voor € 9,50* (tarief voor een hele dag) in de entreehal van MECC Maastricht.

**parkeerkosten zijn € 9,50 per passeren van de slagboom. Indien er binnengereden wordt en de volgende dag pas weer uitgereden zijn de kosten niet € 19,- maar € 9,50*

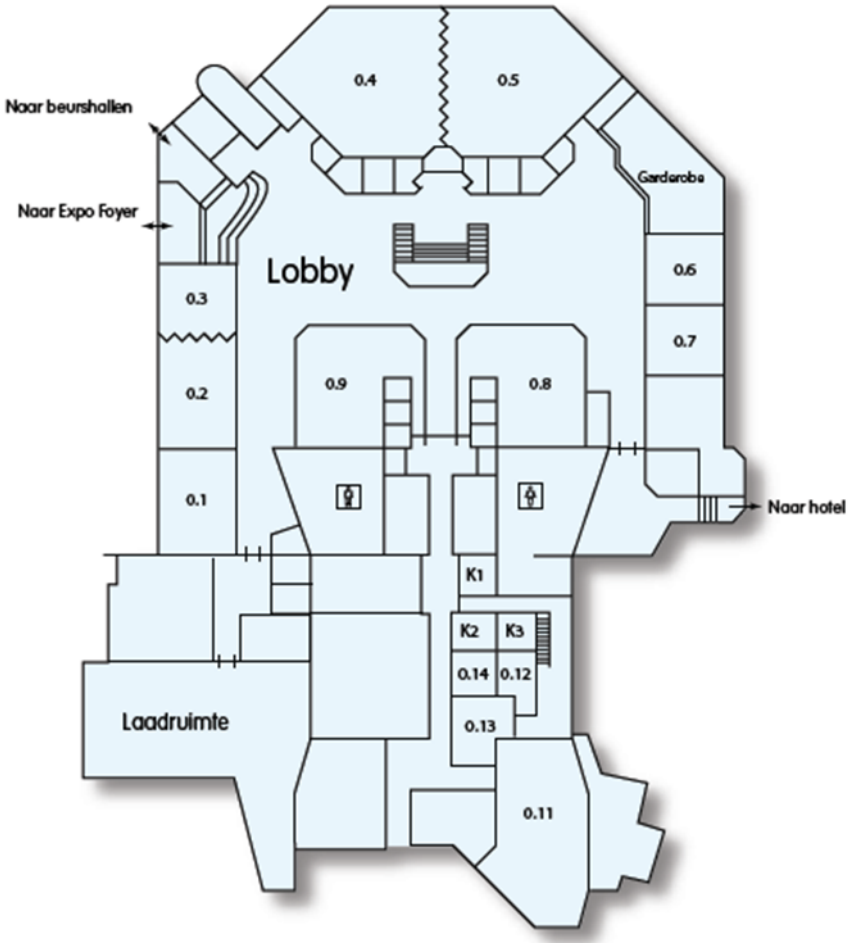
Per bus
Gemiddeld iedere vijf minuten pendelt de stadsbus van Maastricht tussen het centrum, Maastricht CS en MECC Maastricht (halte Forum).

Per trein
Station Maastricht-Randwyck ligt op 250 meter afstand van MECC Maastricht. Er is een regelmatige verbinding met Maastricht C.S., dat is aangesloten op het (inter)nationaal spoorwegennet.

Floorplan

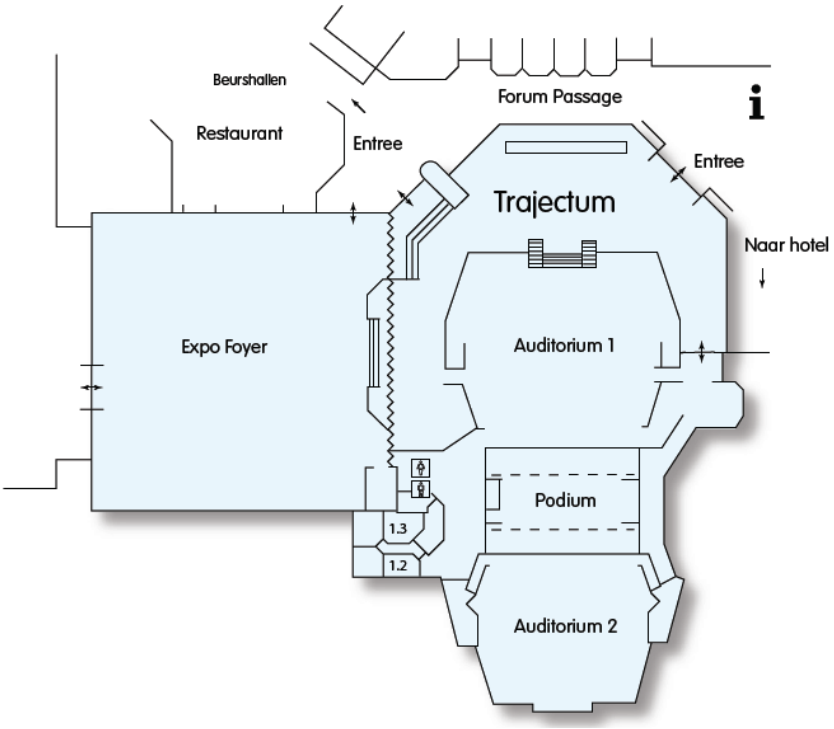
Plattegrond MECC Maastricht

0-niveau



Plattegrond MECC Maastricht

1-niveau



Locatie en tijdstippen van de maaltijden

Dinsdag

Ontbijt dinsdag in de diverse hotels	07.00 - 09.30 uur
Lunch	12.30 - 14.00 uur
Lunch onderwijssessie Auditorium 2 (lunchpakket)	12.30 - 14.00 uur
Congresborrel La Caverne de Geulhem	18.30 - 19.00 uur
Diner en feestavond La Caverne de Geulhem	19.00 - 01.00 uur

Woensdag

Ontbijt woensdag in de diverse hotels	07.00 - 08.30 uur
Lunch	12.00 - 13.00 uur

Bijeenkomsten tijdens Bootcongres

Maandag 26 maart 2012

13.00 – 16.00	Landelijk Overleg Levertransplantatie *Locatie: NH Maastricht, zaal 3-4*
16.30 – 19.00	Landelijk Overleg Transplantatie Thoracale Organen *Locatie: NH Maastricht, zaal 3-4*
16.30 – 19.00	Landelijk Overleg Niertransplantatie *Locatie: NH Maastricht, zaal 7-8*
18.00 – 19.30	Landelijke Werkgroep Transplantatie Verpleegkunde *Locatie: NH Maastricht, zaal 1-3*

Dinsdag 27 maart 2012

08.00 – 10.00 uur	Transplantatie Werkgroep Nederland *Locatie: NH Maastricht, zaal 7-8*
13.30 – 14.00 uur	Landelijk Overleg Regionale Uitnameteams *Locatie: MECC, zaal 0.11*

Schematisch overzicht programma
Dinsdag 27 maart 2012

Dinsdag 27 maart 2012		**Auditorium 2**	**Zaal 0.2/0.3 Berlin-Copenhagen**	**Zaal 0.9 Athens**
08.00 – 10.00	Vergadering TWN			
10.00 – 11.00		Plenaire sessie I Opening congres Lezing Dr. F. Bannink: "Wat gij wilt dat u geschiedt…." De positieve focus in de medische praktijk		
11.00 – 11.30	Koffiepauze			
11.30 – 12.30		Plenaire sessie II Lezing Prof. J.R. Nuñez: "Increasing the donor pool: uncontrolled DCD" 22 years experience in Spain		
12.30 – 14.00	Lunchbuffet	Onderwijssessie		
14.00 – 15.30		Parallelsessie III – Verpleegk./Donatie	Parallelsessie III - Basaal	Parallelsessie III – Klinisch
15.30 – 16.00	Theepauze			
16.00 – 16.45		Plenaire sessie IV – Lezing dr. J. Kooman: "Draagbare kunstnier: de ontwikkeling, stand van zaken en toekomst. Concurrent voor niertransplantatie?"		
16.45 – 18.00		Uitreiking prijzen: Novartis Transplantation Grant 2012 Uitreiking Jon J. van Roodprijs 2012 en lezing door de prijswinnaar		
18.00 18.30 – 01.15	Busvervoer naar la Caverne de Geulhem Dinerbuffet en feestavond			

Schematisch overzicht programma
Woensdag 28 maart 2012

Woensdag 28 maart 2012		**Zaal 0.4/0.5 Brussels-Paris**	**Zaal 0.2/0.3 Berlin-Copenhagen**	**Zaal 0.9 Athens**
08.30 – 10.00		Parallelsessie V – Verpleegk./Donatie	Parallelsessie V – Basaal	Parallelsessie V – Klinisch
10.00 – 10.30	Koffiepauze			
10.30 – 11.00		Plenaire sessie VI Uitreiking ATRP prijs 2012 en lezing door winnaar van de ATRP 2011		
11.00 – 12.00		Ledenvergadering NTV		
12.00 – 13.00	Lunchpauze + guided postersessie			
13.00 – 15.00		Parallelsessie VII – Verpleegk./Donatie Lezing: "Meerwaarde certificering in de ketenzorg: Pretransplantatiescreening als voorbeeld" Dr. E.C.H. van den Ham	Parallelsessie VII – Basaal	Parallelsessie VII – Klinisch Lezing: "Transplantatie van eilandjes van Langerhans: Waar staan wij nu? " Prof. dr. E.J.P. Koning
15.00 – 15.45	Theepauze	Première Film: 'Orgaandonatie: Donorzorg is patiëntenzorg'		
15.45 – 16.45		Plenaire sessie VIII – Lezingen: - K. Glorie: "Optimal policy for participation of non-directed living donors in kidney exchange programs" - Dr. A. Reubsaet: "School-based organ donation education program"		
16.45 – 17.45		Plenaire sessie IX: hoogst scorende abstracts		
17.45 – 18.00		Afsluiting door LOC / vertrek deelnemers		

Sessie I - plenair — Auditorium 2

09.00 Ontvangst en registratie

10.00 Opening M.H.L. Christiaans,
voorzitter lokaal organisatiecomité Maastricht

10.05 **'Wat gij wilt dat u geschiedt…'**
De positieve focus in de medische praktijk
Dr. F. Bannink, Klinisch Psycholoog, Amsterdam

11.00 Koffiepauze

Sessie II - plenair — Auditorium 2

Voorzitter: L.W.E. van Heurn

11.30 **'Increasing the donor pool: uncontrolled DCD.**
22 years experience of Spain'
Prof. J.R. Nuñez, Professor of Surgery, Madrid University, Spain

12.30 Einde sessie II, lunchpauze en postersessie

Dinsdag 27 maart 2012

Onderwijssessie **Auditorium 2**

12.30 Lunchpakket bij ingang van de zaal
voor alle **geregistreerde** deelnemers aan de onderwijssessie

Voorzitter: *C. Baan*

12.45 "De cellulaire (innate) immmuunrespons"
Dr. J. Vanderlocht, staflid, Lab Weefseltypering
Maastricht Universitair Medisch Centrum

13.10 Nieuw zicht op HLA-epitopen
Dr. D.L. Roelen, immunoloog, Afd. Immunohematologie & Bloedtransfusie, Leids Universitair Medisch Centrum

13.35 Histologische beoordeling van een nierbiopt voorafgaand aan niertransplantatie
Dr. C. Peutz-Kootstra, patholoog, Maastricht Universitair Medisch Centrum

14.00 Einde onderwijssessie

Parallelsessie III - klinisch — Zaal 0.9

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten

Voorzitters: M.A.C.J. Gelens en W.G. Polak

14.00 B Cell Repopulation After Alemtuzumab Treatment in Kidney Transplant Recipients – Transient Increase in Transitional B Cells and Long Term Dominance of Naïve B Cells (p. 46)
S. Heidt[1], J. Hester[1], S. Shankar[1], P.J. Friend[2], K.J. Wood[1], [1]Transplant Research Immunology Group, Nuffield Dept. of Surgical Sciences, University of Oxford, Oxford, United Kingdom, [2]Oxford Transplant Centre, Nuffield Dept. of Surgical Sciences, University of Oxford, Oxford, United Kingdom

14.10 Treatment of Acute Renal Allograft Rejection with Alemtuzumab (p. 47)
M.W.F. van den Hoogen[1], W.J. van Son[2], L.B. Hilbrands[1], [1]Radboud University Nijmegen Medical Center, Dept. of Nephrology, [2]University Medical Centre Groningen, Dept. of Nephrology, The Netherlands

14.20 Pregnancy after kidney transplantation: 'Will the mothers see them grow up?' (p. 48)
M. van Buren[1], J. van de Wetering[1], J.Roodnat[1], S. Berger[1], M. Tielen[1], W. Weimar[1], Dept. of Internal Medicine[1], Erasmus MC, University Medical Centre Rotterdam, The Netherlands

14.30 Pediatric Living Donor Liver transplantation: The Groningen experience (p. 49)
M.T. de Boer[1], F.J.F. Rijntjes[1], R. Scheenstra[2], A.P. van den Berg[3], R.J. Porte[1], Dept of Surgery and Liver Transplantation[1], Dept of Pediatric Gastroenterology[2], Dept of Hepatology[3], University Medical Center Groningen, The Netherlands

14.40 Report of the first 5 DCD pancreas transplants within Eurotransplant, excellent results with prolonged warm ischemia times (p. 50)
J. J. Blok[1,3], A.E. Braat[1], J. Dubbeld[1], M.J.J. Verhagen[1], P.J. van der Boog[2], A.F. Schaapherder[1], A.G. Baranski[1], A.O. Rahmel[3], J. Ringers[1], [1]Dept. of Surgery, Leiden University Medical Center, Leiden, [2]Dept. of Nephrology, Leiden University Medical Center, Leiden, [3]Eurotransplant International Foundation, Leiden, The Netherlands

Parallelsessie III - klinisch - vervolg **Zaal 0.9**

14.50 Historically positive complement dependent cytotoxicity cross match test is not a barrier for live-donor kidney transplantation: A pilot study (p. 51)
Ajda T. Rowshani[1], D. Roelen[2], J. van de Wetering[1], J. Roodnat[1], S.H. Brand-Schaaf[2], S.Y. Stein[2], F.H.J. Claas[2], W. Weimar[1], Erasmus Medical Center, Rotterdam, Dept. of Internal Medicine and Kidney Transplantation[1], Leiden University Medical Centre, Leiden, Dept. of Immunohematology & Bloodtransfusion[2], The Netherlands

15.00 A new CYP3A4 polymorphism (CYP3A4*22) is significantly associated with decreased tacrolimus metabolism (p. 52)
R. Bouamar[1], Laure Elens[2,3], R.H.N. van Schaik[2], V. Haufroid[3], I.P. van der Heiden[2], D.A. Hesselink[4], Teun van Gelder[1,4], [1]Dept. Hospital Pharmacy, [2]Dept. Clinical Chemistry, [4]Dept. Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands, [3]Cliniques Universitaires Saint-Luc – UCL, Laboratory of Analytical Biochemistry & Louvain Centre for Toxicology and Applied Pharmacology (LTAP), Bruxelles, Belgium

15.10 Effect of a multifactorial intervention with the aid of nursepractitioners on cardiovascular outcome in kidney transplant recipients: a post hoc analysis of the MASTERPLAN study (p. 53)
A. Van Zuilen[1], M. Bots[2], P. Blankestijn[1], J. Wetzels[3], [1]Nephrology, UMC Utrecht, [2]Julius Center, UMC Utrecht, [3]Nephrology, Radboud University Nijmegen Medical Center, The Netherlands

15.20 Improved intra- and interpatient variability of oral bioavailabilty of tacrolimus after conversion from Tac BID (Prograft) to Tac QD (Advagraf) in stable kidney transplant recipients (p. 54)
F. Stifft[1], L.M.L. Stolk[2], M. Mullens[1], M.H.L. Christiaans[1], Dept. of Internal Medicine, Division of Nephrology[1], and Dept. of Clinical Pharmacology and Toxicology[2], Maastricht University Medical Centre, The Netherlands

15.30 Theepauze

Parallelsessie III - basaal **Zaal 0.2/0.3**

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

Voorzitters: H.J.P.M. Koenen en L.J.W. van der Laan

14.00 Altered MicroRNA expression is associated with the protective effect of preoperative dietary restriction or fasting after renal ischemia reperfusion injury (p. 55)
E.K. van den Akker[1], M. Verweij[1], J. Pothof[2], J.H.J. Hoeijmakers[2], J.N.M. IJzermans[1], R.W.F. de Bruin[1], Dept. of Experimental Surgery[1], Erasmus MC, University Medical Center, Rotterdam, Dept. of Genetics[2], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

14.10 Hypothermic oxygenated machine preservation of donor livers after prolonged ischemia in a porcine model of donation after cardiac death (p. 56)
S. op den Dries[1,2], M. Filipe[1], H. Leuvenink[1], M.T. de Boer[2], T. Lisman[1,2], R.J. Porte[2], Surgical Research Laboratory[1] and Section of Hepatobiliary Surgery[2], Dept. of Surgery, University Medical Center Groningen, The Netherlands

14.20 Compliance, lactate production and pCO2 during In Situ Lung Perfusion (ISLP) are predictors for lung injury in non-heart-beating donors category I – II (p. 57)
C. Van De Wauwer[1], A.J. Munneke[2], G.E. Engels[2], F.M. Berga[1], G. Rakhorst[2], M.E. Erasmus[1], [1]Dept. of Cardiothoracic Surgery, University Medical Center Groningen, [2]Dept. of Biomedical Engineering, University Medical Center Groningen, The Netherlands

14.30 Rabbit Antithymocyte Globulin impairs the capacity for homeostatic proliferation of T cells in kidney transplant patients (p. 58)
A.P. Bouvy[1], M.M.L Kho[1], M. Klepper[1], J.N.M. IJzermans[2], W. Weimar[1], C.C. Baan[1], [1]Dept. of Internal Medicine, [2]Dept. of Surgery, Erasmus MC, University Medical Center Rotterdam, The Netherlands

14.40 A Novel ELISPOT Assay to Quantify HLA-Specific B Cells in HLA-Immunized Individuals (p. 59)

S. Heidt[1], D.L. Roelen[1], Y.J.H. de Vaal[1], M.G.D. Kester[2], C. Eijsink[1] S. Thomas[3], N.M. van Besouw[5], H.D. Volk[3,4], W. Weimar[5], F.H.J. Claas[1], A. Mulder[1], [1]Dept. of Immunohaematology and Blood Transfusion, [2]Dept. of Haematology, LUMC, Leiden, The Netherlands, [3]Institute of Medical Immunology, Campus Virchowklinikum, [4]Berlin-Brandenburg Center for Regenerative Therapies, Campus Virchowklinikum, Charité-Universitäts-medizin Berlin, Germany, [5]Dept. of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

14.50 Everolimus treated renal transplant patients develop a more robust CMV-specific CD8 response compared to cyclosporine or myco-phenolate sodium treated patients (p. 60)

S. Havenith[1,2], S.L. Yong[1,2], K.A.M.I. van Donselaar[1], R.A.W. van Lier[3], I.J.M. ten Berge[1], F.J. Bemelman[1], [1]Renal Transplant Unit, Dept. of Internal Medicine, [2]Dept. of Experimental Immunology, Academic Medical Center, Amsterdam, [3]Lansteiner Laboratory, Sanquin Research, Amsterdam, The Netherlands

15.00 Immediate early gene expression profiles in regenerating living donor livers show a functional shift of key cellular and functional pathways (p. 61)

S.M.G. Fouraschen[1,2], S.M. Kurian[3], J. Wolf[1], J.C. Emond[4], D.R. Salomon[3], A. Shaked[1], L.J.W. van der Laan[2], J. de Jonge[2], Kim M Olthoff[1], [1]Penn Transplant Institute, University of Pennsylvania, Philadelphia, PA, [2]Dept of Surgery, Laboratory of Experimental Transplantation and Intestinal Surgery, Erasmus MC-University Medical Center Rotterdam, The Netherlands, [3]Dept of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA, [4]Dept of Surgery, Columbia University, New York, NY

15.10 Cytomegalovirus seropositivity has a distinct effect on premature immunological ageing within the T cell compartment of end-stage renal disease patients (p. 62)

R.W.J. Meijers[1], N.H.R. Litjens[1], L.E.A. de Wit[1], A.W. Langerak[3], A. van der Spek[3], C.C. Baan[2], W. Weimar[2], M.G.H. Betjes[1], Dept. of Internal Medicine, Section Nephrology[1] and Transplantation[2], Dept. of Immunology[3], Erasmus Medical Center, Rotterdam, The Netherlands

Parallelsessie III – basaal - *vervolg* **Zaal 0.2/0.3**

15.20 Mesenchymal stem cells generate de novo functional CD4+CD25+CD127- regulatory T cells with highly methylated FOXP3 DNA (p. 63)
A.U. Engela, M.J. Hoogduijn, K. Boer, N.H.R. Litjens, R. Kraaijeveld, W. Schoordijk, M.G.H. Betjes, W. Weimar, C.C. Baan, Dept. of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands

15.30 Theepauze

Parallelsessie III – Transpl.verpleegkunde / Donatie Auditorium 2

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

Voorzitters: P.T.R. Ulrichts en R.E. Dam

14.00 Non Heart Beating category II Lung and Kidney Donation: How big is the pool? (p. 64)
D.M. Nijkamp[1], M. Smit[2], B.W.J. Bens[3], M.A.J. Seelen[4], M.E. Erasmus[5], Dept. of Surgery, Section Organ Donation[1], Dept. of Critical Care Medicine[2], Dept. of Emergency Care[3], Dept. of Nephrology[4] and Dept. of Cardiothoracic Surgery and Lung Transplantation[5], University Medical Center Groningen, Groningen, The Netherlands

14.10 Chirurgische technieken voor nierdonatie bij leven in Europa: De stand van zaken (p. 65)
K.W.J. Klop[1], L.F.C. Dols[1], N.F.M. Kok[1], F.J.M.F. Dor[1], W. Weimar[2], J.N.M. IJzermans[1], [1]ErasmusMC University Medical Center Rotterdam, Dept. of Surgery, Division of Transplant Surgery, [2]ErasmusMC University Medical Center Rotterdam, Dept. of Nephrology, The Netherlands

14.20 The method of approaching patients and recruitment in clinical trials (p. 66)
M. Cadogan, N.J. de Leeuw van Weenen, D.A. Hesselink, J. Kal -van Gestel, W. Zuidema, W. Weimar, Dept. of Internal Medicine, Division of Renal Transplantation, Erasmus MC Rotterdam, The Netherlands

14.30 Screening weefselpotentieel (p. 67)
P.E. Vorstius Kruijff[1], N.E. Jansen[2], L.S.M. Muitjens[3], J.G.C. Blok-Singerling[4], B.D.A. Tecklenburg[1], M.W. Huisman-Ebskamp[1], Amphia Top Klinisch Ziekenhuis Breda[1], Nederlandse Transplantatie Stichting Leiden[2], Radboud Universitair Medisch Centrum Nijmegen[3], Bronovo Algemeen Ziekenhuis Den Haag[4], The Netherlands

14.40 Anonymity in living kidney donation: an ELPAT view (p. 68)
F.J.M.F. Dor[1, 2], N. Mamode[2], F. Citterio[2], M. Frunza[2], R. Johnson[2], H. Jung[2], A. Lennerling[2], C. Loven[2], E.K. Massey[2], A. Pascalev[2], S. Sterckx[2], K. van Assche[2], W.C. Zuidema[2], W. Weimar[2], [1]Dept. of Surgery, division of Transplant Surgery, Erasmus MC, Rotterdam, The Netherlands, [2]Working group Living Organ Donation, Ethical, Legal and Psychosocial Aspects of Organ Transplantation (ELPAT), ESOT

Parallelsessie III – Transpl.verpleegkunde / Donatie — Auditorium 2

14.50 Donation indicators in intensive care units in The Netherlands 2007-2010, a review (p. 69)
H.A. Van Leiden[1], N.E. Jansen[1], A.J. Hoitsma[1], Dutch Transplant Foundation[1], Leiden, The Netherlands

15.00 Follow - up van obese nierdonoren (p. 70)
D. Pilzecker, I. Dooper, H. Kloke, Y. Hooghof, Dept. of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

15.10 Psychological wellbeing of unrelated living kidney donors: before & after donation (p. 71)
L. Timmerman[1], W.C. Zuidema[1], R.A.M. Erdman[2], J.N.M. IJzermans[3], W. Weimar[1], E.K. Massey[1]. Dept. of Internal Medicine[1], Erasmus MC, Rotterdam, Dept. of Medical Psychology & Psychotherapy[2], Erasmus MC, Rotterdam, Dept. of General Surgery[3], Erasmus MC, Rotterdam, The Netherlands

15.20 Theepauze

Sessie IV - plenair — Auditorium 2

voorzitter: *R.J. Porte*

16.00 **'Draagbare kunstnier: de ontwikkeling, stand van zaken en toekomst. Concurrent voor niertransplantatie?'**
Dr. J.P. Kooman, Afdeling Interne Geneeskunde
Maastricht Universitair Medisch Centrum

16.45 Uitreiking van Novartis Transplantation Grant 2011

17.00 Uitreiking Jon J. van Roodprijs 2012 en lezing door de prijswinnaar

17.50 Afsluiting en mededelingen

Sociaal programma

18.00 Busvervoer naar La Caverne de Geulhem

Congresborrel aangeboden door Novartis

19.30 Diner *(wijn aangeboden door Astellas)*
en feestavond

Parallelsessie V - klinisch — Zaal 0.9

Voorzitters: M.G.J. Snoeijs en P.Th.W. van Hal

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

08.30 The Clinical Relevance of Serum Gamma Glutamyl Transpeptidase in Liver Transplant Recipients: A Different Role at Different Time Points (p. 72)

E.M. Alkozai[1,2], T. Lisman[1,2], R.J. Porte[2], M.W. Nijsten, [4]Surgical Research Laboratory[1], Section of Hepatobiliary Surgery and Liver Transplantation[2], Dept. of Intensive Care Medicine[3], University Medical Center Groningen, Groningen, The Netherlands

08.40 Robot-assisted live kidney donation (p. 73)

S.M. Hagen[1], K.W.J. Klop[1], L.F.C. Dols[1], T. Terkivatan[1], F.J.M.F. Dor[1], T.C.K. Tran[1], J.N.M. IJzermans[1], Dept. of Surgery[1], Division of Transplant Surgery, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

08.50 Management of anastomotic and non-anastomotic biliary strictures after pediatric liver transplantation (p. 74)

F. Klaver[1], R. Scheenstra[1], E.J. van der Jagt[2], R.J. Porte[3], F.A.J.A. Bodewes[1], Dept. of Pediatric Gastroenterology and Hepatology[1], Dept. of Radiology[2], Dept. of Hepato-Pancreato-Biliary Surgery and Liver transplantation[3], University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

09.00 The role of perirenal and intra-abdominal fat mass in laparoscopic donor nephrectomy (p. 75)

J.A. Lafranca[1], S. Levolger[1], L.F.C. Dols[1], K.W.J. Klop[1], A. Moelker[2], J.N.M. IJzermans[1], F.J.M.F. Dor[1], Dept. of Surgery, Division of Transplant Surgery[1], Erasmus MC, University Medical Center, Rotterdam, Dept. of Radiology[2], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Parallelsessie V - klinisch – vervolg **Zaal 0.9**

09.10 Regional differences in dialysis and (pre-emptive) transplantation (p. 76)
A.C. Hemke[1], M.A. van den Dorpel[2], M.B.A. Heemskerk[1], A.J. Hoitsma[1,3], [1]Dutch Transplant Foundation, Leiden, [2]Maasstad Ziekenhuis Rotterdam, [3]Radboud University Medical Centre Nijmegen, The Netherlands

09.20 The effect of low and ultra-low dosages Thymoglobulin on T, B, and NK cells in kidney transplant recipients (p. 77)
M.M.L. Kho, A.P. Bouvy, M. Cadogan, R. Kraaijeveld, C.C. Baan, W. Weimar, Dept. of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

09.30 Intra-patient variability in tacrolimus trough concentrations and renal function decline in paediatric renal transplant recipients (p. 78)
A.A. Prytuła[1], A.H. Bouts[2], R.A.A. Mathôt[3], T. van Gelder[5], K. Croes[1], W. Hop[4], K. Cransberg[1], [1]Pediatric Nephrology Dept., Erasmus MC - Sophia Children's Hospital, Rotterdam, [2]Pediatric Nephrology Dept., Emma Children's Hospital, Amsterdam, [3]Dept. of Clinical Pharmacy – Clinical Pharmacology Unit, Academic Medical Center, University of Amsterdam, [4]Dept. of Biostatistics, Erasmus MC, Rotterdam, [5]Dept. of Clinical Pharmacology, Erasmus MC, Rotterdam, The Netherlands

09.40 Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver failure argues against routine prophylactic correction of coagulation prior to liver transplantation (p. 79)
T. Lisman[1,2], K. Bakhtiari[3], J. Adelmeijer[1], J.C.M. Meijers[3], R.J. Porte[2], R. Todd Stravitz[4], [1]Surgical Research Laboratory and [2]Section of Hepatobiliary Surgery and Liver Transplantation, Department. of Surgery, UMC Groningen, [3]Department. of Experimental Vascular Medicine, AMC, Amsterdam, The Netherlands, [4]Section of Hepatology and Hume-Lee Transplant Center, Virginia Commonwealth University, Richmond, VA, USA

09.50 Samenvatting door voorzitter

10.00 Koffiepauze

Parallelsessie V - Basaal — Zaal 0.2/0.3

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

Voorzitters: C. Peutz en P. van der Pol

08.30 Novel high-throughput method to study the influence of immune suppressive medication on human DC-induced naïve CD4+ T cell polarization in an autologous setting (p. 80)
T. Oth[1], A. Houben[1], M.C.A. Schijderberg[1], B.L.M.G. Senden-Gijsbers[1], M.H.L. Christiaans[2], W.T.V. Germeraad[1], G.M.J. Bos[1], J. Vanderlocht[3], [1]Dept. of Internal Medicine, Division of Hematology, Maastricht University Medical Center+, Maastricht, [2]Dept. of Internal Medicine, Division of Nephrology, Maastricht University Medical Center+, [3]Dept. of Transplantation Immunology, Tissue Typing Laboratory, Maastricht University Medical Center+, The Netherlands

08.40 Changes of plasma microRNAs in heart transplantation patients do not reflect microRNA changes in the CAV vessel wall (p. 81)
M.M.H. Huibers[1], H. Vroman[1], J. van Kuik[1], E. Siera-De Koning[1], N. de Jonge[2], R.A. de Weger[1], Dept. of Pathology[1] and Cardiology[2], University Medical Center Utrecht, The Netherlands

08.50 Reconstitution of T cells after rATG induction therapy in kidney transplant patients is the result of homeostatic proliferation and not of thymopoiesis (p. 82)
A.P. Bouvy, M.M.L. Kho, M. Klepper, N.H.R. Litjens, M.G.H. Betjes, W. Weimar, C.C. Baan, Dept. of Internal Medicine, Erasmus MC, University Medical Center Rotterdam, The Netherlands

09.00 Infusion of autologous mesenchymal stem cells induces a rapid immunomodulatory response (p. 83)
M.J. Hoogduijn[1], M. Roemeling-van Rhijn[1], A.U. Engela[1], S.S. Korevaar[1], F. Mensah[1], M. Franquesa[1], R.W.F. de Bruin[2], W. Weimar[1], C.C. Baan[1], [1]Transplantation Laboratory, Dept. of Internal Medicine, and [2]Dept. of Surgery, Erasmus MC, Rotterdam, the Netherlands

Parallelsessie V - Basaal **Zaal 0.2/0.3**

09.10 The circulating platelet count is not dictated by the liver, but may be determined in part by the bone marrow – analyses from human liver and stem cell transplantations (p. 84)
T. Lisman[1], G. Pittau[2], F.J.T. Leite[3], M.T. de Boer[1], H.C. Kluin-Nelemans[4], G. Huls[4], L.C.J. te Boome[5], J. Kuball[5], G. Nowak[6], S.T. Fan[7], D. Azoulay[2], R.J. Porte[1], [1]Dept Surgery, UMCG, [2]AP-HP Hôpital Paul Brousse, Villejuif Cedex, France, [3]St. Antonio Hospital, Porto, Portugal, [4]Dept Hematology, UMCG, [5]Dept Hematology, UMCU, [6]Karolinska University Hospital, Stockholm, Sweden, [7]Dept. of Surgery, University of Hong Kong, China

09.20 Subsets of Alternatively Activated Macrophages show differential capacity to produce Reactive Oxygen Species (p. 85)
M.D. Kraaij[1], S.W. van der Kooij[1], C. van Kooten[1], K.A. Gelderman[1,2], Dept of Nephrology[1], Leiden University Medical Center, Dept of Pathology[2], VU University Medical Center, Amsterdam, The Netherlands

09.30 The calcineurin inhibitor tacrolimus inhibits NF-κB activation in effector and regulatory T cells (p. 86)
R. Vafadari[1], R. Kraaijeveld[1], W. Weimar[1], C.C. Baan[1], Dept. of Internal Medicine[1], Erasmus MC, Rotterdam, The Netherlands

09.40 Donor-derived tubular epithelial cells induce class I restricted alloreactivity in kidney transplant recipients (p. 87)
M.W.H.J. Demmers[1], W. Weimar[1], J.N.M. IJzermans[2], A.T. Rowshani[1], C.C. Baan[1], Dept. of Internal Medicine[1], Surgery[2], Erasmus MC, University Medical Center Rotterdam, The Netherlands, A.T. Rowshani and C.C. Baan contributed equally to this study

09.50 Samenvatting door voorzitter

10.00 Koffiepauze

Parallelsessie V – Transpl.verpleegkunde / Donatie Zaal 0.4/0.5

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

Voorzitters: C. Moers en A. Oosterom

08.30 EULOD: The EU-funded Project on Living Organ Donation in Europe (p. 88)
F. Ambagtsheer[1], A. Lennerling[2], A. Pascalev[3], T. Gutmann[4], J. Sándor[5], R. Ploeg[6], F. Dobbels[7], W. Weimar[1], Erasmus MC, Rotterdam, The Netherlands[1], Univ. of Gothenburg, Göteborg, Sweden[2], Bulgarian Center for Bioethics, Sofia, Bulgaria[3], University of Münster, Germany[4],Central European University, Budapest, Hungary[5], University Medical Center Groningen, The Netherlands[6], Katholieke Universiteit Leuven, Belgium[7]

08.40 The role of the living donor coordinator involving the ABO-incompatible kidney transplantation program at the University Hospital Groningen (p. 89)
A.M.S. Roelofs, R.A.M. Meijer-Vogt, J.S.F. Sanders, Depts. of Internal Medicine Division of Nephrology and Surgery, University Medical Centre Groningen, The Netherlands

08.50 Fetal Maternal microchimerism and its role in stem cell and renal transplantation (p. 90)
J.J. van Rood, C. Stevens, D. Roelen, M. Oudshoorn, F. Claas, Leiden University Medical Center, The Netherlands and New York Blood Center, USA

09.00 Are increasing numbers of living kidney donors the consequence of a more liberal acceptance policy? (p. 91)
F. van de Logt[1], H.J. Kloke[1], F.C.H. D'Ancona[2], J.A. van der Vliet[3], Ph.M.M. Dooper[1], A.J. Hoitsma[1], Dept of Nephrology[1], Dept of Urology[2], Dept of Surgery[3], Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Parallelsessie V – Transpl.verpleegkunde / Donatie Zaal 0.4/0.5

09.10 Timing of approach to discuss organ donation: the European jigsaw puzzle (p. 92)
N.E. Jansen[1], H.A. van Leiden[1], B.J.J.M. Haase-Kromwijk[1], A.J. Hoitsma[2], Dutch Transplant Foundation[1], Leiden, Radboud University Nijmegen Medical Center, Dept. Nephrology[2], The Netherlands.

09.20 The influence of ethnicity and socioeconomic factors on the outcome of kidney transplantation (p. 93)
M. Laging[1], E.K. Massey[1], J.A. Kal-van Gestel[1], J.N.M. IJzermans[2], J. van de Wetering[1], W. Weimar[1], J.I. Roodnat[1], Dept.s of Internal Medicine[1] and General Surgery[2], Erasmus Medical Center Rotterdam, The Netherlands

09.30 Health literacy among kidney transplant patients: a literature study (p. 94)
L. Maasdam[1], E.K. Massey[1], W. Weimar[1], Erasmus MC Rotterdam, Kidney Transplant Unit[1], The Netherlands

09.40 The P-PASS and PDRI reviewed in a large European pancreas transplantation center (p. 95)
J.J. Blok[1], A.E. Braat[1], A.F. Schaapherder[1], M.J. Verhagen[1], J.W. de Fijter[2], H. Putter[3], A.O. Rahmel[4], J. Ringers[1], [1]Dept. of Surgery, Leiden University Medical Center, Leiden, [2]Dept. of Nephrology, Leiden University Medical Center, Leiden, [3]Dept. of Medical Statistics, Leiden University Medical Center, Leiden, [4]Eurotransplant International Foundation, Leiden, The Netherlands

09.50 Samenvatting door voorzitter

10.00 Koffiepauze

Sessie VI - plenair — Zaal 0.4/0.5

Voorzitter: *L. Hilbrands*

10.30 Uitreiking Astellas Trans(p)la(n)t(at)ionele Research Prize 2012

10.45 Lezing ATRP-winnaar 2011

Ledenvergadering — Zaal 0.4/0.5

11.00 Ledenvergadering
Nederlandse Transplantatie Vereniging

12.00 Lunchbuffet en guided postersessies

Woensdag 28 maart 2012

Guided postersessie — Groep A - Foyer

Voordrachten in het Nederlands, spreektijd 3 minuten, discussietijd 1-2 minuten.

Moderatoren: M.G.H. Betjes en I. Joosten

1. Effects of corticosteroids on interferon-α signaling and inhibition of hepatitis C infection by plasmacytoid dendritic cells (p. 134)
P. E. de Ruiter[1], P.P.C. Boor[2], Q. Pan[2], J. de Jonge[1], H.J. Metselaar[2], H.W. Tilanus[1], J. Kwekkeboom[2], L.J.W. van der Laan[1], [1]Dept. of Surgery and Laboratory of Experimental Transplantation and Intestinal Surgery, [2]Dept. of Gastroenterology & Hepatology, Erasmus MC-University Medical Center Rotterdam, The Netherlands

2. Optimizing induction of CD8+ regulatory T cells by allogeneic human plasmacytoid dendritic cells (p. 135)
P.P.C. Boor[1], S. Mancham[1], L.W.J. van der Laan[2], H.J. Metselaar[1], J. Kwekkeboom[1], Depts. of [1]Gastroenterology and Hepatology, [2]Surgery, Erasmus MC-University Medical Centre, Rotterdam, The Netherlands

3. Optimizing alloantigen presentation as a tool to monitor indirect alloantigen presentation in renal transplant recipients (p. 136)
E. Breman[1], M.H. Heemskerk[2], D. Roelen[3], F.H. Claas[3], C. van Kooten[1], Dept of Nephrology[1], Leiden University Medical Center, Dept of Hematology[2], Leiden University Medical Center, Dept of Immuno-hematology and Blood Transfusion[3], Leiden University Medical Center, The Netherlands

4. NK cell activation is dependent on HLA-E surface expression and the peptide presented by HLA-E (p. 137)
N. Lauterbach, L. Wieten, L. van Zon, C.E.M Voorter, M.G.J Tilanus. Transplantation Immunology, Tissue Typing Laboratory, Maastricht University Medical Center, Maastricht, The Netherlands

5. Rapamycin inhibits innate and adaptive immune functions of human plasmacytoid dendritic cells (p. 138)
P.P.C. Boor[1], S. Mancham[1], L.W.J. van der Laan[2], H.J. Metselaar[1], J. Kwekkeboom[1], Depts. of [1]Gastroenterology and Hepatology, and [2]Surgery, Erasmus MC - University Medical Centre, Rotterdam, The Netherlands.

Guided postersessie **Groep A - foyer**

6. Aneuploidy in Mesenchymal Stem Cells Cultured for Clinical Application in Solid Organ Transplantation (p. 139)
M. Roemeling-van Rhijn[1], A. de Klein[2], H. Douben[2], S.S. Korevaar[1], F.J.M.F. Dor[3], J.N.M. IJzermans[3], C.C. Baan[1], W. Weimar[1], M.J. Hoogduijn[1], Depts. of Internal Medicine[1], Clinical Genetics[2] and General Surgery[3], Erasmus Medical Center, Rotterdam, The Netherlands

7. Serum HLA-G is associated with liver inflammation rather than with liver graft acceptance (p. 140)
B. van Cranenbroek[1], V. Moroso[2], F. Fai-A-Fat[2], L.J.W. van der Laan[3], H.J. Metselaar[2], I. Joosten[1], J. Kwekkeboom[2], [1]Dept. of Laboratory Medicine, Radboud University Medical Center, Nijmegen, Depts. of [2]Gastroenterology and Hepatology, and [3]Surgery, Erasmus MC, Rotterdam, The Netherlands

8. CMV-specific CD8 T cells in lymph nodes: a rare but special breed (p. 141)
E.B.M. Remmerswaal[1,2], S.H.C. Havenith[1,2], P.L. Klarenbeek[3], M.E. Doorenspleet[3], B.D.C. van Schaik[4], K. van Donselaar[2], F. Bemelman[2], R.E.E. Esveldt[3], A.H. van Kampen[4], F. Baas[5], A. ten Brinke[6], R.A.W. van Lier[1], N. de Vries[3], I.J.M. ten Berge[2], Dept. of Exp. Immunology[1], Renal Transplant Unit[2], Dept. of Nephrology, Division of Int. Medicine, Dept. of Clinical Immunology and Rheumatology[3], Dept. of Clinical Epidemiology[4], Biostatistics and Bioinformatics, Dept. of Genome Analysis[5], Sanquin Research[6], Dept. of Immunopathology, AMC, Amsterdam, The Netherlands

9. Varicella zoster virus vaccination induces virus-specific class II restricted memory responses in seronegative renal transplant recipients (p. 142)
N.M. van Besouw[1], J.M. Zuijderwijk[1], I. Noorlander[1], N.J. de Leeuw van Weenen[1], G.M.G.M. Verjans[2], W. Weimar[1], Depts. of Internal Medicine – Transplantation[1], Virology[2], Erasmus Medical Center, Rotterdam, The Netherlands

Guided postersessie **Groep A - foyer**

10. Recovery of VZV-specific T- and B-cell responses by herpes zoster infection after lung transplantation (p. 143)
N.M. van Besouw[1], P.Th.W. van Hal[2], J.M. Zuijderwijk[1], R. de Kuiper[1], G.M.G.M. Verjans[3], W. Weimar[1], Depts. of Internal Medicine – Transplantation[1], Respiratory Medicine[2], Virology[3], Erasmus Medical Center, Rotterdam, The Netherlands

11. Kinetics and characteristics of monocyte subsets in kidney transplant recipients (p. 144)
E. Vereyken[1], C.C. Baan[1], W. Weimar[1], P.J.M. Leenen[2], A.T. Rowshani[1], Erasmus University Medical Center, Rotterdam, Dept. of Internal Medicine and Kidney Transplantation[1], and Dept. of Immunology[2], The Netherlands

12. Molecular typing methods for the non-classical HLA-E gene (p. 145)
C.E.M. Voorter, N. Lauterbach, T. Olieslagers, M.G.J. Tilanus Dept. of Transplantation Immunology, Tissue Typing Laboratory, Maastricht University Medical Center, Maastricht, The Netherlands

13. The importance of HLA-DPB1 full length polymorphism in stem cell and organ transplantation (p. 146)
N. Lauterbach, C.E.M. Voorter, M. Groeneweg, L. Wieten, M.G.J Tilanus. Transplantation Immunology, Tissue Typing Laboratory, Maastricht University Medical Center, Maastricht, The Netherlands

Guided postersessie — Groep B – zaal 0.8 Rome

Voordrachten in het Nederlands, spreektijd 3 minuten, discussietijd 1-2 minuten.

Moderatoren: K.A. van Donselaar en F. van Reekum

1. Primary varicella infection and disseminated varicella zoster virus reactivation in renal transplant recipients (p. 147)
I. Noorlander[1], N.M. van Besouw[1], M. van Agteren[1], A.A. van der Eijk,[2], W. Weimar[1], Depts. of [1]Internal Medicine, Kidney Transplant Unit and [2]Virology, ErasmusMC, Rotterdam, The Netherlands

2. Pre-transplant parameters predict survival during and after liver transplantation (p. 148)
R. Garritsen[1], D.T. Nguyen[2], H.J. Metselaar[3], H.W. Tilanus[1], G. Kazemier[1], [1]Dept. of Surgery, Erasmus Medical Center, Rotterdam, [2]Dept. of Virology, Erasmus Medical Center, Rotterdam, [3]Dept. of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands

3. An overview of unspecified living kidney donors in The Netherlands (p. 149)
M. de Klerk, W. Zuidema on behalf of the 8 Kidney Transplant Centers in The Netherlands

4. Hepatitis E virus in Renal Transplant recipients in a Tertiary Referral Centre in The Netherlands (p. 150)
I. Noorlander[1], S.D. Pas[2], R.A. de Man[3], A.H.M.M. Balk[4], W.Weimar[1], A.D.M.E. Osterhaus[2], A.A. van der Eijk[2], Depts. of Internal Medicine – Transplantation[1], Virology[2], Gastroenterology and Hepatology[3], Cardiology[4], Erasmus Medical Centre, Rotterdam, The Netherlands

5. Unspecified donation in case of nephrectomy for medical reasons (p. 151)
H.J.A.N. Kimenai[1], F.J.M.F. Dor[1], K.W.J. Klop[1], W.C. Zuidema[2], W. Weimar[2], J.N.M. IJzermans[1], Depts. of Surgery[1] and Internal Medicine, Erasmus MC Rotterdam, The Netherlands

6. The Utrecht experience on the management of HIV positive kidney transplant patients (p. 152)
W. van Snippenburg[1], T. Mudrikova[1], E.M. van Maarseveen[2], A.D. van Zuilen[3], Dept of Internal Medicine & Infectious Diseases[1], Dept of Clinical Pharmacy[2], Dept of Nephrology and Hypertension[3], University Medical Center Utrecht, The Netherlands

7. Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: A systematic review and meta-analysis (p. 153)
I.K.B. Slagt[1,§], K.W.J. Klop[1], J.N.M. IJzermans[1], T. Terkivatan[1], [1]Erasmus MC, University Medical Center, Rotterdam, Dept. of Surgery, The Netherlands

8. Elimination of calcineurin inhibitors in paediatric renal transplant recipients (p. 154)
A.A. Prytula, E. Dorresteijn, R. van Rooij, M.G. Keijzer-Veen, K. Cransberg, Dept. of Pediatric Nephrology, Erasmus MC - Sophia, Rotterdam, The Netherlands

9. Design of a simplified medication regimen in renal transplant patients by using tacrolimus OD (ADVAGRAF®) (p. 155)
C.H.H. Kerkhofs, G.A.J. van Boekel, L.B. Hilbrands, Dept. of Nephrology. Radboud University Nijmegen Medical Centre, The Netherlands

10. Long-term outcome of renal transplantation in patients with a urinary conduit,a case-control study (p. 156)
I.K.B. Slagt[1,§], J.N.M. IJzermans[1], M. Alamyar[1], P.C.M.S. Verhagen[2], W. Weimar[3], J.I. Roodnat[3], T. Terkivatan[1], [1]Erasmus MC, University Medical Center, Rotterdam, Dept. of Surgery, [2]Erasmus MC, University Medical Center, Rotterdam, Dept. of Urology, [3]Erasmus MC, University Medical Center, Rotterdam, Dept. of Nephrology, The Netherlands

11. Treatment of chronic humoral rejection with Intravenous Immunoglobulins (IVIG) - a case series (p. 157)
E.J.R. Litjens[1], J.J.P. Slebe[1], M. Gelens[1], C. Peutz[2], J. Vanderlocht[3], E. van Heurn[4], M.H.L. Christiaans[1], Dept. of Nephrology, Pathology[2], Transplant Immunology[3] and Surgery[4], Maastricht University Medical Center[1], The Netherlands

Guided postersessie **Groep B – zaal 0.8 Rome**

12. Case report: Unilateral right-sided pleural effusion in a renal transplant recipient: Beware of extrarenal manifestations of ADPKD (p. 158)
J.J.P. Slebe[1], E.J.R. Litjens[1], G.H. Koek[2], P.R.H. Callewaert[3], M.A.C.J. Gelens[1], M.H.L. Christiaans[1], Dept of Nephrology[1], Maastricht University Medical Centre, Dept of Gastroenterology[2], Maastricht University Medical Centre, Dept of Urology[3], Maastricht University Medical Centre, The Netherlands

13. Idiopathic giant esophageal ulcer and leukopenia after renal transplantation: a late complication of rituximab? (p. 159)
G.A.J. van Boekel, M. Volbeda, M.W.F. van den Hoogen, L.B. Hilbrands, J.H.M. Berden, Departement of Nephrology, Radboud University Nijmegen Medical Centre, The Netherlands

14. Als de papieren status elektronisch wordt (p. 160)
M. Cadogan, W. Zuidema, N.J. de Leeuw van Weenen, T. Gelder van, W. Weimar Dept. of Internal Medicine, Division of Renal Transplantation, Erasmus Medical Center Rotterdam, The Netherlands

Parallelsessie VII - Klinisch — Zaal 0.9

Voorzitters: J.S.F. Sanders en M.J. Coenraad

13.00 **"Meerwaarde certificering in de ketenzorg: Pretransplantatiescreening als voorbeeld"**
Dr. E.C.H. van den Ham, Afdeling Interne Geneeskunde, Maastricht Universitair Medisch Centrum

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

13.30 Successful pre-transplant immunisation against Varicella in sero-negative kidney transplant candidates (p. 96)
I. Noorlander[1], A.A. van der Eijk[2], N.J. de Leeuw van Weenen[1], G.M.G.M. Verjans[2], W. Weimar[1], N.M. van Besouw[1], Depts. of Internal Medicine – Transplantation[1], Virology[2], Erasmus Medical Center, Rotterdam, The Netherlands

13.40 Genetic variance in ABCB1 and CYP3A5 does not contribute to the development of chronic kidney disease after liver transplantation (p. 97)
D.A. Hesselink[1], Ö. Tapirdamaz[2], S. el Bouazzaoui[3], M. Azimpour[2], B. Hansen[2], L.W.J. van der Laan[4], G. Kazemier[4], J. Kwekkeboom[2], R.H.N van Schaik[3], T. van Gelder[1,5], H.J. Metselaar[2], Depts. of [1]Internal Medicine, [2]Gastroenterology and Hepatology, [3]Clinical Chemistry, [4]Surgery, [5]Hospital Pharmacy, Erasmus MC, Rotterdam, The Netherlands

13.50 Improvement of microvascular damage after living donor kidney-transplantation (p. 98)
M. Khairoun[1], B.M. van den Berg[1], R. Timal[1], E. Lievers[1], A.F. Schaapherder[3] A.J. van Zonneveld[1,2], J.W. de Fijter[1], T.J. Rabelink[1,2], M.E.J. Reinders[1], Dept of Nephrology[1], Einthoven Laboratory for Experimental Vascular Research[2], Dept of Surgery[3], Leiden University Medical Center, The Netherlands

14.00 Terminally differentiated CD8+ T cells reduce the risk for acute kidney allograft rejection (p. 99)
N.H.R. Litjens[1], L.E.A.de Wit[1], R.W.J. Meijers[1], C.C. Baan[2], W. Weimar[2], M.G.H. Betjes[1], Dept. of Internal Medicine, section Nephrology[1] and Transplantation[2], Erasmus Medical Center, Rotterdam, The Netherlands

Parallelsessie VII - Klinisch - *vervolg* **Zaal 0.9**

14.10 Rectal - but not sublingual - administration of tacrolimus results in systemic exposure in healthy volunteers (p. 100)
F. Stifft[1], F. Vanmolkot[1,2], I Scheffers[2], L. van Bortel[2], C. Neef[3], M. Christiaans[1], Dept. of Internal Medicine[1], Drug Research Unit Maastricht[2], and Dept. of Clinical Pharmacy and Toxicology[3], Maastricht University Medical Centre, The Netherlands

14.20 Patients' experiences with an interned-based Disease Management System to monitor creatinine at home: a pilot study (p. 101)
C.L. van Lint, P.J.M. van der Boog, S. van Dijk, A.J. Rabelink. Dept of Nephrology, Leiden University Medical Center, The Netherlands

14.30 Kidney transplant glomerulopathy (TG) treated with intravenous immunoglobulin (IVIG) and prednisolone (p. 102)
M. van Agteren[1], S. Berger[1], J.J. Weening[2], W. Weimar[1], Dept. of Internal Medicine and Nephrology[1], Erasmus Medical Center, Rotterdam, Dept. of Clinical Pathology[2], Tergooiziekenhuizen, Laren, The Netherlands

14.40 The Effect of CNI Withdrawal on Long Term Graft Survival (p. 103)
J.A. Kal-van Gestel[1], J.I. Roodnat[1], J.N. IJzermans[2], W. Weimar[1], [1]Internal Medicin, Section Transplantation, Erasmus MC, Rotterdam, [2]General Surgery, Erasmus MC, Rotterdam, The Netherlands

14.50 Circulating pro-inflammatory CD4+CD28null T cells increase the risk for a cardiovascular event shortly after kidney transplantation (p. 104)
M.G.H. Betjes, L.E.A. de Wit, W. Weimar W, N.H.R. Litjens, Dept. of Nephrology and Transplantation, Erasmus Medical Center, Rotterdam, The Netherlands

15.00 Theepauze

Tijdens de verlengde theepauze zal in zaal 04./05 vanaf 15.15 uur de première van de film 'Orgaandonatie: Donorzorg is patiëntenzorg' plaatsvinden.
De film gaat door de NTS gebruikt worden bij scholing over orgaan-donatie voor medische professionals.

Parallelsessie VII - Basaal — Zaal 0.2/0.3

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

Voorzitters: J. Vanderlocht en N. van Besouw

13.00 Epigenetic analysis demonstrates that natural Treg only infiltrate the cardiac allograft during an acute rejection episode (p. 105)
K. Boer[1], A.M.A. Peeters[1], A.P.W.M. Maat[2], K. Caliskan[3], A.H.M.M. Balk[3], W. Weimar[1], C.C. Baan[1], Dept of Internal Medicine[1], Thoracic Surgery[2] and Cardiology[3], Erasmus University Medical Center Rotterdam, The Netherlands

13.10 Premature immunological ageing of T cells in patients with end-stage renal disease is not changed by renal replacement therapy (p. 106)
R.W.J. Meijers[1], N.H.R. Litjens[1], L.E.A. de Wit[1], A.W. Langerak[3], A. van der Spek[3], C.C. Baan[2], W. Weimar[2], M.G.H. Betjes[1], Dept. of Internal Medicine, section Nephrology[1] and Transplantation[2], Dept. of Immunology[3], Erasmus Medical Center, Rotterdam, The Netherlands

13.20 The compartment of human natural CD4+CD25++CD127- regulatory T cells is filled with cells reactive to various antigens (p. 107)
N.H.R. Litjens[1], K. Boer[2], C.C. Baan[2], M.G.H. Betjes[1], Dept. of Internal Medicine, Section Nephrology[1] and Transplantation[2], Erasmus Medical Center, Rotterdam, The Netherlands

13.30 Dietary restriction and fasting downregulate complement activity (p. 108)
S. Shushimita[1], P. van der Pol[2], R.W.F. de Bruin[1], J.N.M. IJzermans[1], C. van Kooten[2], F.J.M.F. Dor[1], Dept. of Surgery[1], Erasmus MC, University Medical Center, Rotterdam, Dept. of Nephrology[2], Leiden University Medical Center, Leiden, The Netherlands

Parallelsessie VII - *vervolg* **Zaal 0.2/0.3**

13.40 Mannan-binding lectin induces endoplasmic reticulum-stress in tubular epithelial cells following renal ischemia/reperfusion (p. 109)
P. van der Pol[1], N. Schlagwein[1], D.J. van Gijlswijk[1], I.M. Bajema[2], E.F.A. van 't Wout[3], P.S. Hiemstra[3], C. van Kooten[1], Dept. of Nephrology[1], Pathology[2] and Pulmonology[3] Leiden University Medical Center, Leiden, The Netherlands

13.50 Bone marrow derived mesenchymal stromal cells from healthy donors and patients with end stage renal disease have similar phenotypical and functional characteristics (p. 110)
M.E.J. Reinders[1], M. Roemeling-van Rhijn[4], M.J. Hoogduijn[4], M. Khairoun[1], E.Lievers[1], D.K. de Vries[3], S. Schaapherder[3], S. Wong[2], J. Duijs[1], A.J.van Zonneveld[1], J.W. de Fijter[1], C. van Kooten[1], T.J. Rabelink[1], H. Roelofs[2], Dept of Nephrology[1], Dept of Immunohematology[2] and Dept of Surgery[3], Leiden University Medical Center, Dept of Internal Medicine[4], Erasmus Medical Center Rotterdam, The Netherlands

14.00 Donor-derived renal tubular epithelial cells induce recipient memory T-cell proliferation with a CD28null phenotype which is not susceptible to tacrolimus (p. 111)
M.W.H.J. Demmers[1], C.C. Baan[1], M. Janssen[1], N.H.R. Litjens[1], J.N.M. IJzermans[2], W. Weimar[1], A.T. Rowshani[1], Dept. of Internal Medicine[1], Surgery[2], Erasmus MC, University Medical Center Rotterdam, The Netherlands

14.10 Inhibition of human allogeneic skin graft inflammation by ex vivo expanded human Treg in a humanized mouse model (p. 112)
V.L. de Oliveira[1], M. Peppelman[1], E. Fasse[1], P.C.M. van der Kerkhof[2], P.E. van Erp[2], I. Joosten[1], H.J.P.M. Koenen[1], Dept. of Laboratory Medicine, Section Laboratory of Medical Immunology[1], RUNMC, Nijmegen, Dept. of Dermatology[2], RUNMC, Nijmegen, The Netherlands

14.20 Effects of the anti-CD20 antibody rituximab on B cells in human secondary lymphoid organs (p. 113)
E.G. Kamburova[1], K.J.E. Borgman[1], H.J.P.M. Koenen[1], I.J. ten Berge[2], I. Joosten I.[1], L.B. Hilbrands[3], Dept. of Laboratory Medicine, Laboratory Medical Immunology[1], Radboud University Nijmegen Medical Centre, Dept. of Internal Medicine[2], Academic Medical Centre, Amsterdam, Dept. of Nephrology[3], Radboud University Nijmegen Medical Centre, The Netherlands

Parallelsessie VII - Basaal - *vervolg* **Zaal 0.2/0.3**

14.30 Intragraft expression of metallothioneins in kidney transplant patients may be a novel marker of response to anti-rejection treatment with corticosteroids (p. 114)
N.V. Rekers[1], J.D.H. Anholts[1], G.W. Haasnoot[1], M.J.K. Mallat[3], I.M. Bajema[2], J.W. de Fijter[3], F.H.J. Claas[1], M. Eikmans[1], Depts. of Immunohematology and Blood Transfusion[1], Pathology[2], and Nephrology[3], Leiden University Medical Center, Leiden, The Netherlands

14.40 MicroRNA profiles in graft preservation solution are prognostic for biliary strictures after liver transplantation (p. 115)
C.J. Verhoeven[1], W.R.R. Farid[1], P.E. de Ruiter[1], J. de Jonge[1], J. Kwekkeboom[2], H.J. Metselaar[2], H.W. Tilanus[1], G. Kazemier[1], L.J.W. van der Laan[1], Depts. of Surgery[1] and Gastroenterology & Hepatology[2], Erasmus Medical Center Rotterdam, The Netherlands

14.50 Genetic polymorphisms in ABCB1 influence the pharmacodynamic effects of tacrolimus on T cells (p. 116)
R. Bouamar[1], R. Vafadari[2], D.A. Hesselink[2], R.H.N. van Schaik[3], R. Kraaijeveld[2], W. Weimar[2], T. van Gelder[1,2], C.C. Baan[2], Dept of Hospital Pharmacy / Clinical Pharmacology Unit[1], Erasmus MC Rotterdam, Dept of Internal Medicine[2], Erasmus MC Rotterdam, Dept of Clinical Chemistry[3], Erasmus MC Rotterdam, The Netherlands

15.00 Theepauze

Tijdens de verlengde theepauze zal in zaal 04./05 vanaf 15.15 uur de première van de film 'Orgaandonatie: Donorzorg is patiëntenzorg' plaatsvinden.
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Parallelsessie VII - Transpl.verpleegkunde / Donatie Zaal 0.4/0.5

Voorzitters: T. Wind en A.M.S. Roelofs

13.00 **"Transplantatie van eilandjes van Langerhans: Waar staan wij nu?"**
Prof. dr. E.J.P. de Koning, Afd. Nierziekten, Leids Universitair Medisch Centrum

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

13.30 Incisional hernias after laparoscopic donor nephrectomy: A single center experience (p. 117)
K.W.J. Klop[1], F. Hussain[1], O. Karatepe[1], J.N.M. IJzermans[1], F.J.M.F. Dor[1], [1]ErasmusMC University Medical Center Rotterdam, Dept. of Surgery, Division of Transplant Surgery, The Netherlands

13.40 Mild Hyponatremia has a Substantial Influence on Clinical Outcome of Patients on the waiting list and after Liver Transplantation (p. 118)
R. Garritsen[1], H.J. Metselaar[2], J.V. Guarrera[3], S. Henry[3], E. Ratner[3], F. Braun[4], D.C. Broering[4], H.W. Tilanus[1], G. Kazemier[1], [1]Dept. of Surgery and [2]Dept. of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands, [3]Dept. of Molecular Therapies and Organ Preservation, Columbia University Medical Center, New York, United States of America, [4]Dept. of Surgery, University Hospital of Schleswig-Holstein Campus, Kiel, Germany

13.50 Importance of HLA mismatches in living and deceased donor kidney transplantation (p. 119)
M. Laging[1], J.A. Kal-van Gestel[1], F.H.J. Claas[2], J. van de Wetering[1], J.N.M. IJzermans[3], W. Weimar[1], J.I. Roodnat[1]Dept. of Internal Medicine[1], Erasmus Medical Center Rotterdam, Eurotransplant Reference Laboratory Dept. Immunohaematology and Blood Transfusion[2], Leiden, University Medical Center, Dept. of General Surgery[3], Erasmus Medical Center Rotterdam, The Netherlands

Parallelsessie VII - Transpl.verpleegkunde / Donatie Zaal 0.4/0.5

14.00 Systematic review and meta-analysis of the relation between Body Mass Index and outcome of laparoscopic donor nephrectomy (p. 120)
J.A. Lafranca[1], S.M. Hagen[1], L.F.C. Dols[1], L.R. Arends[2], W. Weimar[3], J.N.M. IJzermans[1], F.J.M.F. Dor[1], Dept. of Surgery, Division of Transplant Surgery[1], Erasmus MC, University Medical Center, Rotterdam, Institute of Psychology[2], Erasmus University Rotterdam, Rotterdam, Dept. of Nephrology[3], Erasmus MC, University Medical Center, Rotterdam, The Netherlands

14.10 Q-methodology to explore attitudes towards adherence in recently transplanted kidney patients (p. 121)
M. Tielen[1], M. Laging[1], T. van Gelder[1], W. Weimar[1], E. Massey[1], [1]Dept. of Internal Medicine, Erasmus University Medical Center Rotterdam, The Netherlands

14.20 The Eurotransplant Donor Risk Index in liver transplantation: ET-DRI (Preferred method to define extended criteria donation?) (p. 122)
J.J. Blok[1], J. Ringers[1], R. Adam[2], A.K. Burroughs[3], H. Putter[4], A.O. Rahmel[5], R.J. Porte[6], X. Rogiers[7], A.E. Braat[1], [1]Dept. of Surgery, LUMC, Leiden, The Netherlands, [2]Hôpital Paul Brousse, CHB, Villejuif, France, [3]Liver Transplantation, Royal Free Hospital, London, United Kingdom, [4]Dept. of Medical Statistics, LUMC, Leiden, The Netherlands, [5]Eurotransplant, Leiden, The Netherlands, [6]Dept. of Surgery, UMCG, Groningen, The Netherlands, [7]Dept. of Surgery, GUHMS, Ghent, Belgium

14.30 Are you mother's darling? The NIMA effect (p. 123)
M. Laging[1], J.A. Kal-van Gestel[1], T. Royaards[1], J. van de Wetering[1], J.N.M. IJzermans[2], W. Weimar[1], J.I. Roodnat[1], Dept.s of Internal Medicine[1] and General Surgery[2], Erasmus Medical Center Rotterdam, The Netherlands

Parallelsessie VII - Transpl.verpleegkunde / Donatie Zaal 0.4/0.5

14.40 Children as donors: a national pediatric intensive care study to assess procurement of organs and tissues (p. 124)
M.J. Siebelink[1], M.J.I.J. Albers[2], P.F. Roodbol[3], H.B.M. van de Wiel[4], [1]University of Groningen, University Medical Center Groningen, Dept. of Management affairs, [2]University Medical Center Groningen, Dept. of Pediatrics, Division of Intensive Care, Beatrix Children's Hospital, [3,4]University Medical Center Groningen, Wenckebach Institute for Medical Education, The Netherlands

14.50 Potential donor loss after consent, what are the reasons for non-procurement? (p. 125)
H.A. Van Leiden[1], N.E. Jansen[1], A.J. Hoitsma[1], Dutch Transplant Foundation[1], Leiden, The Netherlands

15.00 Theepauze

Tijdens de verlengde theepauze zal in deze zaal vanaf 15.15 uur de première van de film 'Orgaandonatie: Donorzorg is patiëntenzorg' plaatsvinden.
De film gaat door de NTS gebruikt worden bij scholing over orgaandonatie voor medische professionals.

Sessie VIII - plenair — Zaal 0.4/0.5

Voorzitters: W.C. de Jongh

15.45 **"Optimal policy for participation of non-directed living donors in kidney exchange programs"**
K. Glorie, PhD candidate, Erasmus University Rotterdam

16.15 **"School-based organ donation education program"**
Dr. A. Reubsaet, SIDVO Maastricht

Sessie IX - plenair – hoogst scorende abstracts — Zaal 0.4/0.5

Voordrachten in het Nederlands, spreektijd 8 minuten, discussietijd 2 minuten.

Voorzitters: E.M. van Duijnhoven en A.E. Braat

16.45 Illness perceptions and treatment beliefs about immunosuppressive medication after kidney transplantation (p. 126)
E.K. Massey[1], M. Tielen[1], M. Laging[1], T. van Gelder[1], W. Weimar[1], Dept. of Internal Medicine, Kidney Transplant Unit, Erasmus Medical Center Rotterdam, The Netherlands

16.55 Higher organ donation consent rates by relatives of potential uncontrolled donors versus potential controlled donors after death (p. 127)
J. Wind[1], W.N.K.A. van Mook[2] , M.E.C. Willems[1], L.W.E. van Heurn[1], [1]Dept. of Surgery, Maastricht University Medical Centre, [2]Dept. of Intensive Care Medicine, Maastricht University Medical Centre, The Netherlands

17.05 Cold ischemia time in The Netherlands: Insight in the course of time in the chain of donation and transplantation (p. 128)
K.M. Ooms-de Vries[1], M.B.A. Heemskerk[1], J.W.M. Konijn-Janssen[1], B.J.J.M. Haase-Kromwijk[1], Dutch Transplant Foundation, Leiden, The Netherlands

Sessie VIII - plenair - *vervolg* **Zaal 0.4/0.5**

17.15 The Clinical Relevance of Luminex-Defined Complement Fixing HLA antibodies in Kidney Transplantation (p. 129)
H.G. Otten[1], M.C. Verhaar[2], H.P.E. Borst[1], R.J. Hené[23], A.D. van Zuilen[2], Depts. of Immunology[1] and Nephrology and Hypertension[2], University Medical Centre Utrecht, The Netherlands, [3]Dianet Foundation, Utrecht-Amsterdam, The Netherlands

17.25 Successful treatment of allograft rejection after renal transplantation with autologous bone marrow derived mesenchymal stromal cells (p. 130)
M.E.J. Reinders[1], J.W. de Fijter[1], H. Roelofs[2], I. Bajema[3], D.K. de Vries[4], C. van Kooten[1], D. Roelen[2], W.E. Fibbe[2], T.J. Rabelink[1], Dept of Nephrology[1], Dept of Immunohematology[2], Dept of Pathology[3] and Dept of Surgery[4], Leiden University Medical Center, The Netherlands

17.35 Machine perfusion or cold storage in deceased-donor kidney transplantation – 3-year follow-up (p. 131)
C. Moers[1], J. Pirenne[2], A. Paul[3], R.J. Ploeg[1,4], for the Machine Preservation Trial Study Group, Dept. of Surgery[1], University Medical Center Groningen, The Netherlands, Dept. of Abdominal Transplantation - Transplant Coordination[2], University Hospital Leuven, Belgium, Dept. of General, Visceral and Transplantation Surgery[3], University Hospital Essen, Germany, Oxford Transplant Centre[4], John Radcliffe Hospital, Oxford, United Kingdom

17.45 Afsluiting congres door LOC, vertrek deelnemers

B Cell Repopulation After Alemtuzumab Treatment in Kidney Transplant Recipients – Transient Increase in Transitional B Cells and Long Term Dominance of Naïve B Cells

S. Heidt[1], J. Hester[1], S. Shankar[1], PJ. Friend[2], KJ. Wood[1], [1]Transplant Research Immunology Group, Nuffield Dept. of Surgical Sciences, University of Oxford, Oxford, United Kingdom, [2]Oxford Transplant Centre, Nuffield Dept. of Surgical Sciences, University of Oxford, Oxford, United Kingdom

In organ transplantation, the composition of the B cell compartment is increasingly identified as an important determinant for graft outcome. Whereas naïve and transitional B cells have been associated with long-term allograft survival and operational tolerance, memory B cells have been linked to decreased allograft survival. Alemtuzumab induction therapy effectively depletes B cells, followed by rapid repopulation up to levels exceeding base line. The characteristics of the repopulating B cells are currently unknown. We studied the phenotypic and functional characteristics of repopulating B cells longitudinally in 19 kidney transplant recipients, before and at 6, 9 and 12 months after alemtuzumab induction therapy.

A transient increase in transitional B cells and cells with phenotypic characteristics of regulatory B cells at 6 months, as well as a long-term dominance in naïve B cells was found in alemtuzumab treated kidney transplant recipients, which was not influenced by conversion from tacrolimus to sirolimus at 6 months. Memory B cells remained virtually absent up to 12 months after transplantation, even though T cells were partially repopulated. At all timepoints after treatment, B cells showed unaltered proliferative and IgM-producing capacity as compared to pre-transplant samples, whereas the ability to produce IgG was inhibited long-term.

In conclusion, induction therapy with alemtuzumab results in a long-term shift towards B cells with the phenotypic and functional characteristics that have been associated with operational tolerance in kidney transplant recipients.

Treatment of Acute Renal Allograft Rejection with Alemtuzumab

M.W.F. van den Hoogen[1], W.J. van Son[2], L.B. Hilbrands[1], [1]Radboud University Nijmegen Medical Center, Dept. of Nephrology, [2]University Medical Centre Groningen, Dept. of Nephrology, The Netherlands

Introduction: Steroid-resistant renal allograft rejections are commonly treated with a 10-14 days course of antithymocyte globulin (ATG). Data on the use of alemtuzumab for treatment of acute rejection are sparse. We assessed whether alemtuzumab could be an effective, safe, and more convenient alternative for ATG in the treatment of acute renal allograft rejection.
Patients and methods: We retrospectively analyzed all adult renal transplant patients treated with alemtuzumab (15-30 mg s.c. at 2 subsequent days) for steroid-resistant acute cellular rejection. Patients treated with ATG (Thymoglobulin®, Genzyme, 2.5 mg/kg bodyweight i.v. for 10-14 days) were used as controls. We focused on treatment failure (defined as combined endpoint of graft loss, need for additional anti-rejection treatment or lack of improvement of graft function) within 3 months, infectious and malignant complications, and on infusion-related side-effects.
Results: From 2008 to 2011, we identified 8 patients treated with alemtuzumab and compared them with 17 patients treated with ATG during the same period. The majority of rejections in each group were classified as IIA according to the BANFF-classification (88% versus 71%). The median time interval between rejection and transplantation was 15 days (range 2 – 347) in the alemtuzumab group and 14 days (range 4 – 219) in the ATG group. Two patients in the alemtuzumab group (25%) experienced treatment failure, compared with five patients in the ATG group (29%, NS). The median number of infections per patient within three months after initiation of treatment was two in the alemtuzumab group (range 0 – 6) and three in the ATG group (range 0 – 9, NS). During follow-up, there were two patients who developed a malignancy (one lymphoma at 35 months and one squamous-cell carcinoma at 30 months after treatment). Both malignancies were in the ATG group. An infusion-related side-effect occurred only once in the alemtuzumab group (local hematoma) while all but two patients in the ATG group experienced one or more infusion-related side-effects such as fever and chills ($P<0.01$). The costs of two 30 mg doses of alemtuzumab were €1050, while the median costs of ATG treatment were €2280 (range €855 – €3875, $P<0.01$).
Conclusion: These data indicate that alemtuzumab can successfully be used for the treatment of acute rejection after renal transplantation. The side effects and costs of alemtuzumab are far more favorable than that of ATG.

Pregnancy after kidney transplantation: 'Will the mothers see them grow up?'

M. van Buren[1], J. van de Wetering[1], J.Roodnat[1], S. Berger[1], M. Tielen[1], W. Weimar[1], Dept. of Internal Medicine[1], Erasmus MC, University Medical Centre Rotterdam, The Netherlands

Introduction: As most young women suffering end stage renal disease are infertile, one of the benefits of kidney transplantation is increased fertility and a chance to become pregnant. The available data shows that successful pregnancy after kidney transplantation is possible, but is often complicated by hypertension, proteinuria and deterioration of graft function. In this study we focused on the long-term outcomes after pregnancy in renal transplant recipients.

Methods: We performed a single centre retrospective study of patients transplanted between 1971 and 2010. Medical records were studied of all women at the age of 45 or younger and transplanted in our centre between January 1971 and December 2010. Pregnancies that lasted longer than 6 months were included. Patient and graft survival and pregnancy outcome were recorded.

Results: Between 1971 and 2010, 414 female patients ≤ 45 years received a kidney transplant. Only 7% (30/414) gave birth to one or more children (range 1-4) after kidney transplantation. These 30 women gave birth to 42 live births and one stillborn. In 40% of cases a caesarean section was performed. The women had a median age of 30 years when they gave birth (range 19 - 40). Median MDRD-GFR before delivery: 62 (range 25-96) ml/min/1.73² vs after delivery 51 (range 4-97) ml/min/1.73² was significantly worse (p=0.003). The median transplant-to-delivery interval was 7 (range 1- 17) years. Almost one third (12/43) of these pregnancies were complicated by preeclampsia and two developed HELLP syndrome. Two of them lost their graft in the first year after delivery. Five females died during our follow-up. One female died within a year after delivery, the others died 3, 5, 17 and 18 years after delivery. 74% (32/43) of the children was born healthy, although 42% (18/43) of the children were born prematurely (range 25-41, median 37 weeks). The median birth weight was 2585 grams with a range of 450-3885 grams. One pregnancy ended in intrauterine death.

Discussion: Only a small proportion of women delivered a child after transplantation. One third of these pregnancies were complicated and 40% of the children were premature. Graft function one year after delivery was significant worse compared to 3 months before conception. 17% (5/30) died before their children reached adulthood. Parents should know they may have to raise their children under difficult circumstances in view of late morbidity and mortality after delivery.

Pediatric Living Donor Liver transplantation: The Groningen experience

M.T. de Boer[1], F.J.F. Rijntjes[1], R. Scheenstra[2], A.P. van den Berg[3], R.J. Porte[1], Dept of Surgery and Liver Transplantation[1], Dept of Pediatric Gastroenterology[2] , Dept of Hepatology[3], University Medical Center Groningen, The Netherlands

Background: In 2004 a pediatric living donor liver transplantation (LDLT) program was started in our center. Potential donors are extensively screened by a multidisciplinary team. Aim of this study is to describe the first experiences with donor selection and surgery, as well as outcome after LDLT.
Methods: Clinical and demographic data were collected from 3 separate prospective LDLT databases: screened living donors, operated donors, and transplanted recipients. Patient and graft survival rates were calculated with the Kaplan Meier method.
Results: Between April 2004 and December 2011, 65 potential living donors were screened for donation of part of their liver. Of these, 16 were suitable and willing to proceed to a LDLT procedure. At this point 16 LDLT procedures have been performed in our center starting April 2004.The annual number of procedures in our center has increased steadily over the years, with a peak of 7 procedures in 2011.
Donor characteristics and outcome: Median donor age was 37 yr (29-46 yr). A small majority of donors was male (56%). One donor was an altruistic donor, all other donors were related to the recipient (8 fathers, 6 mothers and one grandfather). Median follow-up was 328 days (6-736 days) and no donors were lost to follow-up. In 15 procedures the left lateral liver segments (segment 2 and 3) of the donor were used, in one case a full left lobe (segments 2,3 and 4) was used. Serious postoperative complications were seen in 3 (19%) donors (pneumonia (1), transient bile leakage (1) and need for urgent reintubation because of apnea after detubation (1). The majority of patients complained about pain in their right upper quadrant postoperatively, even though they received epidural analgesia.
Recipient characteristics and outcome: Median age of the recipients was 10,5 months (6 months – 12,5 yr). One and three year patient survival rates were 94% and 88%, respectively. One child died 49 days after transplantation because of multiple organ failure caused by sepsis from bowel necrosis and another child died 2,9 years after LDLT due to the consequences of treatment of a Burkitt lymphoma. One and three year graft survival rates were both 88%.
Conclusions: In an era of donor organ shortage, pediatric LDLT is a safe alternative for postmortal transplantation. Pediatric liver transplantation with a partial liver graft from a living donor results in excellent patient and graft survival.

Report of the first 5 DCD pancreas transplants within Eurotransplant, excellent results with prolonged warm ischemia times

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Introduction: On February 1st, 2011 the first donation after cardiac death (DCD) pancreas transplantation in Eurotransplant was performed in our center. Since then 4 more DCD pancreas grafts were transplanted. Successful use of DCD pancreas grafts have been reported before, always with rather short (14-18 min) 1st Warm Ischemia Period (WIP). For logistical reasons we usually deal with longer 1st WIP in The Netherlands.
Objective: Evaluation of 5 DCD pancreas transplants performed in our center.
Methods: Description of all 5 DCD pancreas transplants performed in our center. RESULTS All 5 transplants were from DCD donors from The Netherlands (4 simultaneous pancreas kidney, 1 pancreas after kidney). Donor characteristics: donor ages were 11, 17, 25, 29 and 42 (mean age 25), all male gender, BMI values of 18, 21, 22, 25 and 25 (mean BMI 22), cause of death: 2 CVA, 1 trauma, 1 anoxia, 1 meningitis, 2 donors had a cardiac arrest, mean most recent amylase 142 U/L, mean ICU-stay 2.7 days, P-PASS's were 12, 14, 15, 15 and 18 (mean P-PASS 14.8).Transplant characteristics: all donors were allocated regionally (The Netherlands), mean 1st warm ischemic period (WIP) (time of cardiac arrest till start cold perfusion) 15 minutes (range 10-19), mean cold ischemia time 9.6 hours, mean 2nd WIP 31 minutes. In American literature the warm ischemic period is defined as time from withdrawal of ventilatory support to the initiation of cold perfusion, according to these standards, mean 1st WIP was 32 min. Recipient characteristics: mean recipient age 42 years, mean time on waiting list 531 days. At this moment all pancreas and kidney grafts have good function. One patient had a BK-virus infection and after tapering of immunosuppressive therapy an episode of rejection. All other transplants were without complications.
Conclusion: Pancreas grafts from selected DCD donors are an additional source for pancreas transplantation. Interestingly, in these first 5 cases there was a much longer 1st WIP compared to previous reports. Nevertheless, initial results of these 5 DCD pancreas transplantations are excellent.

Historically positive complement dependent cytotoxicity cross match test is not a barrier for live-donor kidney transplantation: A pilot study

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At present, the increasing numbers of HLA sensitized renal transplant candidates bear a steadily growing need to develop new strategies to bypass the barrier of HLA sensitization. One approach could be to take advantage of the kinetics in both the presence and complement binding characteristics of antibodies against HLA antigens.
Here, we report on successful kidney transplantation in 5 candidates with historically positive CDC cross match tests (XM) who were not able to induce complement dependent cytotoxicity of their donor lymphocytes repeatedly when their current sera from one year to 6 months before transplantation onwards were tested.
Between February 2010 and July 2011, 5 patients received a transplant from a live-donor with a current negative CDC XM while the historical CDC XM test was positive. Immunosuppressive regimen consisted of CD25 mAb, prednisolone, tacrolimus and mycophenolate mofetil. The dosing and tapering scheme did not differ from routine schedule. Patient's present kidney functions expressed as serum creatinine (µmol/l) (eGFR(ml/min)) are : 107 (46), 83 (69), 204(26), 96 (53) and 135 (57) with respectively 0.11, 0.06, 0.34, 0.12 and 0.13 g/l protein loss in urine. Three of these 5 patients experienced deterioration of graft function based on acute C4d negative cellular rejection with a humoral component, C4d negative thrombotic microangiopathy, and acute C4d positive mixed humoral and cellular rejection. In the last two patients donor specific antibodies were detectable. These episodes were treated with high dose methylprednisolon, intravenous immunoglobulins and plasmapheresis when indicated.
In conclusion, live-donor kidney transplantation is feasible despite a historically positive CDC cross match test when the current CDC XM is negative. Concerns about the higher rejection rate and long-term graft function raise the need to develop strategies to prevent acute (humoral) rejection in this group of patients.

A new CYP3A4 polymorphism (CYP3A4*22) is significantly associated with decreased tacrolimus metabolism

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Background: Tacrolimus (TAC) is a widely used immunosuppressant with a narrow therapeutic window. Underexposure is associated with acute rejection, whereas overexposure is associated with nephrotoxicity. TAC pharmacokinetics varies considerably between individuals and therapeutic drug monitoring (TDM) is used to guide therapy. TAC is metabolized by CYP3A4 and CYP3A5. Genetic polymorphisms in the *CYP3A5* gene explain part of the interindividual variability in tacrolimus dose requirement (with *CYP3A5* expressers needing higher doses to reach comparable exposure as non-expressers). No relevant *CYP3A4* polymorphisms were known until recently, when a new *CYP3A4* intron 6 polymorphism (rs35599367C>T, *CYP3A4*22,* minor allele frequency 5%) was described that was associated with decreased CYP3A4 activity. We hypothesized that *CYP3A4*22* carriers would require less TAC to reach adequate plasma concentrations.
Methods: 185 renal transplant recipients on MMF/TAC (participating in the FDCC-study) were genotyped for *CYP3A4*22* and *CYP3A5*3*. TAC predose concentrations were determined on day 3 and 10, and on month 1, 3, 6 and 12.
Results: No linkage equilibrium was observed between the *CYP3A4*22* and the *CYP3A5* allele. Mean TAC dose requirement was 33% lower for *CYP3A4*22* carriers compared to wildtype patients (CI-95%: -46% to -20%, p=0.018). *CYP3A4*22* and *CYP3A5*3* were associated with supratherapeutic TAC concentrations (>15 µg/L) during the first 3 days after transplantation: OR=8.7 for *CYP3A4*22* carriers + *CYP3A5*3/*3* (p=0.027), OR=4.2 for *CYP3A4*1/*1* + *CYP3A5*3/*3* (p=0.002), compared to *CYP3A4*1/*1* + *CYP3A5*1* carriers. TAC dose-adjusted C0 concentrations were +179% for CYP3A poor metabolizers (*CYP3A4*22* carriers + *CYP3A5*3/*3*) (p<0.001), +101% and +64% for CYP3A intermediate metabolizers (*CYP3A4*1/*1* + *CYP3A5*3/*3*) (p<0.001) and (*CYP3A4*22* carriers + *CYP3A5*1* carriers) (p=0.020), respectively, compared to CYP3A extensive metabolizers (*CYP3A4*1/*1* + *CYP3A5*1* carriers).
Conclusion: The novel *CYP3A4*22* polymorphism is associated with significantly decreased TAC metabolism and increases the risk of supratherapeutic TAC concentrations after transplantation. Therefore the *CYP3A4*22* polymorphism should be considered in parallel with *CYP3A5* genotype status in order to decrease TAC-toxicity after renal transplantation.

Effect of a multifactorial intervention with the aid of nurse practitioners on cardiovascular outcome in kidney transplant recipients: a post hoc analysis of the MASTERPLAN study

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Introduction and aims: The MASTERPLAN study evaluated if strict implementation of current guidelines with aid of a nurse practitioner improved cardiovascular outcome in patients with chronic kidney disease(CKD). Despite small but significant improvements of blood pressure(BP), LDL-cholesterol and proteinuria in the intervention group(IG), no differences in the primary outcome were observed. We performed a post hoc analysis in prevalent transplant recipients that participated in the study.
Methods: MASTERPLAN is a randomized controlled clinical trial, performed in nine Dutch hospitals. 788 patients with CKD (eGFR 20-70 ml/min/1.73m2) were randomised to either receive care by the nephrologist (control group, CG) or intensified care with added nurse practitioner support(IG). At baseline stratification on transplant status was performed. Both groups were subject to identical guidelines. Patients were followed for a median of 4.9 yrs. The primary endpoint was a composite of myocardial infarction, stroke and cardiovascular death. Also changes in quality of care of cardiovascular risk factors were evaluated.
Results: We analysed 110 transplant recipients (66M), age 51 (12) yrs , eGFR 40(13) ml/min/1.73m^2. Mean follow-up after transplantation 7.5 (5.4) years. Oscillometric BP 132(19)/ 79(10) mmHg, LDL 2.68 (0.84) mmol/l, 26% diabetes, 26% prior CVD, 22% smokers, BMI 26(6) kg/m^2 .
The intervention resulted in significantly lower diastolic blood pressure 77 vs 81 mmHg (p=0.006), no significant differences were noted for systolic BP 132 vs 133 mmHg (p=0.09), LDLcholesterol 2.43 vs 2.62 mmol/l, p= 0.13), proteinuria 0.65 vs 0.83 g/day (p=0.29), smoking cessation, body weight, physical activity or sodium excretion. The primary outcome occurred in 33.1/1000py in IG and in 25.2/1000py in CG (HR 1.33, 95%CI 0.46 to 3.84). Incidence of ESRD was 39.1 vs 38.6/1000py (HR 0.99, 95%CI 0.39 to 2.49).
Incidence rate in the transplanted group was not different compared to the non transplanted for the primary endpoint (HR 1.36, 95%CI 0.76 to 2.4) and ESRD (HR 1.31 95%CI 0.79 to 2.2). There were no adverse consequences associated with the intervention.
Conclusion: In this subgroup of 110 patients only diastolic BP is significantly better in IG than in CG. For all other factors direction of difference was identical however no statistical significant changes were found. The intensified treatment did not significantly reduce the rate the composite endpoint or the rate of ESRD.

Improved intra- and interpatient variability of oral bioavailabilty of tacrolimus after conversion from Tac BID (Prograft) to Tac QD (Advagraf) in stable kidney transplant recipients

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Introduction: Tacrolimus is a cornerstone immunosuppressive drug in organ transplantation. Originally registered as a twice daily formulation (Prograf, Tac BID), recently a prolonged-release once daily formulation (Advagraf, Tac QD). Tac QD has been registered as bioequivalent and proven to have the same efficacy and safety. However, the intra- and interpatient variability in the oral bioavailability of both formulations have not thoroughly been compared yet. A lower variability has been reported to be related to a better clinical outcome. Methods Stable renal transplant patients (n=40) on Tac BID were converted on 1:1 mg base to Tac QD in an investigator-driven, open label two-sequence comparative pharmacokinetic study. Dried blood spot samples were collected 5 times (1 week apart of each other) in each sequence for 8-point AUC0-24 (24-hour blood concentration-time curve). Samples were analyzed by HPLC-MS/MS. AUC0-24 was calculated by the trapezoidal rule (geometric mean with 95% confidence interval [CI]). Main outcome measures are intra- and inter-patient variability expressed as coefficient of variation (CV) of the log-transformed values. Statistics: student's T-test. Results All patients completed the study as by protocol without clinical events. AUC0-24 was comparable for Tac QD and Tac BID (resp. h/L (CI 205.84 – 233.36, p= 0.37) with·gμ213.28 (CI 200.54 – 226.83) and 219.17 an average ratio of 1.00 (90%CI 0.99 – 1.01). Tac QD showed a significantly reduced interpatient CV (22.2% vs 24.0%, p=0.03) and intrapatient CV (10.9% vs. 14.14%, p= 0.01) compared to Tac BID. Conclusion: The drug exposure of Tac QD shows less variability (both inter- and intrapatient) compared to Tac BID in stable renal transplant patients. The clinical consequences of this has to be in determined.

Altered MicroRNA expression is associated with the protective effect of preoperative dietary restriction or fasting after renal ischemia reperfusion injury

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Background: Ischemia-reperfusion injury (I/RI) is an inevitable consequence after transplantation and may lead to delayed graft function and rejection. Previously we showed that preoperative dietary restriction (DR) or fasting protects mice against I/RI . The underlying mechanism, however, is not fully understood. MicroRNAs are small non-coding RNAs which regulate mRNA-expression of approximately 60% of the genome. We performed genome-wide miRNA profiling to elucidate their contribution to this protection and identify potential therapeutical targets to prevent I/RI.
Materials and methods: C57/Bl6 mice were divided in three groups: DR (70% of needed calories for 28 days), three days of water only fasting and ad libitum (AL) access to food. Thereafter, I/RI was induced by bilateral clamping of the renal artery and vein for 37 minutes. At 0, 2, 6, 24 and 48 hours after reperfusion, kidneys were collected. RNA was isolated for profiling using an Exiqon platform with 569 microRNAs. We measured differential microRNA expression after DR or fasting but before induction of I/RI (timepoint 0).
Results: Thirty-two microRNAs were significant differentially expressed at timepoint 0 in the DR group, and 18 in the fasted group as compared to AL fed mice($p<0.01$). Seven overlapped between DR and fasting. These microRNAs regulate pathways affected by dietary restriction including mTOR and IGF-signaling. Following reperfusion, significance disappeared within 2-6 hours due to a decrease in miRNA expression in the AL-group.
Conclusion: Our results suggest that altered microRNA expression after dietary restriction may be involved in the protection against renal I/RI. The decrease in expression levels of these microRNAs in the AL-group after reperfusion suggest that downregulation before ischemia contributes to the protective effect of DR. Silencing these microRNAs in vivo will enable us to assess their therapeutic potential to prevent I/RI.

Hypothermic oxygenated machine preservation of donor livers after prolonged ischemia in a porcine model of donation after cardiac death

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Background: Livers derived from donation after cardiac death (DCD) are increasingly accepted for transplantation. However, compared to donation after brain death, DCD livers suffer additional warm ischemic injury, leading to reduced viability and lower graft survival after transplantation. Oxygenated machine perfusion might allow resuscitation of DCD livers and improve organ viability. In this study, we compared oxygenated hypothermic machine perfusion (HMP) with simple cold storage (SCS) of DCD pig livers.
Methods: Using standard procurement technique of *in situ* perfusion with cold UW solution (4 °C), livers were obtained from Yorkshire pigs (90-110 kg) after 30 min of cardiac arrest. Donor livers were subsequently preserved for 4 hr by SCS (n=4) or by 4 hr of oxygenated HMP (14 °C, n=4). To mimic transplantation, all livers were subsequently reperfused for 2 hr at 37 °C with oxygenated, heparinized porcine whole blood. The machine perfusion system used in this study is pressure-controlled and allows combined pulsatile arterial and continuous portal venous perfusion of the liver (Liver Assist®, Organ Assist, Groningen, Netherlands). During and after machine perfusion, samples were taken from the perfusion fluid or blood for biochemical analyses. Biopsies were taken from the liver and extrahepatic bile ducts at several time points.
Results: Biochemical markers of liver cell injury, alanine aminotransferase (ALT) en aspartate aminotransferase (AST), were significantly higher after reperfusion of SCS livers, compared to HMP livers (248 vs 71 [p=0.03] and 4234 vs 956 [p=0.03], respectively). Hepatic artery blood flow at 1 hour after reperfusion was higher in the HMP group, compared to the SCS group (269 [IQR 71-270] ml/min vs 76 [IQR 22-128] ml/min), although this did not reach statistical significance (p=0.23). Gross appearance confirmed better preservation of HMP livers as these livers appeared more homogenously perfused after reperfusion. Histological evaluation of liver and bile duct biopsies, however, did not show major differences between SCS or HMP livers.
Conclusion: Oxygenated HMP of livers from DCD donors is associated with better restoration of hepatic artery blood flow upon graft reperfusion and a lower hepatic release of ALT and AST, compared to livers preserved by SCS. However, differences in histological injury were minimal and further optimization of machine preservation of DCD livers may require normothermic rather than hypothermic perfusion.

Compliance, lactate production and pCO2 during In Situ Lung Perfusion (ISLP) are predictors for lung injury in non-heart-beating donors category I – II

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Introduction: Non heart beating donors (NHBD's) are an important alternative to extend the donor pool in lung transplantation. In category I – II, lung function is often not available at the time of procurement. In this study we evaluate the use of a lung perfusion system in the donor in the assessment of these lungs.
Methods: Domestic pigs (n = 12/n = 4 per group) were sacrificed by ventricular fibrillation. This was followed by 20 minutes of cardiopulmonary resuscitation. Heparin (15000IU) was administered after a 5 minutes hands off period. In group I, this was followed by 1 hour of WI and 2 hours of topical cooling (TC) [1h-ISLP]. In group II, sacrification was followed by 2 hours of WI and 1 hour of TC [2h-ISLP]. In group III, there was a minimal period of WI and no TC [C]. In all 3 groups the lungs were evaluated during 60 minutes with an in situ lung perfusion system. Biopsies were taken from 4 different parts of the lung. W/D weight ratio was calculated as an index of pulmonary edema.
Results: Compliance and Δ PO_2/FiO_2 were significantly higher in [C] compared to [1h-ISLP] and [2h-ISLP] at 60 minutes of reperfusion ($p = 0{,}0052$ and $p = 0{,}0077$, respectively). CO_2 in the outflowing perfusate (pCO_2) at the end of the reperfusion was higher in [2h-ISLP] versus [C] ($p = 0.0463$). Pulmonary vascular resistance was lower in [C] compared to [1h−ISLP] and [2h-ISLP] ($p > 0.05$). Lactate production by the lung was higher in [2h-ISLP] compared to [C] ($p>0.05$). W/D weight ratio was significantly lower in [C] compared to [2h-ISLP] in the apical anterior lung biopsy and the basal anterior lung biopsy ($p<0.05$). A high W/D weight ratio was correlated with a lower compliance, higher lactate production and a higher pCO_2 ($p<0.05$).
Conclusion: ISLP is a safe and non-injurious way to assess lungs from NHBD category I – II in the donor. These data suggests that compliance, pCO_2 and lactate production are independent predictors for lung injury.

Rabbit Antithymocyte Globulin impairs the capacity for homeostatic proliferation of T cells in kidney transplant patients

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Introduction: Short term rabbit antithymocyte globulin (rATG) induction therapy leads to long-lasting depletion of T cells. Numbers of T cells return to baseline levels approximately one year after kidney transplantation. The biological mechanism of this phenomenon is not elucidated yet. Here we studied the hypothesis that this could be explained by an effect on the homeostatic proliferation of T cells.
Material and Methods: The phenotype and homeostatic proliferation capacity of T cells from renal transplant recipients (n=14) treated with rATG induction therapy (3 x 2 mg/kg/day) in combination with tacrolimus, mycophenolate mofetil (MMF) and steroids were investigated the first year after transplantation by whole blood phospho-specific flow cytometry. Patients (n=23) treated with the non-depleting basiliximab induction therapy (day 0, 4, 20 mg) served as a control group.
Results: After a significant decrease in the absolute number of CD4 and CD8 T cells one week after rATG therapy ($p<0.0001$), T cells repopulate. However, while CD8 T cells reach baseline levels 3 months after induction therapy, CD4 T cells do not reach 40% of their baseline levels 12 months after transplantation. Functional analysis of the repopulated T cells revealed an impaired IL-7 induced Signal Transducer and Activator of Transcription 5 (STAT5) phosphorylation capacity of these cells. CD4 memory T cells, including central memory (CD45RO+CCR7+) and effector memory (CD45RO+CCR7-) subpopulations showed a decrease in the proportion of IL-7 induced phosphorylation of STAT5 ($p<0.04$ vs pre-transplantation). Also the CD8 memory T cells demonstrated to have impaired IL-7 induced STAT5 phosphorylation capacity that even decreased further during follow-up the first year after transplantation ($p<0.022$ vs pre-transplantation). This decreased STAT5 phosphorylation capacity included the central memory, effector memory and EMRA (CD45RO-CCR7-) subpopulations. T cells of basiliximab treated patients did not demonstrate impaired IL-7 induced STAT5 phosphorylation responses.
Conclusion: CD4 and CD8 T cells showed a long-lasting impaired IL-7 induced phosphorylation capacity of STAT5 after rATG induction therapy which can explain the absence of full immune reconstitution approximately one year after rATG induction therapy.

A Novel ELISPOT Assay to Quantify HLA-Specific B Cells in HLA-Immunized Individuals

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Quantification of the humoral alloimmune response is generally achieved by measuring serum HLA antibodies, which provides no information about the cells involved in the humoral immune response. Therefore, we have developed an HLA-specific B cell ELISPOT assay allowing for quantification of B cells producing HLA antibodies.
Enriched B cells were pre-activated in a CD40L-driven fashion before assayed in the HLA-specific B cell ELISPOT. We used recombinant HLA monomers as target in the ELISPOT assay. Validation was performed with human B cell hybridomas producing HLA antibodies of defined specificity. Subsequently, we quantified B cells producing HLA antibodies in HLA-immunized individuals, non HLA-immunized individuals and transplant patients with serum HLA antibodies.
B cell hybridomas exclusively formed spots against HLA molecules of corresponding specificity with the sensitivity similar to that found in total IgG ELISPOT assays. HLA immunized healthy individuals showed up to 182 HLA-specific B cells per million total B cells while non-immunized individuals had none. Patients who were immunized by an HLA-A2-mismatched graft had up to 143 HLA-A2-specific B cells per million total B cells.
In conclusion, we have developed and validated a highly specific and sensitive HLA-specific B cell ELISPOT assay, can be used to determine the frequency of peripheral HLA-specific B cells in transplant recipients. This technique constitutes a new tool for quantifying humoral immune responses.

Everolimus treated renal transplant patients develop a more robust CMV-specific CD8 response compared to cyclosporine or mycophenolate sodium treated patients

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Cytomegalovirus (CMV) is the most frequent occurring viral infection after renal transplantation. As compared to other immunosuppressive treatment, mTOR-inhibitors are reported to protect against CMV disease. Here, we questioned whether the mTOR-inhibitor everolimus (EVL) influences the CMV induced T-cell response. We studied 26 CMV-seropositive kidney transplant recipients treated with prednisolone(P), cyclosporine A (CsA) and mycophenolate sodium (MPS) for the first 6 months after transplantation, followed by double therapy consisting of either P/EVL (n=10), P/CsA (n=7) or P/MPS (n=9). All patients were CMV-IgG positive prior to transplantation and 78% developed a CMV-reactivation before randomization to double therapy. CD27-effector-type CD8+T-cells and CD27-CD28-CD4+T-cells, known to be associated with CMV-infection, were measured before, at 6, 12 and 24 months after transplantation. In addition, we determined CMV-specific CD8+T-cells using tetramers for pp65- and IE-antigen. In the P/EVL treated patients, total CD8+T-cells (p=0.02), CD27-effector-type CD8+T-cells (p=0.004) and CD27-CD28-CD4+T-cells (p=0.004) increased significantly in time after transplantation. In the P/CsA and P/MPS treated patients we observed no significant increase. Indeed, also CMV-specific CD8+T-cells (p=0.009) significantly increased in P/EVL treated patients. The significant increase in (CMV-specific) effector-type CD4+ and CD8+T-cells in EVL treated patients offers a likely explanation for the low incidence of CMV related pathology in these patients.

Immediate early gene expression profiles in regenerating living donor livers show a functional shift of key cellular and functional pathways

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In the setting of adult-to-adult living donor liver transplantation, healthy donors undergo resection of 40-60% of their liver volume. While the majority of donors do well, significant morbidity and mortality remains associated with the procedure. Most donors show incomplete regeneration in the first 3-6 months, with a significant incidence of post-operative complications and a small but present risk of liver failure or even death. Better understanding of factors influencing liver regeneration may provide possible targets for intervention, minimizing subsequent morbidity and mortality. Aim of this study is to identify differences in early hepatic gene expression profiles between donors with successful and less successful regeneration of their remnant liver mass. 24 right lobe donors from two A2ALL centers had volumetric imaging of their total liver volume before and 3 months after donation. Regeneration of their remnant liver was quantified by absolute growth and % volume increase. Using Affymetrix Human Gene 1.0 ST array chips, liver biopsies from these donors were analyzed for gene expression at baseline (PRE) and in remnant left lobes immediately after resection (POST). Data were analyzed using Partek software and p-values <0.005 using an ANOVA-test were considered significant. Pathway analysis was done using Ingenuity Pathway Analysis (IPA). Class comparison between POST and PRE biopsies showed activation of pathways related to acute phase responses, cell death and cellular growth and proliferation, while metabolic functions, such as lipid metabolism, were markedly inhibited. Significant differences were seen in the gene expression patterns between livers with varying degrees of regeneration. Livers with more successful regeneration demonstrated more activation of pathways related to cellular signaling and cell proliferation, whereas less successful regenerating donors displayed limited change in gene expression, with patterns focused on inhibition of lipid, amino acid and carbohydrate metabolism.
Conclusion: Living donors with successful liver regeneration show differential expression of a high number of genes immediately post-resection compared to baseline, markedly different from those with deficient regeneration. The lack of significant change in genomic profile in the poorly regenerating livers suggests a possible inhibition or delay in initiation of recovery and regeneration molecular pathways, and may identify potential areas for intervention.

Cytomegalovirus seropositivity has a distinct effect on premature immunological ageing within the T cell compartment of end-stage renal disease patients.

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Background: Cytomegalovirus (CMV) infection substantially influences circulating T cell differentiation and may reduce the telomere length of T cells in healthy individuals. These changes indicate an ageing effect of CMV on the normal immune system. End-stage renal disease (ESRD) patients are known to have a premature immunological aged T cell compartment that may underlie the ESRD-related T cells immune deficiency. The aim of this study was to examine whether CMV contributes to premature immunological T cell ageing in ESRD patients.
Methods: For this purpose, we studied the circulating T cells by three different assays which are indicative for the immunological age of the T cell system. First, the T cell receptor excision circle (TREC) content was measured, which indicates the output of naïve T cells from the thymus. Relative telomere length (RTL) was determined as a measure of repeated rounds of cell proliferation and multiparameter flowcytometry was used to establish the differentiation status of circulating T cells. Data were obtained from of ESRD patients without renal replacement therapy (RRT) (n=15 CMVpos, n=15 CMVneg, eGFR<15 ml/min) and patients RRT (n=30 CMVpos and n=30 CMVneg).
Results: CMV seropositivity did not influence the already decreased TREC content in ESRD patients. However, $CD8^+$, but not $CD4^+$ T cells of CMV-seropositive ESRD patients had significant (p=0.03) shorter telomeres than their age-matched CMV-seronegative counterparts. Especially, the younger ESRD patients (<50 years) had a significant lower (p=0.04) CD8 RTL value (i.e. 11.07% for the CMV-seropositive versus 13.01% for their CMV-seronegative counterparts). The T cell differentiation status of both $CD4^+$ as well as $CD8^+$ T cells was significantly affected by CMV in that the T cell composition was shifted towards memory T cells. CMV-seropositive patients had a significant lower absolute number of naïve $CD4^+$ ($p<0.05$) and more terminally differentiated $CD8^+$ T cells when compared to CMV-seronegative patients. In addition, significantly ($p<0.05$) increased percentages of $CD4^+$ as well as $CD8^+$ T cells lacking CD28 were observed in CMV-seropositive patients. Overall, CMV-effects on T cells were not restored by RRT.
Conclusion: Based on these results we conclude that CMV seropositivity has a distinct effect on the CD4 and CD8 T cell differentiation status but only a marginal effect on the other ageing parameters.
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Mesenchymal stem cells generate de novo functional CD4+CD25+CD127- regulatory T cells with highly methylated FOXP3 DNA

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Introduction: The ability of mesenchymal stem cells (MSC) to apply immunosuppression makes them interesting candidates for cellular therapy in solid organ transplant recipients. MSC exert their function through the inhibition of effector T cell proliferation. In animal models, MSC treatment led to an increase of CD4+CD25+CD127-FOXP3+ regulatory T cells (Treg). The present study aimed to elucidate the cell population of origin for Treg induction by MSC.
Methods: MSC were derived from perirenal fat tissue of kidney donors. PBMC were isolated from blood bank donors, CD25- cells and natural Treg (nTreg) were obtained by cell separation. Induction of Treg was achieved through allogeneic stimulation of CD25- effector cells in the presence of MSC. CD4+CD25- T cells and CD4+CD25+CD127- T cells were sorted and analyzed, the functionality was tested in secondary mixed lymphocyte reactions (MLR) and the methylation status of the *FOXP3* gene's Treg-specific demethylated region (TSDR) was determined.
Results: In the presence of MSC a significant induction of CD25+CD127-FOXP3+ cells within the CD4+ T cell population originating from CD25- effector cells was observed (p=0.001). These *de novo* CD4+CD25+CD127-FOXP3+ T cells inhibited effector T cell proliferation as effectively as nTreg (62% [p=0.007] and 48%, [p=0.003], respectively), the CD4+CD25- T cells had no suppressive effect on T cell proliferation. Both CD4+CD25+CD127-FOXP3+ T cells and CD4+CD25- T cells had a highly methylated TSDR (93% and 99%, respectively). This indicates that the newly induced CD4+CD25+CD127-FOXP3+ T cells are of CD25- origin and distinct from nTreg, which have a highly demethylated TSDR.
Conclusion: This study demonstrates that MSC contribute to the generation of an immunosuppressive environment not solely through the inhibition of allo-activated effector T cells, but also through the induction of *de novo* CD4+CD25+CD127-FOXP3+ Treg from CD25- cells which by themselves possess repressive capacities. This apparent diversity of MSC function emphasizes the potential of MSC immunotherapy in solid organ transplantation.

Non Heart Beating category II Lung and Kidney Donation: How big is the pool?

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Background: NHB category II (NHB II) transplantation has not been performed in our center yet. To expand the existing donor pool, NHB II lung and kidney donors after unsuccessful cardiopulmonary resuscitation could be used for transplantation.
Aim: To asses the size of the NHB II donor pool for lung and kidney transplantation in a large university hospital in The Netherlands. Exclusion criteria that are specific to NHB II lung and kidney donation are age over 65 years and pre-existing lung and kidney disease.
Methods: The prospective emergency room (ER) database of our university hospital was analyzed to detect potential NHB II lung and kidney donors in patients that were admitted from January to December 2010. Data on cardiopulmonary resuscitation, age, medical history, and on national donor registry status were collected.
Results: In total, 61 patients who were admitted to our ER died after unsuccessful out of hospital and/or ER cardiopulmonary resuscitation. Twenty-nine (47.5%) patients were older than 65 years. The remaining 32 (52.5%) patients were 65 years or younger and did meet the age criteria for NHB II lung or kidney donation. Of these 32 patients, 17 patients died in the ER. Nine patients were excluded for medical reasons or were registered as refusing donation. As a result, eight out of 17 (47%) patients could have been used as NHB II lung donors, and six of these patients could also have been used as NHB II kidney donors.
Conclusion: In 2010, in a large university hospital with a lung and kidney transplant program, eight patients proved to be potential NHB II lung donors and six of these patients also proved to be potential kidney donors after unsuccessful treatment for cardiac arrest in the emergency room. Non heart beating II lung and kidney donation could be an important source of donor organs to expand the existing lung and kidney donor pool.

Chirurgische technieken voor nierdonatie bij leven in Europa: De stand van zaken

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Achtergrond: De toename van nierdonatie bij leven heeft geleid tot de ontwikkeling van nieuwe chirurgische technieken. In 2004 werden Europese transplantatiecentra met een enquête gepeild over hun levende donor programma. Het doel van deze studie was om de huidige status van de chirurgische techniek in Europa vast te leggen en mogelijke ontwikkelingen te beschrijven.
Methode: Honderdnegentien transplantatiecentra in 12 Europese landen ontvingen een vragenlijst. De vragen betroffen onder andere het aantal levende donor nefrectomieën, de gebruikte techniek, redenen om voor de rechter- dan wel linker nier te kiezen en redenen om een open of een endoscopische techniek te gebruiken.
Resultaten: Zesennegentig centra (81%) hebben gerespondeerd. In de responderende centra werden ongeveer 2813 donornefrectomieën verricht, het aantal levende donoren varieerde tussen de 0 en 124 per centrum. In 31 centra (32%) werden alleen open technieken gebruikt. Zeven centra (7%) gebruikten zowel open als endoscopische technieken en achtenvijftig centra (61%) gebruikten alleen endoscopische technieken. De belangrijkste reden om voor een open benadering te kiezen was gebrek aan bewijs dat endoscopische tech-nieken beter zijn. In 7 centra werden nog klassieke lumbutomieën uitgevoerd. Acht centra (14%) beperkten hun endoscopische programma tot de linker nier. In de overige centra werd in gemiddeld 29% (range 2% - 98%) van de donoren de rechternier verwijderd. Het aantal centra dat enkel endoscopische tech-nieken gebruikte nam toe met 15% sinds 2004, het aantal centra dat enkel open technieken gebruikte daalde met 13%. Tweeënzeventig centra (75%) accepteerden donoren met een BMI boven de 30 kg/m^2, de mediane bovengrens in deze groep was 35 kg/m^2 (IQR 33-35). Donoren met hypertensie werden geaccepteerd in 80 centra (83%), het merendeel van deze centra (67%) accepteerden donoren met één anti-hypertensivum. Donoren met een ASA-klasse boven 1 werden geaccepteerd in 58% van de centra.
Conclusie: Er is een toename van het aantal levende donornefrectomieën in Europa, ook is er een toename van het aantal centra dat minimaal invasieve technieken gebruikt voor nierdonatie bij leven. Desondanks wordt de klassieke lumbotomie nog steeds toegepast in Europa, wat betekent dat er nog ruimte voor verbetering is.

The method of approaching patients and recruitment in clinical trials

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Background: In 250 subjects, who received a kidney transplant six months or longer ago, the conventional tacrolimus formulation (Prograft) was converted to the slow-release tacrolimus formulation (Advagraf) as part of a non-randomized, clinical cohort study. The difference between these two formulations is that tacrolimus-Prograft has to be taken twice a day, while the slow-release formulation can be taken only once a day. The latter may result in improved patient compliance. Duration of this study (*i.e.* follow-up after conversion to tacrolimus-Advagraf) was one year. Study visits were always combined with routine outpatient appointments, so extra visits to the hospital were not necessary. Enrollment started in December 2009 and the last patient was included in September 2011. We studied whether the time after transplantation or the informed consent procedure affected participation in research.
Methods: We approached 311 patients in two different ways in an attempt to obtain informed consent. One-hundred seventy-two subjects received an informed consent form and were given at least two weeks time to consider participation. Then they received a phone call asking about their decision. If patients were willing to participate, they were switched from tacrolimus-Prograft to tacrolimus-Advagraf at the next scheduled visit to the outpatient clinic. One-hundred thirty-nine subjects received an informed consent form during a visit to the outpatient clinic and were given the opportunity to participate immediately in this trial after reading the informed consent form without a two-week time-out period.
Results: Of the 172 patients who received both the written information and the telephone call, 115 (67%) agreed to participate. In contrast, of the 139 patients that were given the opportunity to participate immediately, 135 (97%) gave informed consent. The difference in enrollment between the methods of approaching was statistically significant ($p<0.0001$). The time after transplantation had no influence on the consent rate to participate.
Conclusions: Subjects given time to consider participation in the trial gave their consent significantly less frequently compared with patients who could participate immediately.

Screening weefselpotentieel

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Doel: Of de arts bij overlijden van een patiënt terecht of onterecht een medisch geschikte weefseldonor heeft herkend of afgewezen is geheel afhankelijk van de kennis over criteria en contra-indicaties voor weefseldonatie. De bevinding van de arts wordt ingevuld op het donatieformulier en door een donorwerver ingevoerd in een database van de NTS. Echter er is nog nooit in Nederland op basis van medisch dossier onderzoek nagegaan of artsen het ware potentieel aan weefseldonoren achterhalen. Het 'Don Quichot' onderzoek uit 1998, waarop dit onderzoek als vervolg kan worden gezien, bracht alleen het potentieel aan weefseldonoren in kaart op basis van een door de arts ingevuld uitgebreid donatieformulier. Gezien het afnemend aantal patiënten dat overlijdt in ziekenhuizen en een toename van de leeftijd dient het weefselpotentieel inzichtelijk te worden gemaakt.
Methode: In drie ziekenhuizen, een UMC, een STZ en een algemeen ziekenhuis, zijn de medische dossiers van alle klinische overledenen van het jaar 2011 gescreend door de donatiefunctionarissen en transplantatiecoördinatoren. Hierbij is de geschiktheid voor bot, cornea, hartkleppen en huid tot de leeftijd van 86 jaar in kaart gebracht. Deze bevindingen zijn afgezet tegen de uitkomsten van het donatieformulier.
Resultaten: In de eerste drie kwartalen zijn 953 overledenen gescreend. In de groep tot de leeftijdgrens van 86 jaar voor weefseldonatie werden door de arts 204 van de 267 geschikte donoren herkend. Dit is 23,6% minder dan het gemeten potentieel uit de medische dossiers. Van het totale potentieel (n=481) werd 21,2% gemist (n=102), bot 1/21 (4,8%), hartkleppen 4/53 (7,5%), huid 19/143 (13,3%) en cornea 78/264 (29,5%).
Conclusie: Op basis van deze voorlopige cijfers is geconstateerd dat het oordeel van de arts in 23,6 % afwijkt van het potentieel gemeten vanuit het medisch dossier. Dit betekent dat 21,2% van het medisch geschikte weefselpotentieel in de drie ziekenhuizen niet optimaal werd benut. De data over de resterende maanden van 2011 zullen worden gepresenteerd tijdens het Bootcongres.

Anonymity in living kidney donation: an ELPAT view

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Introduction: There is a wide variation in the practice of maintaining anonymity before and after living donor transplantation in both unspecified donation (altruistic donors) and specified indirect donation (paired exchange schemes). Further debate and clarification of the ethical and normative issues is clearly required.
Methods: A multidisciplinary team, including transplant surgeons and physicians, ethicists and philosophers, donor co-ordinators, lawyers and psychologists was convened by ELPAT (Ethical, Legal and Psychosocial Aspects of Transplantation), a section of ESOT, to consider this issue. A summary of existing practice across Europe, and arguments for and against anonymity was collected, and recommendations formulated.
Results: Some countries practice complete anonymity in perpetuity, whilst others make no attempt to ensure anonymity at all. Others adopt a permissive approach, with anonymity preserved prior to transplantation, but allow removal of anonymity by mutual consent of donor and recipient several months after transplantation. Examples of significant harm to both donor and recipient from loss of anonymity were identified, including withdrawal from transplantation, implicit or explicit demand for reward and loss of idealisation. The main ethical argument against preserving anonymity was that this was paternalistic, whilst practical difficulties in enforcement were identified.
Conclusions: There was a clear recommendation that anonymity should be maintained prior to either unspecified or specified indirect transplantation. Preservation of anonymity subsequently was considered ideal, and should only be lost under carefully controlled conditions to minimise potential harm to both donor and recipient.

Donation indicators in intensive care units in The Netherlands 2007-2010, a review

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Purpose: As long as there is a shortage of transplantable organs and a considerable number of patients still die on the waiting list, we have to make great efforts to optimize deceased donation. From 2008 the Dutch government launched a Masterplan in order to increase the number of deceased donors, including regional initiated different projects to stimulate donation in hospitals. What are the results thus far, can we see any trends in the donation indicators and what are the differences between donor regions and types of hospitals?
Material and Methods: Medical records of 28583 patients died in the ICU from 72 Dutch hospitals during the years 2007-2010 were reviewed. Data regarding donation were collected in a centrally registered database (MSO). We quantified the number and percentage of potential organ donors (OD) each quarter a year, including potential heart beating and non-heart beating OD < 66 years. From this OD potential donation indicators were evaluated, ie. consultation of the Donor Register, requesting of and consent given by relatives and final procurement defined by the conversion rate (number procured/potential). Donor indicators were also compared between the 7 donor regions and different types of hospitals. Results: The number of patients who died on the ICU as well as the number of potential OD fluctuated (no trends), on average 1786 deaths each quarter (7146/year) and 149 potential OD each quarter (596/year), resulting in a potential OD ratio of 7.1-9.3% (mean 8.3%). Among potential OD the recognition by doctors was high (97-100%, no trend), but consultation of the Donor Register and requests of the relatives did not increase and fluctuated between 84-94% and 93-97% respectively. Among donors without objection in the DR the consent rate of relatives fluctuated considerably between 40-60% (mean 49%, no trend). Final conversion rate did not increase and fluctuated between 26-40% (mean 32%). Differences between regions and types of hospitals will be presented at the meeting.
Conclusion: Donor indicators in the ICU between 2007 and 2010 show that donor recognition is almost optimal and consultation of the DR as well as requesting relatives is not improving. Because the refusal rate of relatives, the main reason of donor loss, fluctuates considerably, it will be difficult to evaluate the projects in the regions to show any positive effect. Further details of 2011 will be expected in March 2012.

Follow - up van obese nierdonoren

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Inleiding: In 2008 rapporteerden wij op dit congres over het verloop van het gewicht van obese nierdonoren (BMI > 30). De obese nierdonoren hadden bij de start van de donorscreeningprocedure gemiddeld een BMI van 33,2 (30,2-38,0), zij vielen voor de operatie af tot een BMI van 30,6 (29,3-33,9). 2-3 jaar na de donatie was de BMI echter weer gestegen tot 32,6 (29,1-38,5). Aangezien obesitas op de lange termijn tot gezondheidsrisico's kan leiden, gingen wij nu na of het gewicht van deze obese nierdonoren verder is toegenomen en of er aanwijzingen zijn voor nierschade of cardiovasculaire complicaties.
Vraagstelling: Hoe is het huidige gewicht van de obese nierdonoren die in 2004 en 2005 hebben gedoneerd en is er sprake van nierfunctieverlies, proteïnurie en/of cardiovasculaire complicaties?
Methode: Prospectief vervolgen van obese nierdonoren die in 2004 in 2005 hebben gedoneerd.
Resultaten: In 2004 en 2005 hebben in totaal 12 obese donoren hun nier gedoneerd op een totaal aantal van 96 donoren. Het betrof 9 mannen en 3 vrouwen. Hun gemiddelde leeftijd is nu 57 jaar (31-75). 6-7 jaar na de donatie was de BMI 33,2 (29,4-40). Van de 12 obese nierdonoren waren er 2 in gewicht afgevallen in vergelijking met het gewicht vóór de donatie, de overigen waren verder aangekomen.Bij allen was het serum kreatinine 6-7 jaar na de donatie stabiel in vergelijking met de follow-up in 2007. 8 van de 12 obese nierdonoren hadden hogere RR dan 120/80 (dynamap), 5 van de 12 gebruikten antihypertensiva: 3 nierdonoren twee, 2 nierdonoren drie middelen. Bij 1 nierdonor werd proteïnurie en albuminurie vastgesteld 7 jaar na nierdonatie. Bij de overige 11 was dit niet het geval. Eén nierdonor had angineuze klachten, 1 nierdonor kreeg een hartinfarct waarvoor PTCA met plaatsing van 2 stents.
Conclusie: 83% van de obese nierdonoren zijn 6 tot 7 jaar na de nierdonatie verder aangekomen in gewicht. Alhoewel 67 % een verhoogde RR heeft is er slechts bij 1 van de 12 proteïnurie aanwezig en is bij alle 12 de nierfunctie, gemeten aan de hand van het serum kreatinine, stabiel gebleven. Bij 16% zijn cardiovasculaire complicaties opgetreden.

Psychological wellbeing of unrelated living kidney donors: before & after donation

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Background: The aim of this study was to expand upon and improve the analysis of our previous study, examining the level of psychological complaints before and after unrelated living kidney donation and the demographic characteristics associated with change in complaints.
Method: 57 unrelated living kidney donors completed the Symptom Checklist (SCL-90) before (2-13 months) and after (3-42 months) donation. Self-reported experiences of the donation, socio-demographic and procedural characteristics were reported.
Results: At group level, average total scores were compared with Dutch norm scores and were classified into 7 categories from very low to very high. Mean psychological complaints before (M=111.8) and after donation (M=121.8) fall in the below-average and average categories respectively. To investigate changes in scores over time at the individual level, we grouped predonation scores into low scorers (very low-average) and high scorers (above average-very high). Before donation 41 donors were low scorers and 16 were high scorers, after donation 33 were low scorers and 24 high scores. Of the predonation low scorers, 12.2% showed a decrease in category between pre- and postdonation, 41.5% remained in the same category and 46.3% showed an increase. From the predonation high scores, 25% showed a decrease in category, 37.5% remained in the same category and 37.5% showed an increase. Donors who experienced minor medical complications (n=15) were more likely to report an increase in complaints after donation ($p<.05$). No other medical or socio-demographic characteristics were related to the pre- or postdonation score, or to the change in score after donation and predonation score did not predict an increase ($p=.69$) or a decrease ($p=.25$) in the score.
Conclusion: At the group level, our findings are consistent with our previous study. At the individual level, we see fluctuations in psychological complaints of many (60%) living unrelated donors. Since minor medical complications of the donation procedure were associated with an increase in psychological complaints, health care professionals should be aware of this association when educating and supporting unrelated living kidney donors. However, observed increases may also be caused by underreporting before donation in an attempt to pass the screening. Whether the fluctuations are attributable to emotional instability or the donation process remains unclear and requires further research.

The Clinical Relevance of Serum Gamma Glutamyl Transpeptidase in Liver Transplant Recipients: A Different Role at Different Time Points

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Background: Gamma glutamyl transpeptidase (GGT) is a cell membrane bound enzyme that plays a key role in the synthesis and degradation of the anti-oxidant glutathione. In large epidemiological studies in the general population, chronically elevated serum GGT has been associated with increased cardiovascular mortality. After liver transplantation (LT), serum GGT is usually transiently elevated. We have noted that serum GGT can be elevated in other critically ill patients as well. The clinical significance of elevated GGT in LT recipients or other critically ill patients, however, is unclear. The aim of this study was to determine the clinical relevance of serum GGT levels in LT recipients early or long-term after transplantation.
Methods: A consecutive series of 522 adult patients who underwent LT between 1990 and 2009 were included in this study. Changes in serum GGT levels over time were compared with changes in serum markers of hepatobiliary injury: ALT and AST. In addition, we compared GGT levels in short-term (90 days) and long-term (3 years) survivors and non-survivors.
Results: After LT, serum GGT levels gradually increased, reaching a peak at day 7, and slowly normalized thereafter. This pattern is different from that of hepatocellular injury markers AST and ALT, which have a peak immediately after LT and a rapid normalization thereafter. Serum GGT levels at day 7 were significantly higher in patients who were still alive at day 90, compared to those who did not survive more than 90 days (median [IQR], 273 U/l [160-713] vs 164 U/l [80-213], $p<0.0001$). In sharp contrast with this, serum GGT levels at 6 months after LT were inversely associated with 3-year survival: the higher the GGT level, the lower the survival.
Conclusion: Serum GGT levels early after LT are significantly higher in 90-day survivors compared to non-survivors. In contrast with this, but in accordance with the general population, an elevated GGT at 6 months after LT is associated with lower 3-year survival. These findings may be explained by the key role of GGT in glutathione metabolism by viewing GGT as an acute marker of an appropriate hepatic response in the early recovery phase after LT and a chronic marker for chronic oxidative stress and increased mortality in the long-term.

Robot-assisted live kidney donation

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Background: Laparoscopic donor nephrectomy has become the gold standard to procure kidneys in live donors because of less surgical trauma and subsequently less pain, shorter convalescence time and superior quality of life as compared to open approaches. Recently, we expanded our surgical armamentarium with the da Vinci robot. The advantages of the da Vinci robot are: 560-degrees rotatable instruments, the use of high definition 3D-technology, an enlarged image, the computerized corrections of undesirable vibrations and an improved surgeons' comfort. We evaluated the results of the first 18 left-sided da Vinci-assisted donor nephrectomies.
Methods: From December 2009 until December 2011 eighteen donors have been operated using the da Vinci Surgical System. Inclusion criteria were a body mass index lower than 25 and a left-sided kidney with a single artery. Data were collected prospectively and compared with donors (1:2) extracted from our laparoscopic donor nephrectomy database.
Results: Baseline characteristics were similar in both groups. There were no significant differences in blood loss (100 vs. 100 ml, p=0.60), warm ischemia time (4.5 vs. 4.5 min, p=0.97), length of hospital stay (3 vs. 3 days, p=0.68) and increase in serum creatinin (35 vs. 36 µmol/l, p=0.73). The operating time of the da Vinci donor nephrectomy was significantly longer than the laparoscopic donor nephrectomy (247.5 vs. 226.5 min, p=0.04). There were no surgical complications or conversions in both groups. Surgeon comfort was highly appreciated in the da Vinci group.
Conclusion: Robot-assisted live donor nephrectomy seems a safe and feasible procedure without additional risk of postoperative complications. A steep learning curve was observed in the da Vinci group. However, further studies are required to establish the safety, efficacy, benefits, and limits of this technique.

Management of anastomotic and non-anastomotic biliary strictures after pediatric liver transplantation

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Background: Post transplantation biliary strictures (BS) are reported in 5-15% of the pediatric liver transplant patients. They are managed by either non-surgical treatment (NST) or reconstructive surgical treatment (ST). Currently it is not possible to predict if patients are more likely to respond to NST or will need surgical intervention regardless of NST. Therefore the aim of this study was to evaluate in a pediatric liver transplant population outcome and predictive factors for the failure of NST for BS.
Methods: We retrospectively studied the prevalence, management and complications of BS after pediatric liver transplantation in the period between January 1990 and June 2009. All biliary imaging studies were systematically reviewed and classified in a blinded manner. Successful NST was defined as recovery of cholestatic biochemistry, without the necessity for ST or retransplantation. Risk factors analyzed in relation to treatment outcome included recipient, transplantation, and treatment related variables, as well as biliary stricture type and severity.
Results: A total of 233 liver transplantations were performed in 185 children. Biliary strictures were reported in 34 grafts (14.6%). Solitary anastomotic strictures (AS) were found in 14 grafts (6.0%). 20 grafts (8.6%) showed signs of nonanastomotic strictures (NAS) of which 7 grafts (35%) had severe NAS. Of the patients with BS 25 (75%) were primarily treated with NST. In 6 cases (24%) the NST was successful. NST was more likely to fail in patients with severe stricturing. None of the other analyzed variables was associated with higher risk of failure of NST. During a median follow-up of 8.9 years (range 0.9-18.5) no mortality or severe complications occurred after NST and all minor complications (13 patients, 54%) could be treated effectively. In 14 cases reconstructive surgery was performed and 8 patients needed retransplantation, including 2 after ineffective ST.
Conclusion: NST can be a safe and successful therapy, however only in a small number of patients. In 75% of the children in our transplant group surgical intervention was inevitable. Therefore surgical intervention in an early stage could spare these children the complications and impact of NST. We conclude that NST is not an overall effective but safe procedure for the treatment of BS after pediatric liver transplantation. Since predictors for successful NST are still not available, in our opinion, NST remains the primary therapeutic modality.

The role of perirenal and intra-abdominal fat mass in laparoscopic donor nephrectomy

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Background: The exact relation between Body Mass Index (BMI) and outcome of laparoscopic donor nephrectomy (LDN) is unknown. A recent meta-analysis showed that a high BMI does not correlate with perioperative complications. Perirenal and intra-abdominal fat burden may have a stronger correlation with perioperative complications and long-term results of LDN. Therefore, we measured the amounts of perirenal and intra-abdominal fat of live kidney donors and correlated these with outcome of LDN. Methods: We analysed 62 CT-scans of live kidney donors that underwent LDN in our center between 2004 and 2010, and measured: Perirenal fat volume (cm3) (PFV), distances in mm of perirenal (PRF, from Gerota to the kidney), abdominal (IAF, from the aorta to the linea alba) and subcutaneous fat (SCF, from skin to abdominal wall. The PFV was calculated selecting the perirenal fat (in Gerota) from the most cranial to the most caudal slice of the CT-scan. All these measurements were correlated with each other, with donor BMI, and with the following outcome parameters of LDN: Warm ischemia time, operation duration, estimated blood loss, complications, length of stay, decrease in glomerular filtration rate (1 year) and increase in 1 year-serum creatinine using bivariate correlations. Because of the limited number of available CT-scans, we repeated the analyses on a larger group of donors (n = 480) with pre-operative MRI-scans. Results The PFV did not correlate with any of the outcome measures, neither did the PRF, IAF and SCF. Remarkably, MRI-scan analyses demonstrated that IAF correlates significantly with operation duration, estimated blood loss, conversion, BMI and differences in GFR and 1 year serum creatinine.
Conclusion: In a large cohort of live kidney donors, we have demonstrated that IAF is strongly correlated with outcome of LDN whereas perirenal fat is not. We conclude that the measurement of IAF may be a valuable tool to predict peri- and postoperative outcome of LDN.

Regional differences in dialysis and (pre-emptive) transplantation

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Renal transplantation is the optimal treatment modality for most patients with end stage renal disease (ESRD). As the concept of equity of care is important, we wondered how the transplantation rates relate to the numbers of patients with renal replacement therapy (RRT) (hemodialysis, peritoneal dialysis or kidney transplantation), across the 28 municipal health service (GGD) regions in The Netherlands. RRT data were collected from the Dutch Renal Replacement Registry, the number of inhabitants for each GGD region were collected from the RIVM. For each GGD region, we calculated the number of inhabitants under and above the age of 70 years with RRT (the RRT-prevalence) at the beginning of 2010 and the new RRT patients (RRT-incidence) in 2010. In addition we calculated the number of patients that underwent transplantation in 2010, either preemptive or after dialysis treatment had been initiated. In different GGD regions,the RRT use varies from 556 till 1136 per million inhabitants. The proportion of patients living with a functioning transplant in this RRT-group varies from 60% till 80%. In 2010 the pre-emptive transplantation proportion among the incident RRT patients younger than 70 years (the transplantable patients) varies from 0% to 33%. The number of transplantations after dialysis divided by the total number of dialysis patients at the beginning of 2010 varies from 8% till 23%.The number of pre-emptive transplantations in the total number of transplantations ranges from 0% to 50% The share of pre-emptive transplantations among the total number of living donor transplantations ranges from 0% till 67%. In the group of patients of 70 years of age or older the number of patients on RRT varies from 951 till 2096 per million inhabitants, of which 1-21% are living with a functioning transplant. The vast majority of older patients start and stay on dialysis, although in some regions pre-emptive transplantations are carried out, with a maximum of 9% of the incident older patients. A maximum of 7% of the number of prevalent older patients was transplanted after the start of dialysis treatment.
Based on the analysed data we conclude that there are remarkable regional differences in the use of dialysis and (pre-emptive) transplantation. Reasons for differences should be subject of further research.

The effect of low and ultra-low dosages Thymoglobulin on T, B, and NK cells in kidney transplant recipients

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Introduction: Rabbit Anti-Thymocyte Globulin (r-ATG) is a polyclonal antibody preparation, used to prevent and treat acute rejection episodes after organ transplantation. However, despite more than 40 years of clinical use, the optimal dose of r-ATG is still not defined. To find a better balance between efficacy and infectious complications, we embarked on a controlled study and monitored the effect of low and ultra-low dosages Thymoglobulin (Genzyme) on peripheral T, B, and NK cells.
Patients and methods: Kidney transplant recipients received either 0.5 mg/kg, 1.0 mg/kg or 2.0 mg/kg on the first 3 consecutive days post-transplantation. A total of 40 patients were enrolled, including 11 controls. All patients were treated with Prednisolon, Advagraf (Astellas) and Mycophenolate Mofetil (Roche). T (CD3+), B (CD19+) and NK (CD16+56+) cells were analysed by flowcytometry. Baseline cell counts were compared to forty age and sex matched healthy persons. Post-transplantation cell counts of the 3 Thymoglobulin groups were compared to the 11 control patients, who received no Thymoglobulin.
Results: Absolute numbers of T, B, and NK cells were comparable in all patients pre-transplantation, but T and B cells were lower than in healthy persons ($p=0.007$ and $p=0.0003$). In the first week, T cells and NK cells were significantly lower in all Thymoglobulin groups compared to controls. B cells were not affected. At one month NK cells had returned to control numbers in all groups, while T cells had already recovered to control counts in the 0.5 mg/kg group. During follow-up, T cells in the 1.0 mg/kg group also returned to control values, but at one year the patients in the 2.0 mg/kg group still had significantly lower T cells ($p=0.03$). Patient and graft survival, rejection and infection incidence and renal function did not differ between groups.
Conclusion: Patients with end stage renal disease have significantly lower peripheral T and B cell counts than healthy persons. (Ultra-) low Thymoglobulin schedules deplete peripheral lymphocytes in a dose dependent way. In view of the duration of lymphocyte depletion an induction dose of 3 x 1.0 mg/kg Thymoglobulin might be optimal for kidney transplant recipients.

Intra-patient variability in tacrolimus trough concentrations and renal function decline in paediatric renal transplant recipients

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Background: High intra-patient variability in tacrolimus (TCL) exposure is a risk factor for allograft loss and late acute rejection. We hypothesized that a higher intra-patient variability leads to a faster decline in glomerular filtration rate (GFR) in paediatric renal transplant patients and that adolescents have a higher intra-patient variability due to poorer adherence .
Methods: We included 69 children aged 3.5-18 years who had undergone renal transplantation between April 1996 and May 2009 in two paediatric nephrology centres in The Netherlands. We analyzed TCL trough concentrations over a period of one year and calculated TCL trough concentrations variability using variability coefficient (VC). We investigated the correlation between the TCL trough concentrations variability and the decline in estimated GFR over two years (ΔeGFR).
Results: The median intra-patient variability in TCL concentrations was 30.1% (range 8.6-77.6) and the median ΔGFR after one year follow-up -2ml/min/1.73m² (range -55-68) and after 2 years -1ml/min/1.73m² (range -65-18). There was no correlation neither between VC and ΔGFR after one and two years of follow-up, nor between the patients' age and VC. Although children with late acute rejection had a higher VC (P= 0.045), their ΔeGFR did not differ significantly from the remainder of the study population.
Conclusions: We were unable to provide evidence that a high variability in TCL exposure leads to a faster decline in renal function, although children with late acute rejection have a higher variability in TCL exposure. Adolescents do not have a higher intra-patient variability in TCL trough concentrations than younger children.

Intact thrombin generation and decreased fibrinolytic capacity in patients with acute liver failure argues against routine prophylactic correction of coagulation prior to liver transplantation

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Patients with acute liver failure (ALF) have profound alterations in their hemostatic system. Per definition, these patients have an INR >1.5, which prompts many centres to prophylactically administer fresh frozen plasma prior to invasive procedures including liver transplantation. It has been well established that hemostatic potential in patients with cirrhosis is in a rebalanced status due to a concomitant decrease in pro- and antihemostatic drivers, and more and more centres accept that prophylactic correction of coagulation prior to invasive procedures is not indicated in these patients. The hemostatic changes in patients with ALF are similar, but not identical to the changes in cirrhosis and have not been studied in great detail. Here, we performed plasma-based overall assays of coagulation and fibrinolysis to examine the hemostatic status of patients with ALF. The thrombin generation capacity of plasma from patients with ALF sampled on the day of admission to the hospital was indistinguishable from that of healthy controls, provided thrombomodulin, the physiological activator of the anticoagulant protein C system was added to the test mixture. The capacity to lyse fibrin clots was profoundly impaired in patients with ALF on admission (no lysis in 73.5% of patients compared to 2.5% of the healthy controls), which was associated with decreased levels of the profibrinolytic plasminogen and increased levels of plasminogen activator inhibitor type 1, a prime regulator of fibrinolytic potential. The intact thrombin generating capacity and the hypofibrinolytic status persisted during the first week of admission. In conclusion, patients with ALF have a normal thrombin generating capacity and a decreased capacity to remove fibrin clots. These results contrast with routine laboratory tests such as the PT/INR, which are per definition prolonged in patients with ALF and suggest a bleeding tendency. These novel findings may have important consequences for the hemostatic management of patients with ALF. Specifically, prophylactic correction of coagulation by administration of fresh frozen plasma should be performed cautiously.

Novel high-throughput method to study the influence of immune suppressive medication on human DC-induced naïve CD4+ T cell polarization in an autologous setting

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Polarization of CD4+ T cells has a essential role in the induction of immune responses against the allograft after transplantation. Dendritic cells (DC) play a crucial role in the induction of these post-transplantation immune responses, but there is limited information in the human setting about the factors which are able to modulate these CD4+ T cell responses. We developed a miniaturized, autologous co-culture system with a unique multi-faceted read-out tool, allowing a high-throughput screening of the influence of exogenous factors on autologous T cell polarization. The combination of quantitative RT-PCR coupled to a protein multiplexing platform allows monitoring of the transcriptional events associated with T cell polarization and matching these profiles to their cytokine secretion. This system can be applied to assess the influence of exogenous factors on T cell polarization as demonstrated by our observation that the amount (and not only the presence) of IL-12 production correlates with the magnitude of the Th1 response. This was evidenced by a higher expression of Th1 signature genes (Tbet, IFN-γ and TNF-α) and a higher secretion of Th1 cytokines in presence of increasing doses of IL-12. At present we are studying whether this study can provide more insight in the exact function of immunomodulatory medication which is given after kidney trans-plantation. Using this system we showed that rapamycin does not prevent the transcriptional induction of Tbet, the master regulator of Th1 polarization. However, it does repress the secretion and transcription of IFN-gamma, the main effector cytokine of Th1 cells. It remains to be established whether CD4+ T cells exposed to rapamycin during their interaction with DC regain their effector function when rapamycin is washed away.
In conclusion, we have generated a novel high-throughput tool to study how exogenous signals influence CD4+ T cell skewing in autologous setting. This system will not only provide valuable insight into the exact mechanisms by which immunosuppressive drugs alter the immune response, but it will also be of added value for other researchers in the field.

Changes of plasma microRNAs in heart transplantation patients do not reflect microRNA changes in the CAV vessel wall

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Background: Chronic rejection is the most important limiting factor for long term survival after heart transplantation (HTx) due to cardiac allograft vasculopathy (CAV). CAV is characterised by a concentric hyperplasia of the neointimal layer of the coronary vessels. Recently the importance of microRNAs (miRs) was discovered in multiple vascular diseases. MiRs are small RNAs that regulate translation of mRNA into protein. Beside the presence of miRNAs inside cells, they are also present in blood.
Goal: Determine changes in miR expression in coronary vessel wall and plasma of HTx patients at different stages of CAV development to determine their potential biomarker and/or therapeutic role.
Methods: Plasma of CAV patients was analyzed at two time points (6 and 52 weeks) after HTx. At each time point two plasma pools of n=3 were included. Pooled plasma of healthy individuals was used as control. CAV vessels were obtained after autopsy and CAV stage was determined. The intimal layer was isolated by laser microdissection. MiR expression of plasma and vessel wall was determined using miR arrays, measuring up to 754 miRs. Criteria for miR selection were: (1) fold changes >2x, (2) Cq-values <32 and (3) the miR should be detectable in all samples.
Results: The arrays done on plasma samples show a changed miR expression pattern between 6-, 52-week and control plasma. Some miRs were clearly up- (miR-122) or down-regulated (let 7e) after HTx compared to control. In intimal layers of CAV vessels miR up- (miR-21) and down-regulation was found to a max of 100x (miR-197). Some miRs fluctuated in expression over the CAV stages (miR-484). Only one miR was found in plasma (up-) and in intimal tissue (down-regulated) of CAV patients.
Conclusions: The difference between control and HTx patient plasma and tissue suggests that miRs in CAV patients do indeed alter. However, the changes in plasma miRs do not reflect miR changes in the CAV vessel wall. These latter MiRs might be considered potential therapeutic targets.

Reconstitution of T cells after rATG induction therapy in kidney transplant patients is the result of homeostatic proliferation and not of thymopoiesis

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Introduction: Rabbit antithymocyte globulin (rATG) induction therapy is followed by peripheral immune reconstitution. To define the biology of this phenomenon we studied two key mechanisms involved in the reconstitution of the peripheral CD4 and CD8 T cell pool: thymopoiesis and homeostatic proliferation driven by STAT5 (Signal Transducer and Activator of Transcription) activating cytokines.
Material and Methods: Adult patients were treated with rATG (3 x 2mg/kg/day, n=8) or anti-CD25 antibody basiliximab (day 0, 4, 20mg, n=8) induction therapy in combination with tacrolimus, mycophenolate mofetil (MMF) and steroids. Flow cytometric analyses were performed to study Ki67, a molecular marker of proliferation, in combination with CD31, the marker of recent thymic emigrants (RTEs) in naïve T cells (CD45RO-CCR7+) and regulatory T cells (CD4+FoxP3+CD127-). Ki67 expression was also analyzed in central memory (CD45RO+CCR7+), effector memory (CD45RO+CCR7-) and EMRA T cells (CD45RO-CCR7-).
Results: In our rATG treated patient population we found no evidence of increased thymopoiesis. At one month after transplantation the percentage of RTEs (Ki67-CD31+ ^{thymic}naïve T cells), of both CD4 and CD8 T cells, was comparable between rATG and basiliximab treated patients. Also, we found no evidence for increased homeostatic proliferation of the Ki67+CD31- ^{central} naïve CD4 and CD8 T cells, responding upon self-antigens in rATG treated patients. In contrast, the CD4/CD8+Ki67+CD31+ ^{central} naïve T cell subset, in which proliferation depends on homeostatic cytokines, all Ki67+ memory CD8 T cell subsets, the Ki67+ CD4 central memory T cell subset and Ki67+ regulatory T cells were proportionally higher in the rATG patient group compared to the basiliximab group ($p< 0.03$ for all subsets). Our findings were supported by whole blood STAT5 analysis that demonstrated elevated levels of phosphorylated STAT5 in peripheral naïve and memory T cells of the rATG group 1 month after depletion but not in the basiliximab group ($p<0.04$).
Conclusion: Our results show that rATG has no effect on thymic output. Homeostatic proliferation and not thymopoiesis is the main mechanism by which the peripheral CD4 and CD8 T cell pool reconstitutes.

Infusion of autologous mesenchymal stem cells induces a rapid immunomodulatory response

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Introduction: Mesenchymal stem cells (MSC) have potent immunosuppressive properties *in vitro* and are therefore considered as a potential therapy in organ transplantation. It is however questionable whether the *in vitro* effects of MSC are analogous to those present after infusion of MSC *in vivo*. Data indicate, for instance, that MSC are undetectable in the recipient 24 hours after infusion. In the present study we infused MSC in healthy mice and examined the effect on concentrations of inflammatory proteins in the circulation.
Methods: Cultured syngeneic MSC (500,000) of passage 4-6 were infused via the tail vein of C57Bl/6 mice. After 4, 20, 68 hours and 9 days animals were sacrificed and serum collected. Concentrations of 34 chemokines, cytokines, and acute phase proteins were analyzed by Milliplex bead arrays.
Results: All animals tolerated the MSC infusion well. Apart from a reduced spleen size (50% at day 9) no macroscopic effects of MSC infusion were observed. Four hours after treatment with MSC increased serum levels of IL6 (5-fold) and the acute phase protein SAP (2-fold) were observed. Furthermore, the neutrophil attractant CXCL1 and neutrophil activator G-CSF were increased 3 and 4-fold, respectively. Between 20h and 68h after MSC infusion concentrations of these proteins returned to basal levels. In contrast, levels of pro-inflammatory IL1α and MIP2, which is produced by activated macrophages, dropped up to 6 and 30-fold 20h and 68h after MSC infusion compared to controls. Concentrations of all cytokines and chemokines examined returned to basal levels at day 9.
Conclusions: Intravenous infusion of autologous MSC induces an acute phase response within 4 hours after infusion, which subsides after 20 hours when signs of immunosuppression can be observed. These results are of importance for timing of potential MSC therapy in experimental and clinical transplantation studies.

The circulating platelet count is not dictated by the liver, but may be determined in part by the bone marrow – analyses from human liver and stem cell transplantations

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The circulating platelet count varies considerably between individuals, but within a single individual the platelet count is remarkably stable over time. Although genetic variation has been shown to affect platelet count, the precise mechanisms that control maintenance of a given platelet count within an individual has not been established. By examining changes in platelet counts in patients undergoing liver transplantation or stem cell transplantation, we tested the hypothesis that the liver, which is the primary site of synthesis of thrombopoietin, or the bone marrow, which harbours megakaryocytes from which platelets are produced, controls the circulating platelet count within a single individual. We compared the platelet count prior to and after liver transplantation in more than 250 patients transplanted for familial amyloidotic polyneuropathy (FAP). In contrast to most patients undergoing liver transplantation, patients with FAP have completely normal liver function and histology (i.e. no fibrosis or cirrhosis) and thus normal platelet counts prior to transplantation. Furthermore, we compared platelet counts in 89 living liver donors with the platelet count in the recipients of these grafts after transplantation. Finally, we compared the platelet count in 105 donors of hematopoietic stem cells with the platelet count in the recipients after transplantation. We observed an association between the platelet count prior to and after 3 or 12 months after liver transplantation in patients with FAP ($r=0.48$, $p<0.0001$ at 3 months, $r=0.39$, $p<0.0001$ at 12 months), whereas the platelet count in a living liver donor did not correlate to the platelet count in the recipient at 3 or 12 months after transplantation ($r=0.16$, $p=0.26$ at 3 months, $r=0.11$, $p=0.30$ at 12 months). In contrast, the platelet count of related donors of hematopoietic stem cells correlated to the platelet count in the donor at least 6 months after transplantation ($r=0.25$, $p=0.011$). Taken together, these results suggest that the liver is not involved in maintenance of the circulating platelet count, whereas the bone marrow does appear to play a role in this process.

Subsets of Alternatively Activated Macrophages show differential capacity to produce Reactive Oxygen Species

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Introduction: Recently we have shown that M-CSF generated-Mph2 have a high ROS producing capacity, and that these Mph2 can suppress T cell responses in a ROS-dependent manner. Anti-inflammatory APC may be instrumental in down-regulating T cell responses against allografts. However, it is know that Mph display a high plasticity and different Mph2 subsets have been identified, raising the question whether they have all similar ROS-producing capacities, and what the contribution is of ROS in APC-T cell interaction.
Methods: Monocytes (Mn) were differentiated into macrophages with either M-CSF (Mph2), IL-4 (Mph2a), or IL-10 (Mph2c). The ROS producing capacity of these Mph was tested by flow cytometry, as well as mRNA and protein levels of two NADPH oxidase (NOX2) proteins. The effect of catalase, a specific inhibitor of the most stable ROS, hydrogen peroxide (H2O2→H2O), on Mn and the Mph2 subsets was investigated.
Results: Upon PMA stimulation, Mph2 and Mph2c showed a high ROS producing capacity, whereas only low ROS production was observed in activated Mph2a. Also fully differentiated Mph2 cultured for a short period in IL-4 showed a reduced ROS producing capacity, suggesting an important role for IL-4 signaling pathways. Mph2a expresses lower mRNA and protein levels of NOX2 protein $gp91^{phox}$ compared to Mph2 and Mph2c, whereas no differences were observed for $p47^{phox}$. Catalase did not show a direct effect on activated T cells, however proliferation was enhanced by catalase when T cells were stimulated with Mph2c. Catalase did not affect HLA-DR or CD86 levels on Mn and Mph2 subsets, however incubation with catalase increased the production of IL-6, IL-10, IL-12p40, and TNF-α by these cells.
Conclusion: The ROS producing capacity is dependent on Mph type, Mph2a has a low ROS production, whereas Mph2 and Mph2c have a high ROS producing capacity. Mph2a expresses low $gp91^{phox}$ levels, possibly explaining the low ROS producing capacity. Catalase has no direct effect on the T cell, but does affect the APC by increasing the cytokine production of Mn and Mph2 subsets. Catalase increases the T cell proliferation with a ROS-producing Mph, indicating a role of hydrogen peroxide in the APC-T cell communication.

The calcineurin inhibitor tacrolimus inhibits NF-κB activation in effector and regulatory T cells

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Background: The calcineurin inhibitor, tacrolimus (TAC), inhibits the protein phosphatase activity of calcineurin, leading to suppression of the nuclear translocation of NFAT and subsequent T cell activation. Apart from NFAT also the transcription factor NF-κB plays a key functional role in T cell activation. Therefore, blockade of the NF-κB activation cascade by immunosuppressive drugs may prevent immune activation. Here we studied whether TAC in primary T cells interferes in NF-κB activation. Sotrastaurin, a protein kinase C blocker which inhibits NFKB phosphorylation, was used as positive control in this study.
Methods: After anti-CD3/CD28 activation of CD3+ T cells from healthy volunteers NF-κB phosphorylation (p65, S529) and its downstream target TNFα protein were measured by flow cytometry in CD4+CD25+CD127+ effector T cells, CD8+ T cells and in CD4+CD25+CD127- regulatory T cells (Tregs) (n=6) in the absence and presence of TAC 10 ng/mL, sotrastaurin 500nM (positive control), and everolimus 200 ng/mL (negative control). In addition, by Q-PCR the mRNA expression level of NF-κB (NF-κB1, p102) in CD3+ T cells was determined.
Results: Anti-CD3/28 activation induced NF-κB phosphorylation in 33.2% (95% CI 25.6-31.1) of CD4+CD25+CD127+ effector T cells, in 30.4 % (95% CI 25.6-31.1) of CD8+ T cells, and in 21.4 % (95% CI 15.8-27.0) of CD4+CD25+CD127- Tregs. Sotrastaurin inhibited NF-κB activation in effector T cells by 92.9% ($p<0.01$ vs. no drug), in CD8+ T cells by 89.7% ($p<0.01$), and in Tregs by 86.4% ($p<0.01$), while everolimus did not affect this activation pathway. Surprisingly, TAC 10 ng/mL also inhibited NF-κB phosphorylation, by 65.1% ($p<0.01$) in effector T cells, by 45.5% ($p<0.01$) in CD8+ T cells, and by 44.5 % in Tregs ($p<0.05$). TAC also inhibited mRNA transcription of NF-κB. Moreover, TAC and sotrastaurin also suppressed TNFα protein expression in the studied T cell populations (all $p < 0.01$) confirming the inhibition of NF-κB signaling by these agents.
Conclusions: This is the first study to show the novel suppressive effect of TAC on the NF-κB activation pathway and its responsive effector molecules in T cells.

Donor-derived tubular epithelial cells induce class I restricted allo-reactivity in kidney transplant recipients

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Introduction: Although it is known from in vitro studies that human renal tubular epithelial cells (TEC) have stimulatory capacities, their effect on alloreactivity in organ transplant patients is unknown. In the present study, the immunostimulatory effect of donor TEC on recipient anti-donor T-cell reactivity was examined by analysing the function and characteristics T cell subsets before and after clinical kidney transplantation.
Material and Methods: Recipient T-cell reactivity against donor TECs was investigated in pre-transplant and post-transplant co-culture system and trans-well experiments of 6 living-kidney donor-recipient pairs. For TEC/PBMC co-culture, recipient PBMCs vs donor TEC (allogeneic co-culture) and donor PBMCs vs donor TEC (autologous co-culture) were used. By flow cytometry the proliferative response of CD3, CD4, CD8 naïve (CD45RO- CCR7+), effector memory (CD45RO+CCR7+), central memory (CD45RO+CCR7-) and effector memory RA (EMRA, CD45RO-CCR7-) was measured.
Results: After stimulation by TEC an allogeneic response was measured in the CD8+ T-cell subset, but not in CD4+ T-cells. No autologous induced CD8+ T-cell proliferation was found. The proliferative response in the pre-transplantation co-culture was 5.7% ± 1.2 and in the post-transplantation co-culture a response of 6.6% ± 3.1 was found. In addition, transwell experiments revealed that the TEC induced CD8+ T-cell proliferation was cell-cell contact dependent. Co-cultured CD8+ T-cells also expressed the activation marker CD69. Additionally, the vast majority of the CD8+ responding T-cells where of the memory phenotype, effector memory T cells (47%), EMRA (25%) and of central memory T cells (13%). No proliferation of the naïve CD8+ T-cell was found.
Conclusion: Donor-derived TECs induce a class I restricted effector memory T-cell response in kidney transplant recipients.

EULOD: The EU-funded Project on Living Organ Donation in Europe

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Introduction The EULOD project received a grant of €1.100.000 from the European Commission to establish an inventory of living donation practices, explore and promote living donation as a way to increase organ availability, and develop tools that improve the quality and safety of living organ donations in Europe. 11 institutions from 10 European countries are involved. The project runs from April 2010 to March 2012. Methods: EULOD consists of two research teams. The first team focuses on living unrelated donation practices in Europe. The second team works on legal restrictions and safeguards for living donations in Europe. EULOD is supported by the European platform on Ethical, Legal and Psychosocial Aspects of Organ Transplantation and the European Society for Organ Transplantation. Results: A survey was sent to transplant centers in 44 European countries. The response rate is 90%. The survey investigates the prevalence of living donation in Europe, the types of living donations and screening processes. This study will result in a manuscript on living organ donation practices in Europe. Second, focus groups have been conducted in 4 countries to gain deeper understanding of possible barriers to living organ donation. These data are subjected to a normative analysis and used for the development of recommendations in support of living organ donation in Europe. Thirdly, an analysis of European living organ donation laws has been conducted. This study will result in a paper on the normative arguments that dominate the policy discussion on restrictions of the donor-recipient relationship in unrelated living donor transplantation. The second gives a comparative legal analysis on living organ donation laws in Europe, focusing especially on the existing procedural safeguards for the living donor. Both articles will result in a best practice proposal on legal restrictions and safeguards for living unrelated donation. Finally, organ trade legislation was analyzed and organ trafficking cases were collected. This study will result in recommendations to improve effectiveness of anti-organ trafficking legislation. Conclusion: The six scientific papers will be published in April 2012 on www.EULOD.org. The consortium intends to contribute to European policy needs, including the increase of organ availability, making transplantation systems more efficient and accessible and improving the quality and safety of organ donation and transplantation in Europe.

The role of the living donor coordinator involving the ABO-incompatible kidneytransplantation program at the University Hospital Groningen

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Background: In November 2008 our hospital started with the ABO-incompatible kidney transplantation program according to the Swedish-protocol.The living donor coordinator (LDC) plays an important role in starting and continuing. She is the spider in the web.This abstract gives an overview of the role of the LDC.
Goals of the project actions: The program started because of the growing waiting list for post-mortem kidney transplants and because a large number of patients who bring a living kidney donor ABO-blood type incompatible and are not matchable in the Dutch exchange program. The role of the LDC is crucial.
Interventions: The LDC works together with the physicians and other workers of the transplantation team. The role of the LDC can be divided in 3 phases: the pre-transplant phase (out clinic), the transplant phase (in clinic) and the post-transplant phase (in and out clinic).Phase 1, the LDC and transplant-nephrologists inform the patient and donor about the inclusion-criteria and pro's and con's of the transplantation/donation. The LDC remains the main contact throughout the process for patient and donor. When the inclusion-criteria are met, the transplant is put on track. The LDC prepares, plans, organizes. It is an active and responsible role, being there for patient /donor, contacting the physicians and other disciplines, preparing for the multi disciplinary meeting. Phase 2, the LDC has a more guiding role, checking if all is going well, can the transplantation/donation proceed. Also after transplan-tation/donation. Phase 3, the care and coordination of the donor has priority, the patient is still admitted. The LDC contacts the donor, check's the patients well-being, plan's follow-up and evaluation.
Outcomes: From November 2008 until December 2011 13 ABO-incompatible kidney transplants were performed. The role of the LDC is crucial throughout the process is to maintain the continuity for donor/patient, physicians and other workers, in and out of clinic. The main goal is to maintain and improve the donor and patient care and QoL in the ABO-incompatible kidney transplant program. Research, follow-up, monitoring health of donor and patient are necessary.

Fetal Maternal microchimerism and its role in stem cell and renal transplantation

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During pregnancy trans placenta traffic occurs of maternal and fetal cells, which leads to life long mutual microchimerism. This results in the induction of immune and regulator memory T cells in the mother against the Inherited Paternal Antigens of her child. Decades after birth a few hundred of these microchimeric memory cells are able to prevent relapse of leukemia after a maternal stem cell transplant to her child. Similar cells are also present in Cord Blood (CB) and can after a hemopoietic stem cell transplantation (HSCT) with CB prevent relapse of acute leukemia). Likewise the fetus recognizes from the fourth month onwards the Non Inherited Maternal Antigens (NIMA) on the chimeric maternal cells, which enter its circulation and induce immune and regulator cells against the NIMA. After CB transplantation these immune and regulator cells directed against the NIMA can improve neutrophil recovery, reduce relapse of Myeloid leukemia and as a result improve transplant related mortality in HLA mismatched patients, if these mismatched antigens are identical to the NIMA. In that case the mismatched antigens become"acceptable mismatches". The role of NIMA matching in organ transplantation has been well established: as acceptable mismatches regarding antibody formation, for HLA-A mismatched antigens from post mortal kidney donors and for the living donor setting. However the possible impact of anti IPA microchimeric immune cells has so far not been studied. These cells could however explain why maternal renal allografts have a worse prognosis than NIMA mismatched haploidentical sibling grafts. The possible impact of these findings on the selection of living unrelated kidney donor recipient pairs will be presented.

Are increasing numbers of living kidney donors the consequence of a more liberal acceptance policy?

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Introduction: During the past 10 years the number of living kidney donors (LKD) has increased considerably. In our hospital a mean of 40 LKD (41% of kidney transplantations) underwent a nephrectomy each year between 2000 and 2004, increasing to 55 LKD (50% of transplantations) each year between 2005 and 2009. We investigated whether this increase was caused by a more liberal acceptance policy.
Methods: Only those patients who wished to proceed as potential LKD after an initial informative visit were included. In our NOTR database we analyzed the data of 732 potential LKD who visited the nephrologist between 2000 and 2009.
Results: In our cohort 53% was female, mean age was 50 (range 18 to 77) years and BMI 26 (range 16 to 42) kg/m^2. 117 of 732 LKD (16%) were refused as donor: reasons were insufficient renal clearance, diabetes, malignancy, proteinuria, multiple renal arteries or veins, asymmetrical renal function, psychosocial problems or combinations of these factors. In addition to primary refusal, another 95 of 732 LKD (13%) who were approved for donation never donated their kidney. Reasons were recipient related in 69 of 95 patients: the recipient died or could not receive a transplant because of other illnesses. For some recipients in a cross-over procedure another LKD was found and 19 recipients received a postmortal transplant. Donor related reasons were (16 of 95 patients): 8 potential LKD did not want to donate any longer, 5 had familial reasons and 3 could not give their kidney in a cross-over setting. Mixed reasons were seen in 10 of 95 patients: donor and recipient decided to stop the procedure or contact between donor and recipient was lost. During 10 years of observation the mean percentage of the potential LKD which underwent a nephrectomy was 71%. In the period from 2000 to 2004 and from 2005 to 2009 this percentage was 74 and 69%, respectively.
Conclusion: With increasing numbers of LKD the percentage of potential LKD who eventually donated their kidney declined slightly. Therefore, acceptance policy for potential kidney donors in our hospital has not become more liberal throughout the past 10 years.

Timing of approach to discuss organ donation: the European jigsaw puzzle

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Purpose: The moment of asking consent for organ donation from the relatives is according to the Dutch law on organ donation, as in many other countries, only allowed *after* death of the potential donor. In case of non-heart beating donation Maastricht category III the relatives must however always be requested to donate prior to death of the patient. In practice, in The Netherlands in case of heart beating donation the family is also often approached before the formal brain death diagnosis is confirmed. This is due to practical considerations, the time-consuming additional ancillary test like EEG and apnoea are than only performed after consent for donation. It seems we are the only country where organ donation is requested before death. What is the practice in other European countries, are there differences in the moment of asking.
Methods: Four countries participated in our study, Spain, the United Kingdom, Sweden and The Netherlands. A literature study was performed to find out the differences in the law on organ donation and the legal consent systems. Local protocols were assessed to identify the different types of organ donation, including protocols for family approach. A questionnaire was conducted to inventory the practice of the moment of asking for organ donation and sent to a number of intensivists of the participating countries.
Results: In some hospitals in Spain families are approached for organ donation even before the potential donor is admitted to the intensive care unit. This is a recently changed practice. The reasons for this early approach are, changing of the profile of potential donors from young donors in car accidents to older donors with stroke, less available beds on the ICU, and financial aspects. In the United Kingdom organ donation is often discussed with the bereaved prior to a confirmed brainstem death. In Sweden there is more and more early approach with relatives, when discussing the meaningfulness of continuing intensive care treatment.
Conclusion: The preliminary results of our study reveal less differences in practice in the moment of asking between countries than expected. Families are approached to consent for organ donation prior to death confirmation in all participating countries, although this is against the law. The lack of sufficient intensive care beds plays an important role for this early approach. The final results will be presented at the congress.

The influence of ethnicity and socioeconomic factors on the outcome of kidney transplantation

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Background: In our previous study we showed that an accumulation of unfavourable clinical and socioeconomic factors precludes living donor kidney transplantation. In the present study we analyzed the influence of these factors on long term graft survival.
Methods: This retrospective study included all 1338 patients who received a kidney transplant between 2000 and 2011 in the Erasmus MC Rotterdam. Both clinical and socioeconomic variables were studied. Clinical variables were: recipient age, gender, ethnicity, original disease, re-transplants, ABO blood type, maximum PRA, previous treatment, transplantation year, donor age, gender and type (living or deceased), and HLA mismatches. Each recipient's post-code was linked to a post-code area information data-base, to extract socioeconomic information on: urbanization level, percentage non-Europeans in the area, income, and housing value. Chi square, ANOVA and univariate and multivariate Cox Proportional Hazards analyses were performed.
Results: Graft survival censored for death was significantly influenced by donor and recipient age, PRA max, HLA mismatches, and donor type. Graft survival uncensored for death was significantly influenced by recipient and donor age, transplantation year, donor type, PRA max. Socioeconomic factors and ethnicity did not have a significant influence on survival.
Conclusion: Though the access to living donor kidney transplantation is influenced by ethnicity and socioeconomic factors, these factors do not influence the prognosis once transplantation has been performed.

Health literacy among kidney transplant patients: a literature study

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Introduction: Recently performed research showed us that 56% of the patients were re-hospitalized within 1 year after kidney transplantation (median twice). We hypothesized that apart from medical issues patients might have difficulties in the understanding and use of information, because of a low health literacy (HL) level. HL is de patient's degree of capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. Our research question was: What is known about HL and kidney transplantation and is there a relationship between the level of HL and complications after kidney transplantation?
Methods: We performed a literature study on HL among chronically ill patient populations with a focus on kidney transplant recipients in particular. We searched in the following databases: Pubmed, Psycinfo and Cinahl. Search terms included combinations of health literacy, interventions, and kidney transplantation.
Results: We made a final selection of 22 articles, 12 about HL in general, 4 about HL and kidney transplantation/diseases, and 6 about HL and other chronic illnesses. Additionally, there were 3 publications from national organizations about HL. The level of low HL among kidney (transplant) patients varied, from 32% to 72%, according to 2 studies. Six studies assessing HL among chronically ill patients showed that low HL levels varied between 23% and 52%. Studies examining the relationship between HL and complications after kidney transplantation were not found. We detected 3 studies among heart failure and diabetes patients that were focused on improving self-management among low HL patients, which resulted in decreased hospitalization rates and death.
Discussion: We can conclude that little is known about HL and kidney transplantation or the relationship with complications. Transplant patients with low HL levels are probably vulnerable as of the complexity of the post transplant self-management regime. More research is needed to explore HL among kidney transplant patients and the relationship with complications.

The P-PASS and PDRI reviewed in a large European pancreas transplantation center

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Introduction: In 2008 the preprocurement pancreas suitability score (P-PASS) was introduced within Eurotransplant. A P-PASS<17 is believed to be significantly associated with higher graft survival compared to P-PASS≥17. In 2010 the Pancreas Donor Risk Index (PDRI) was developed within UNOS as a tool for prediction of survival after pancreatic transplantation. This model is yet to be validated within Eurotransplant.

Objective: Analysis of scoring systems for prediction of graft survival after pancreatic transplantation: P-PASS and PDRI. METHODS Retrospective database analysis of donor, transplant and recipient characteristics of all (n = 186) pancreas transplants performed in our center between October 1999 (start of modern immunosuppressive induction therapy) and December 2010. Results: The P-PASS<17-group was 56% (n=104) versus 42% (n=78) in the P-PASS≥17-group (2% missing). Mean P-PASS was 16, (n=182, range:10-22). Mean PDRI was 1.32 (n=169, range:0.70-2.31). Follow-up was complete. Kaplan-Meier-curves for graft-survival (death-censored) showed no significance for P-PASS (p=0.368), 5-year graft-survival was 86% vs. 80% for P-PASS<17 and P-PASS≥17. After increasing the P-PASS cut-off-point to 20, there still was no significant difference between both groups (p=0.491), 5-year graft-survival 84% vs. 77%. For PDRI, KM-curves were significantly different (p=0.032) for PDRI<1.2 and PDRI≥1.2, with a 5-year graft-survival of 91.9% vs. 77.4%. Separate Cox-regression analysis of the P-PASS and PDRI, corrected for recipient factors, showed no significant relation with graft-survival for P-PASS (cut-off 17 p=0.252 and cut-off 20 p=0.702), but a significant relation for PDRI with graft survival (cut-off 1.2 p=0.037).

Conclusion: Analysis of the results from pancreas transplants in this single-center-study showed excellent results (overall 5-year graft-survival 82%), even for pancreata with higher P-PASS (17-22). In our center, the P-PASS has no prognostic value. It is safe to use pancreata from donors with higher P-PASS. The PDRI is a significant predictor for outcome after pancreas transplantation with a cut-off point 1.2. However, even for higher PDRI scores, outcome was good and therefore safe to use.

Successful pre-transplant immunisation against Varicella in sero-negative kidney transplant candidates

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Background: Varicella zoster virus (VZV) infection is endemic in The Netherlands. Vaccination against VZV is not implemented in the Dutch childhood vaccination program. In immune compromised hosts, both primary infection with VZV as well as reactivation may have a disastrous clinical course. In the period 1999-2002, four adult renal transplant recipients in our centre developed severe primary VZV infection, of whom two patients died. Therefore, in May 2003 we routinely started to vaccinate VZV-seronegative patients on the waiting list for renal transplantation.
Aim: We questioned whether end-stage renal disease patients with non-protective VZV-antibody titres were able to mount protective IgG antibody titres against VZV.
Methods: Kidney transplant candidates with nonprotective VZV titres were vaccinated twice with a live attenuated varicella vaccine at an interval of 6 weeks. We analysed the patients vaccinated between May, 2003 and September, 2011. VZV IgG titres were determined prior to vaccination and 6 weeks after the vaccination procedure.
Results: 39 patients on the waitlist (mean age: 45.3 ± 13.8 years) had non-protective VZV IgG titres and were vaccinated. One patient was transplanted immediately after the first vaccination and two patients were transplanted two weeks after the second vaccination. 28 of the remaining 36 patients (77.8%) developed protective antibody-titres after the vaccinations. No adverse events were noted in relation to the vaccinations. None of the 39 patients developed clinical VZV-infection and 32 patients have been transplanted.
Conclusion: VZV-seronegative potential kidney transplant candidates are able to mount protective IgG antibody-titres against VZV and none experienced severe VZV-infection after transplantation.

Genetic variance in ABCB1 and CYP3A5 does not contribute to the development of chronic kidney disease after liver transplantation

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Introduction: Chronic kidney disease (CKD) after liver transplantation (LT) is a major clinical problem that appears to be associated with non-genetic, as well as genetic determinants. The use of the nephrotoxic calcineurin inhibitors (CNIs) cyclosporine A (CsA) and tacrolimus (Tac) is considered to be an important risk factor for CKD after LT. However, it is unknown why certain patients are more prone to suffer from the nephrotoxic effects of these agents than others. We therefore studied the influence of single-nucleotide polymorphisms (SNPs) in the genes of the CNI-metabolizing enzyme CYP3A5 and the CNI- transporting ABCB1, in addition to clinical variables, on the development of CKD after LT. Methods: In a retrospective study, the pre- and post-transplantation clinical variables were correlated by multivariate Cox-regression analysis to the development of CKD [defined as a glomerular filtration rate <60 mL/min/1.73m^2] in 399 LT-recipients that were transplanted in our center between 1986 and 2009. In addition, the *CYP3A5* 6986A>G and *ABCB1* 3435C>T SNPs were determined in both recipients and their respective donors to study the influence of genetics on the development of CKD. Results: After a median follow up of 9.2 years (95%-CI: 8.1-10.2) CKD developed in 195 patients (48.8%). Cox proportional hazard analysis indicated that that an increased risk of CKD was associated with increasing age at the time of LT, female gender [hazard ratio (HR) 1.6, p<0.01], use of CsA rather than Tac (HR 1.9, p<0.01), Caucasian ethnicity rather Black ethnicity (HR 2.7, p<0.01), and the period of LT (with a lower risk in the more recent era). The investigated SNPs in *ABCB1* and *CYP3A5* (or combinations thereof) were not correlated with the development of CKD.
Conclusion: An individual's risk to develop CKD after LT is associated with several clinical factors but is not explained by genetic variations in recipient or donor *CYP3A5* or *ABCB1*. Genotyping of LT recipients is therefore unlikely to aid in preventing CKD.

Improvement of microvascular damage after living donor kidney-transplantation

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Background**:** Chronic kidney disease (CKD) is associated with loss of microvasculature and endothelial damage. Capillaroscopic studies in advanced CKD patients showed an impaired functional and structural capillary density in the skin. These abnormalities may represent manifestations of ongoing systemic microvascular damage. Recently, sidestream dark-field (SDF) imaging has emerged as a noninvasive tool to visualize the microcirculation. Kidney transplantation (KTx) is the ultimate treatment option for patients with CKD and might have beneficial effects on this microvascular damage. In this study, we investigated the effects of KTx on systemic microvasculature using SDF imaging before and after KTx.

Methods**:** Mean capillary density and microvascular morphology were visualized with SDF imaging of the oral mucosa. Ten CKD patients were studied longitudinally before (D0), 1, 6 and 12 months after living donor KTx. Furthermore, circulating levels of growth factors that control microvascular structure, including Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2), were measured using ELISA.

Results: Our study showed no differences in capillary density at different time points. However, we found more capillary tortuosity at D0 and reversibility 12 months after KTx (respectively mean 1.98±0.13, SEM and 1.45±0.16, $p<0.05$). In line with these findings, endothelial destabilization marker Ang-2 showed an improvement 1 month after KTx compared with D0 (2676±326 pg/ml and 5147±904 respectively, $p<0.05$). In contrast to Ang-2, Ang-1 levels did not show any significant difference at different time points. The Ang-1/Ang-2 ratio tended towards improvement after KTx, but did not reach statistical significance ($p=0.09$).

Conclusion: The microcirculation, as assessed by SDF, was disturbed in CKD patients. Interestingly, KTx resulted in an improvement of microvascular tortuosity and an improvement of markers for endothelial dysfunction. Our findings indicate a clinical implication of SDF imaging to assess microvascular alterations after KTx.

Terminally differentiated CD8+ T cells reduce the risk for acute kidney allograft rejection

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Background: End-stage renal disease (ESRD) is associated with lymphopenia and increased T cell differentiation. This phenomenom may be the cause of the ESRD-related impairment of T-cell immunity but clinical evidence in support for this conclusion is scarce. We tested the hypothesis that a more profound ESRD-related T cell dysregulation reduces the risk for acute rejection (AR) in kidney transplants.
Methods: In a prospective study, 185 ESRD patients receiving a kidney allograft were included and followed for 1-2 years. Prior to transplantation, circulating $CD4^+$ and $CD8^+$ T cells were quantified. T cell differentiation was established by determining the percentages of naïve T cells, central-memory T cells, effector-memory T cells and the highly differentiated Tem cells which have regained CD45RA expression (Temra cells). In addition, the frequency of T cells without expression of the co-stimulatory molecule CD28 was measured. Data from age-matched healthy individuals were used for comparison.
Results: In 47 patients, a biopsy-proven AR occurred. Confirming previous results, the ESRD patients had significantly lower T cell counts with a more differentiated phenotype compared to healthy controls. Patients with AR showed the least signs of T cell dysregulation with significantly higher absolute numbers of CD4 T cells, naïve CD4 and CD8 T cells and less terminal differentiation of memory CD4 and CD8 T cells compared to non-rejecting (NR) patients. For instance the percentage of $CD8^+$ Temra cells was significantly lower ($p<0.05$) in patients with AR when compared to NR patients, i.e 16% versus 25%, respectively. After multivariate proportional hazard logistic regression analysis, only the frequency of terminally differentiated $CD8^+$ Temra cells (per percent 4% decrease of risk, $p=0.006$, per tertile 34% decrease in risk, $p=0.002$) and the number of HLA mismatches (per mismatch 33%, $p=0.005$) predicted the risk for AR. The CD28 cell surface expression was lost in over 80% of these $CD8^+$ Temra cells, confirming their status of highly differentiated T cells.
Conclusion: Advanced ESRD-related T cell dysregulation yielding an increased frequency of terminally differentiated $CD8^+$ T cells is associated with less AR after kidney transplantation. This confirms the results of previous studies which indicated that these cells may act as suppressor CD8 T cells and expansion of CD28null CD8 T cells is associated with decreased T cell immunity.

Rectal - but not sublingual - administration of tacrolimus results in systemic exposure in healthy volunteers

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Introduction: The immunosuppressant tacrolimus (Tac) is usually administered by oral route. When oral administration is not feasible, other routes of administration may be useful. Previous research suggested that Tac may be administered by sublingual or rectal route. However, reliable pharmacokinetic data are sparse. Methods Three single, fixed dose formulations of Tac (sublingual 3 mg, rectal 15 mg, and oral 7 mg) were administered in a random sequence in 18 healthy subjects, using a cross-over study design. For sublingual administration, powder obtained from capsules was applied under the tongue for a period of 15 min, after which the mouth was rinsed with water. The subject tried not to swallow during these procedures. For rectal administration a suppository containing powder obtained from capsules was used. Main outcome parameters were maximum blood concentration (Cmax), time to reach Cmax (Tmax), and AUC0-24. Results Six male and 12 female subjects (age 39 ± XX years, weight 80.3 ± YY kg) completed the study. After sublingual administration no measurable blood concentrations were observed (< g/L) inμ2 16 subjects.. In 2 subjects, 1 without and 1 with documentation of swallowing, g/L,μg/L and 22 μmeasurable blood concentrations were observed (Cmax of 7 respectively). Rectal administration resulted in a longer Tmax (4.2 vs. 1.6 hours, p<g/L, p=0.002) comparedμg/l vs. 23.1 μ0.001), and a lower Cmax (34.5 to oral administration. After rectal administration all subjects had clinically h/L), however dose-normalised·gμrelevant systemic exposure (mean AUC0 24 291.5 h/L/mg,·gμAUC0-24 was lower compared to oral administration (19.4 vs. 27.8 p=0.02).
Conclusion: In contrast to previous research, the present study shows that "true" sublingual administration (without swallowing) of tacrolimus does not result in systemic exposure. Rectal administration of tacrolimus results in a clinically relevant systemic exposure and may represent an alternative formulation when oral administration is not feasible.

Patients' experiences with an interned-based Disease Management System to monitor creatinine at home: a pilot study

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Introduction: The recent development of an innovative creatinine measurement device (StatSensor® Xpress-i™ Creatinine Meter) makes it possible to monitor kidney function at home. When self monitoring is supported by an internet-based Disease Management System (DMS), the frequency of policlinic visits could be reduced.
Aims and objectives: In this pilot study, we assessed the feasibility of self monitoring creatinine at home from a patients' point of view.
Methods: Thirty patients who received a kidney from a living donor measured their creatinine level, blood pressure, temperature and weight at home during the first 12 weeks after transplantation. They recorded their measurements in a DMS to which their nephrologists had access as well. At 3 time points during participation, patients completed a questionnaire. In addition, 10 patients were invited for an in-depth interview.
Results: Patients highly valued the self management options (M = 7.8 on a 10 point scale). They especially appreciated receiving an automatic warning when their creatinine level increased, and the prompt notification of changes in their condition (M = 4.5 and M= 4.3 on a 5 point scale, respectively). Patients considered the use of the StatSensor® as pleasant and useful (M = 4.5 and M = 4.4 on a 5 point scale, respectively): by monitoring kidney function themselves, patients felt reassured and hence policlinic visits were experienced as less stressful. Seven patients even spontaneously expressed their wish to continue using the creatinine meter after the study period. Several patients had doubts regarding the reliability of the StatSensor®. However, patients' opinion about reliability was not associated with the actual variation in self measured creatinine values (p = .21). Finally, patients emphasized the need for active involvement of their nephrologists, as many nephrologists paid only little attention to the self measured values.
Conclusion: Self monitoring of creatinine by using an interned-based DSM was highly valued by patients and therefore seems a feasible option for implementation in post kidney transplantation care. However, for this self management initiative to be successful, attention should be paid to involving nephrologists and embedding self monitoring in the regular care process.

Kidney transplant glomerulopathy (TG) treated with intravenous immunoglobulin (IVIG) and prednisolone

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Background: Transplant glomerulopathy (TG) is histologically characterized by double contours of the glomerular and peritubular capillary basement membranes. It is a manifestation of chronic humeral rejection resulting in proteinuria and graft dysfunction. The role of alloantibodies in chronic renal allograft deterioration is increasingly recognized. The prognosis of TG is poor and there is no established treatment for this condition.
We therefore started a pilot study to evaluate the effect of intravenous immunoglobulin and prednisolone on the slope of creatinine course and the amount of proteinuria in kidney transplant patients diagnosed with TG.
Methods: Kidney transplant biopsies were performed on indication, mostly because of deterioration of kidney transplant function and/or proteinuria. If the morphologic changes fitted the diagnosis TG, these patients received treatment with IVIG (1gram/kg once) and prednisolone (1gram during 3days).
Results: Since 2009 until December 2011 13 patients were treated with IVIG and prednisolone because of TG. Median time to diagnoses since trans-plantation was 5 years (range 1-18.5 years). Median increase in creatinine during 12 months prior to diagnosis was +67 µmol/l. 9 treated patients have a follow-up period of at least 6 months. The median delta creatinine was -2 µmol/l during the first 6 months after treatment. During this first half year 7/9 patients showed a favourable change in slope of creatinine slope, while at 1 year 4/8 had a lower creatinine than at time of diagnosis. These persistent responders presented with proteinuria of 1 gram/10mmol creatinine at the start of treatment and decreased to 0.5gram/10mmol creatinine after 1 year. The other 4/8 presented with 2.75 gram/10mmol creatinine and at 1 year increased to 4.5 gram/10mmol creatinine.
Conclusion: In the majority of patients diagnosed with TG treatment with intravenous immunoglobulin and prednisolone resulted in improvement of kidney function. Also the amount of proteinuria was successfully lowered in these patients.

The Effect of CNI Withdrawal on Long Term Graft Survival

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Background: Discontinuation of CNI therapy in order to prevent long term nefrotoxicity and graft failure has shown a beneficial, but short term, effect on renal function. We studied the long term effect of CNI withdrawal on graft survival and wondered whether preceding CNI withdrawal affects the prognosis once renal function deteriorates.
Methods: In our centre patients were selected that had been transplanted between 1971 and July 2010 and had a graft survival of at least 1 year (n=2194). Within this population we studied two subpopulations: 1) those with serum creatinin values >200 umol/L (HC, n=915), versus those with stable creatinin (SC, n=1279) and 2) those who had been switched to CNI free regimen (CNI<, n=656). Cox proportional Hazards analyses were performed in both populations with graft survival as the event studied. Time was calculated from transplantation onwards in population 1 and from CNI< in population 2. Patient related parameters studied were: age, gender, transplant year, previous transplants, pre-treatment, history of cardiac disease and diabetes. Transplant related characteristics studied were: donor type, age and gender, direct graft function (DGF), acute rejection and HLA mismatches. In population 2, extra variables were included: time between transplantation and CNI< and delta creatinin in the year before CNI<.
Results: Mean observation time in the whole population was: 7.9 ± 6.5 years and was not significantly different between HC and SC patients. Mean observation time in CNI< was 10.5 ± 6.0 years, and after CNI< 7.0 ± 5.7 years. In population 1) 374/915 (41%) HC and 330/1279 (26%) SC patients were CNI< patients ($p<0.001$). Graft survival in HC patients was significantly influenced by: rejection, CNI< and transplant year. Preceding CNI< increased graft failure risk (RR=1.3). In population 2) graft survival was significantly influenced by: patient age, rejection, DGF and delta creatinin before CNI<. The higher delta creatinin before CNI<, the higher the RR (RR=1.005/umol creatinin).
Conclusion: In patients with HC, preceding CNI withdrawal has a significant negative effect on graft survival. In the CNI< population, increasing serum creatinin values before CNI< has a significant negative influence on graft survival. Withdrawal of CNI is not warranted to prevent long term graft failure.

Circulating pro-inflammatory CD4+CD28null T cells increase the risk for a cardiovascular event shortly after kidney transplantation

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Background: An unusual population of pro-inflammatory $CD4^+$ T cells that have lost the co-stimulatory molecule CD28 ($CD4^+$CD28null T cells) is expanded in patients with end-stage renal disease (ESRD). $CD4^+$CD28null T cells are associated with cardiovascular disease and may cause atherosclerotic plaque instability by their highly pro-inflammatory nature. In this study we tested the hypothesis that expansion of $CD4^+$CD28null T cells in ESRD poses a risk factor for an atherosclerotic vascular event (AVE) after kidney transplantation.
Methods: In a prospective study the number of circulating $CD4^+$CD28null T cells was established in 295 ESRD patients, prior to receiving a kidney allograft. All patients were screened for a history of symptomatic atherosclerotic disease and routinely evaluated for cardiovascular disease (CVD) by a cardiologist before kidney transplantation. Besides age and gender, the traditional risk factors for atherosclerotic disease were recorded. During the first year after transplantation, patients were followed for the occurrence of an AVE.
Results: A medical history of CVD was present (CVDpos) in 31% of ESRD patients. The percentage (10.3% vs 5.6%, p=0.002) and absolute number (38 versus 22 x 10^3/mL, p=0.01) of $CD4^+$CD28null T cells were increased in CVDpos patients compared to patients without documented CVD (CVDneg). Within the first year after transplantation, an AVE occurred in 20 patients, 5 cases (2.3 %) in the CVDneg group and 15 cases (18.3 %) in the CVDpos group. Over 80% of all AVEs occurred within 3 months after transplantation with a median time from transplantation to event of 5 days. Univariate analysis showed that besides CVDpos (HR 8.1, p<0.001), age (HR 1.04, p=0.02), dylipidaemia (HR 8.8, p=0.004) and the % of $CD4^+$CD28null T cells (1.04 per % increase, p=0.01) were significantly associated with the occurrence of a post-transplantation AVE. In a multivariate analysis, only CVDpos remained a significant risk factor with a significant and positive interaction between the terms CVDpos and the % of $CD4^+$CD28null T cells (HR 1.05, p<0.001). Within the CVDpos group, the incidence of an AVE was 13% in the lowest tertile compared to 25% in the highest tertile of % $CD4^+$CD28 null T cells.
Conclusion: The expansion of circulating $CD4^+$CD28null T cells is highly associated with the presence of CVD in ESRD patients and increases the risk for an atherosclerotic vascular event shortly after kidney transplantation.

Epigenetic analysis demonstrates that natural Treg only infiltrate the cardiac allograft during an acute rejection episode

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FOXP3+ regulatory T cells (Treg) infiltrate the cardiac allograft after transplantation, however, it is unknown whether these infiltrating cells are derived from the thymus (nTreg) or are induced in the periphery (iTreg). Using demethylation of the FOXP3 gene as a marker for nTreg, we investigated the origin of infiltrating cells in heart transplant biopsies during both immunological quiescence and acute rejection. The proportion of demethylated FOXP3 DNA was determined with a quantitative PCR based method with a sensitivity limit of 0.06%. In total, 49 EMB (endomyocardial biopsies) were analyzed of 13 heart transplantation patients who experienced at least 1 rejection episode requiring anti-rejection therapy (ISHLT rejection grade 2R, rejectors) within the first 3 months after transplantation and 8 patients who remained free from rejection during this period (non-rejectors). EMB were taken before transplantation (time-zero biopsies, n=19), before and during acute rejection (AR) for the rejectors (n=22) and within the first 3 months for the non-rejectors (n=8).
In time-zero biopsies, no evidence for nTreg was detected. However, after transplantation the proportion of nTreg marker significantly increased in the EMB where cellular infiltrates were present. Grade 1R EMB (n=10) displayed a proportion of 0.36% nTreg and grade 2R EMB (n=13) 0.61% nTreg ($p=0.001$ and <0.0001 versus time-zero respectively). This proportional increase in nTreg marker was predominantly observed in EMB of patients who subsequently developed a rejection (grade 2R) requiring therapy. No evidence for accumulation of nTreg was observed in the EMB of non-rejectors.
In conclusion, rejectors display a higher proportion of nTreg marker after heart transplantation, already before histologically proven AR occurs. This indicates that nTreg home in the graft during alloreactivity where they dampen rather than prevent the rejection process.

Premature immunological ageing of T cells in patients with end-stage renal disease is not changed by renal replacement therapy

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Background: End-stage renal disease (ESRD) patients have a defective T cell mediated immune system, which is related to excessive premature immunelogical ageing. The aim of this study is to examine whether this premature ageing is changed by renal replacement therapy (RRT).
Methods: Healthy individuals (n=60), ESRD patients (n=30, eGFR<15 ml/min) without RRT, and patients treated with hemodialysis (n=30) or peritoneal dialysis (n=30) were included in the study. Groups were matched for age, sex and CMV serostatus. We studied the circulating T cells by 3 different assays which are indicative for the immunological age of the T cell system. First, the T cell receptor excision circle (TREC) content was measured, which indicates the output of naïve T cells. Relative telomere length (RTL) was determined as a measure of repeated rounds of cell proliferation and flowcytometry was used to establish the differentiation status of circulating T cells.
Results: ESRD patients were significantly more affected ($p<0.05$) compared to HC with respect to the parameters determined, i.e. ESRD patients had significant less TRECs ($p<0.001$), shorter telomeres within both $CD4^+$ as well as $CD8^+$ T cells. T cells were more differentiated towards memory T cells. Especially the elderly patients who received RRT, have a significant decrease in percentage $CD8^+$ memory T cells (i.e. 92.6% versus 80.0%, $p<0.05$). Moreover, memory T cells were more differentiated as indicated by enhanced proportions of T cells lacking expression of co-stimulatory molecule CD28. The percentage of pro-inflammatory CD8CD28null T cells was significantly higher ($p<0.001$) compared to HC, i.e. 31.9% of the $CD8^+$ T cells lack the CD28 receptor in the HC versus 40.0% in ESRD patients. Overall, we did not observe a difference in premature immunological ageing when ESRD patients not on dialysis were compared to patients on dialysis. However, RRT in the elderly patient group (>50 years) reduced the increase in the $CD8^+$ memory T cell compartment ($p<0.05$). We were unable to detect any significant differences between T cells from patients treated with peritoneal dialysis and hemodialysis patients.
Conclusion: Based on the analysis of aging parameters we conclude that the immunological age of T cells from ESRD patients is increased by on average 20-30 years compared to HC. Dialysis treatment does not substantially alter premature immunological ageing.
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The compartment of human natural CD4+CD25++CD127- regulatory T cells is filled with cells reactive to various antigens

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Background: The population of regulatory $CD4^+CD25^{++}CD127^-FoxP3^+$ T cells (Tregs) is composed of thymus-derived (natural, nTregs) or Tregs induced in the periphery (iTregs). nTregs have a highly demethylated TSDR *FoxP3* and are believed to be important for control of autoreactive T cells. Tregs are important to control alloreactive T cells and could be used for cell therapy to induce tolerance to an allograft. Recognition of natural alloantigen-specific Tregs could facilitate a targeted approach for such a therapy. Expression of CD40L (CD154) can be used to detect antigen-specific $CD4^+$ T cells. In this study, we used specific expression of CD154 to study the presence of antigen-specific Tregs.
Methods: Highly enriched fractions of Tregs and $CD4^+$ effector T cells ($CD4^+$Teff) were sorted and stimulated with various antigens in the presence of aCD40 to maintain CD154 on the cell surface. Subsequently, these CD154-expressing Tregs were sorted and tested either immediately for their suppressive capacity or following polyclonal (using CD3/CD28 beads) or antigen-specific expansion, respectively. The demethylation of TSDR *FoxP3* was determined for the different Treg-fractions. In addition, in depth phenotypic analyses were performed on the different Treg-fractions.
Results: Using different viral, vaccination as well as alloantigens, we detected similar frequencies of antigen-specific $CD154^+$T cells in both fractions with great specificity and sensitivity. Ag-specific $CD154^+$Tregs had a memory phenotype, no cytokine production after polyclonal stimulation, stable FoxP3 expression and a highly demethylated TSDR *FoxP3*. Sorted $CD154^+$Tregs were superior in suppressing Ag-specific responses when compared to $CD154^-$Tregs. $CD154^+$Tregs could be efficiently expanded in an Ag-specific manner, which enhanced their suppressor activity. After booster vaccination, the ratio of Ag-specific $CD4^+$Teff:Treg temporarily increased substantially due to an increase in $CD154^+CD4^+$Teff but not Tregs.
Conclusion: These data show for the first time that the compartment of circulating human nTregs is filled with Ag-specific T cells for a variety of antigens. Isolation and expansion of Ag-specific nTregs may be of potential benefit for Treg-therapy to induce tolerance in the setting of kidney transplantation.

Dietary restriction and fasting downregulate complement activity

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Background Seventy-two hours of preoperative fasting (F) or 2 weeks of 30% dietary restriction (DR) offers robust protection against renal ischemia-reperfusion injury (IRI) in mice. However, the mechanism remains to be elucidated. We hypothesize that immunomodulation plays a pivotal role. Innate immunity, especially the complement system, is crucial in the pathophysiology of IRI. Therefore, we investigated the impact of fasting and dietary restriction on complement activation pathways. Materials and Methods Male C57Bl/6 mice were fed ad libitum (AL) or underwent 72 hours fasting or 30% dietary restriction for 2 weeks (n=8/group). Consequently blood was drawn and serum was aliquoted and stored at -80oC. Functional activity of the complement activation pathways (classical (CP), lectin (LP) and alternative pathway (AP)) was assessed by ELISA using immobilized ligands. Deposition of C3 and C9 as a measure of complement activity along with concentration of upstream complement initiating proteins (MBL-A and –C, and C1q) was determined. Results A significant downregulation in CP and LP activity by dietary restriction and in CP, LP and AP activity by fasting was observed, compared to the ad libitum group. The activation of both C3 and C9 in the dietary restriction and fasting group was significantly downregulated ($p \leq 0.002$) in CP, LP and AP (except for C3 activation in the AP of the dietary restriction group). The MBL-A concentrations were significantly lower ($p \leq 0.001$) after dietary restriction and fasting, 15.4 µg/ml (DR) and 12.4 µg/ml (F) compared to 19.9 µg/ml in ad libitum mice. MBL-C concentrations were also significantly lower ($p \leq 0.0001$) in the dietary restriction and fasting groups, 89.4 and 49.5 µg/ml respectively compared to 109.6 µg/ml in the ad libitum group. C1q concentration was only significantly lower in the fasted group ($p \leq 0.0001$). Conclusion Dietary interventions downregulate complement activation pathways. Compared to dietary restriction, fasting has a more pronounced effect. CP seems to be more affected by dietary restriction while AP is most affected by fasting. To our knowledge, our data for the first time show that DR and fasting cause downregulation of complement activation pathways. Therefore, we conclude that complement downregulation may be one of the mechanisms by which dietary interventions protect against renal IRI.

Mannan-binding lectin induces endoplasmic reticulum-stress in tubular epithelial cells following renal ischemia/reperfusion

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Background: Ischemia/reperfusion (I/R) injury is a key event in kidney transplantation. Recently, we demonstrated a crucial role for Mannan-binding lectin (MBL), the initiator of the lectin pathway of complement, in the pathogenesis of tubular injury following renal I/R, which was completely independent of complement activation. Inhibition of MBL was fully protective against renal I/R injury. We showed that renal I/R was accompanied by vascular leakage of MBL into the interstitial space, where exposure of tubular epithelial cells (TEC) to MBL induces tubular cell death. In the present study we explored the underlying mechanism of this MBL-mediated tubular injury.
Methods: In vivo, rats (n=6 per group) were subjected to 45 minutes of unilateral renal ischemia, while the contralateral kidney was removed. Serum was collected at consecutive time points to assess kidney function (creatinine levels). After 2, 5 or 24 hours of reperfusion, kidneys were harvested and rats were sacrificed. Renal tissue was analyzed for histology, deposition of MBL and mRNA expression of ER-stress genes sXBP-1, BIP and CHOP. In vitro, human tubular epithelial cells (HK-2) were incubated with purified human MBL (0-10 µg/ml) for 24 hours and analyzed for sXBP-1, BIP and CHOP mRNA expression. Results: Exposure of human tubular epithelial cells (TEC) to purified MBL in vitro resulted in a dose-dependent binding, internalization and trafficking of MBL to the endoplasmic reticulum (ER) followed by epithelial cell death. Therefore, spliced (s)XBP-1 mRNA, a marker of ER-stress was assessed, demonstrating a twenty-fold induction of sXBP-1 within two hours of MBL exposure. D-mannose, a ligand for MBL, completely prevented splicing of XBP-1. Assessment of rat sXBP-1 following I/R in vivo revealed an extensive induction of ER-stress within 2 hours following reperfusion with a maximum at 24 hours. ER-stress at 2 hours was accompanied by intra-epithelial presence of MBL, loss of tubular cell adhesion followed by tubular cell death within 24 hours following reperfusion.
Conclusions: These findings demonstrated that following reperfusion of the ischemic kidney, exposure of tubular epithelial cells to circulation-derived MBL induces ER-stress, leading to tubular cell death. These data identify MBL as a novel therapeutic target in kidney transplantation.

Bone marrow derived mesenchymal stromal cells from healthy donors and patients with end stage renal disease have similar phenotypical and functional characteristics

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Introduction: Mesenchymal stromal cells (MSCs) are pluripotent cells that have immunosuppressive and reparative effects both *in vitro* and *in vivo*. In clinical transplantation, treatment with allogeneic MSCs holds the risk of inducing HLA-reactivity, and therefore autologous MSCs are to be preferred. Although already used in clinical trials, it is unclear whether autologous bone marrow derived (bm)-MSCs obtained from patients with end stage renal disease (ESRD) display similar characteristics and functions as MSCs from healthy donors (HD).
Methods: 10 adult patients with ESRD and 10 HD underwent bm aspiration. bmMSCs were isolated and expanded *ex vivo* and tested for phenotype and functionality *in vitro*.
Results: ESRD-MSCs and HD-MSC showed a similar morphology and osteogenic and adipogenic differentiation capacity. Profiling of miRNA expression in ESRD-MSCs was comparable to HD-MSCs, suggesting a broad overlap. In addition both groups were > 90% positive for CD73, CD90 and CD105 and negative for CD34 and CD45. Of importance for their clinical utility, the growth characteristics were similar between both groups, and we obtained sufficient numbers of MSCs with a low passage within a time span of 4-5 weeks. RNA profiles of self renewal genes (Oct4, c-myc, Sox-2, Klf4), factors involved in repair and inflammation (Angiopoieitin 1 and 2, Vascular Endothelial Growth Factor, IL-8, IL-6, PDL1 and TGF-beta) were also compa-rable between both groups. Importantly, we found that ESRD-MSCs displayed the same immune-suppressive capacities as HD-MSCs, as shown by a dose-dependent inhibition of PBMC proliferation, a decrease in the proinflammatory cytokines TNFα and IFN-γ production and a concomitant increase in the production of IL-10.
Conclusion: Expanded bmMSCs generated from ESRD patients were shown both phenotypically and functionally to be similar to bmMSCs from healthy donors. These findings are important for potential clinical use to maximize safety for the recipient.

Donor-derived renal tubular epithelial cells induce recipient memory T-cell proliferation with a CD28null phenotype which is not susceptible to tacrolimus

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Introduction: It is known that memory T-cell activation can result in a donor-specific effector immune response. Memory T cells are considered to be sensitive to calcineurin inhibition. Clinically tubulitis still occurs despite treatment with potent immunosuppressive drugs. Here we investigated the proliferative responses and tissue damaging capacities of recipient T cells induced by donor-derived renal tubular epithelial cells (TECs). In addition, we studied their susceptibility to currently used immunosuppressive drugs.
Materials and Methods: Recipient PBMCs were co-cultured with donor-derived TECs for 7 days (N=5). As control, autologous co-cultures of donor PBMCs and donor-derived TECs were used. By flow cytometry the proliferative response of CD3, CD4, CD8 naïve ($CD45RO^-CCR7^+$), effector memory ($CD45RO^+CCR7^-$), central memory ($CD45RO^+CCR7^+$) and effector memory RA (EMRA, $CD45RO^-CCR7^-$) was measured. In addition, we determined the tissue damaging capacities of proliferating T cells by intracellular staining for Granzyme B and IFN-γ. Finally we assessed the inhibitory effect of tacrolimus (10ng/ml), everolimus (10ng/ml) and prednisolone (200ng/ml) on the induced T-cell proliferation.
Results: Up to 8.3% ± 1.9% of the recipient $CD4^+$ T-cells and 5.7% ± 1.2% of the $CD8^+$ T-cells mounted a proliferative response upon donor TECs encounter. This response was mainly executed by effector memory $CD4^+$ and $CD8^+$ T cells with a $CD28^{null}$ phenotype comprising of 40-50% ± 8.2% of the proliferating T-cell pool. The $CD28^{null}$ memory T cells expressed the serine protease Granzyme B (34.7-40.9%) and produced after polyclonal stimulation the proinflammatory cytokine IFN-γ (5.3-13.1%). Tacrolimus (10 ng/ml) suppressed donor TEC induced PBMC proliferation by 20% as compared to 80% inhibition of mixed leukocyte reaction (MLR). Surprisingly, tacrolimus could not inhibit the donor TEC induced proliferation of $CD28^{null}$ effector memory T cell, whereas everolimus and prednisolone inhibited $CD4^+$CD28null T-cell proliferation by 37% ± 12.3% and 75% ± 1.1%, respectively. $CD8^+CD28^{null}$ T-cell proliferation was not affected by any of the drugs tested.
Conclusion: Donor-derived TECs induce recipient memory T-cell proliferation. Tacrolimus only slightly inhibits this proliferative response, while $CD28^{null}$ proliferation was not inhibited at all.

Inhibition of human allogeneic skin graft inflammation by ex vivo expanded human Treg in a humanized mouse model

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Treg cell-therapy is of interest for therapeutic intervention in transplant rejecttion and autoimmunity. Although clinical Treg-therapy trials have started, the *in vivo* behavior of ex-vivo expanded human Treg is unclear. Therefore, we investigated the effect of ex-vivo expanded CD4+CD25+CD127low human Treg-cells on the inflammatory response of human skin allograft in a humanized-SCID mouse model. First, we demonstrated that ex-vivo expanded human Treg-cells maintained suppressive capacity *in vitro*. Next, these expanded Treg were studied *in vivo* in our humanized mouse model, in brief human skingrafts were transplanted on immunodeficient SCID/beige mice, after healing mice were infused (i.p.) with allogeneic hu-PBMC with/without Treg-cells. After 3-weeks inflamed skin-grafts, spleen and peripheral blood were harvested and analyzed by histology and/or flowcytometry. Analysis of inflamed human skingrafts revealed that Treg infusion restored the inflammation related aberrant K10/K16 epidermal marker expression and influx of hu-CD8 T-cells. The Infusion of Treg also affected the systemic response, they inhibited human CD4+ and CD8+ T cell activation and proliferation as indicated by reduced Ki67. We showed that under the conditions tested, ex-vivo expanded Treg-cells reduce but do not fully prevent hu-PBMC induced skin inflammation *in vivo*. The observed reduction of skin transplant inflammation by human Treg encourages the use of Treg-therapy in transplantation.

Effects of the anti-CD20 antibody rituximab on B cells in human secondary lymphoid organs

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A single dose of the anti-CD20 monoclonal antibody rituximab (RTX) induces a nearly complete B-cell depletion in peripheral blood. However, there remains a residual B-cell population in secondary lymphoid organs, such as spleen and lymph nodes. An intriguing question that remains to be answered is whether these remaining B cells are modified due to binding by RTX. To mimic the *in vivo* situation, where B cells are exposed to RTX but only partially depleted, spleen cells obtained from organ donors were incubated *in vitro* with RTX and a low concentration of complement. The distribution of B-cell subsets was analyzed after 3 days of culture in the presence or absence of CpG-B. Incomplete B-cell depletion followed by culture in the absence of CpG-B resulted in a IgD^+CD27^- (naïve) : IgD^-CD27^+ (switched memory) B-cell ratio that was comparable to the non-depleted condition. However, after culture in the presence of CpG-B, the B cells that survived the depletion procedure showed a reduced naïve : switched memory ratio. In contrast to the total splenic B-cell population, the depletion surviving B cells did not contain IL-10 producing cells after culture with CpG-B. Moreover, B cells were also characterized *ex vivo* in peripheral blood and lymph nodes obtained during renal transplant surgery from patients (n=4) who had received RTX 4 weeks before transplantation. As described in literature, a complete depletion of B cells in the peripheral blood was obtained after a single dose of RTX, however in the lymph nodes the frequency of B cells was comparable to that of untreated control patients. Remarkably, the remaining lymph node B cells from RTX-treated patients showed a lower percentage of IgD^+CD27^- and a higher percentage of IgD^-CD27^+ B cells compared to lymph node B cells of untreated patients.
In conclusion, exposure of both spleen and lymph node B cells to RTX results in a shift of B cells from a naïve to a switched memory phenotype.

Intragraft expression of metallothioneins in kidney transplant patients may be a novel marker of response to anti-rejection treatment with corticosteroids

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Steroid resistant acute rejection is a risk factor for inferior renal allograft outcome. We aimed to find molecular markers in the graft for steroid resistant rejection. From 873 kidney transplant recipients (1995-2005) patients with a first rejection episode were selected for study using strict inclusion criteria and clinical end point definition. Using whole-genome expression arrays we studied the gene expression patterns in 36 biopsies with acute rejection, 18 from steroid resistant subjects and 18 from steroid responsive subjects. Steroid resistance was defined as requirement for anti-thymocyte globulin treatment within two weeks after corticosteroid treatment. Clinical and histomorphologic parameters were similar between treatment response groups. Whole genome expression analysis revealed that the expression of metallothioneins (MT), a group of small cysteine-rich proteins involved in regulating zinc metabolism, is significantly ($P<0.000001$) associated with response to steroid treatment. Eight MT isoforms (MT-1A, -1E, -1F, -1G, -1H, -1M, -1X, -2A) were highly expressed in kidney allografts and showed significantly higher expression in steroid resistant acute rejection. Multivariate logistic regression analysis using the Lasso method resulted in a predictive model for steroid resistance containing five markers as independent covariates, MT-1G, CYP4A11, F2R, FTHL7 and TIMP-1 (90% specificity and 60% sensitivity AUC = 0.72). Validation with real-time qPCR confirmed microarray findings. Relatively high intragraft expression of metallothioneins during acute rejection is associated with resistance to steroid treatment. The findings are in line with earlier findings of increased percentages of metallothionein-positive macrophages in lung allograft recipients with steroid resistant acute rejection. Metallothioneins regulate intracellular concentrations of zinc, through which they can inactivate the DNA binding capacity of zinc-finger transcription factors, such as the glucocorticoid receptor.

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

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Background and Aims: (Non)anastomotic biliary strictures after liver transplantation (LT) are common. Recently, hepatocyte and cholangiocyte-abundant microRNAs (miRNAs) have been identified as sensitive markers for liver injury in serum. The release of miRNAs during liver injury has lead to the hypothesis that they could act as potential non-invasive biomarkers in preservation solutions to predict biliary strictures in recipients after LT. The aim of this study is to investigate whether differences in the balance of hepatocyte- and cholangiocyte-derived miRNAs in graft preservation solution are prognostic of biliary strictures after LT.
Methods: Perfusate flushes from 33 consecutive liver grafts were collected at the end of cold ischemia time (CIT) and the cell-free solutions were analyzed for the presence of hepatocyte-abundant miRNAs (miR-122 and miR-148a) and cholangiocyte-abundant miRNAs (miR-30e miR-222 and miR-296) by quantitative RT-PCR. Mann-Whitney U tests and ROC-curves were generated to compare ratios of miRNAs between recipients that developed biliary strictures (n=13) versus recipients that did not (n=20).
Results: Perfusates from grafts that developed post-LT biliary strictures contained significantly higher ratios of hepatocyte- (miR-122, miR-148a) and cholangiocyte- (miR-296, miR-30e, miR-222) specific miRNAs ($P<0.01$). ROC analysis shows that perfusates with higher ratios of hepatocyte- vs cholangiocyte-abundant miRNAs are more likely to develop biliary strictures after LT compared to perfusates with lower ratios (AUC=0.865, P=0.0002).
Conclusion: This study demonstrates that ratios of hepatocyte vs cholangiocyte-derived miRNAs in perfusates during LT differ between grafts that develop biliary strictures and grafts that do not. Based on these ratio's, biliary strictures after LT could be predicted with high sensitivity and specificity. This non-invasive detection of specific miRNAs in preservation solution in an early phase of LT may represent a novel method to help identify liver grafts at risk of developing biliary strictures after LT.

Genetic polymorphisms in ABCB1 influence the pharmacodynamic effects of tacrolimus on T cells

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Background: Tacrolimus (TAC) has a large interindividual variability in pharmacokinetics and quantification of its effect is difficult. Tac is a substrate of P-glycoprotein (P-gp, encoded by *ABCB1*), an efflux-pump which is expressed more on CD8 T cells than on CD4 T cells. Single-nucleotide polymorphisms (SNPs) are associated with interindividual differences in P-gp activity and hence may influence intralymphocytic TAC concentrations and efficacy, especially in CD8 cells. Here we studied the influence of SNPs in *ABCB1* and of verapamil-induced P-gp inhibition on the biological effect of TAC on T cells. Methods: The influence of *ABCB1* genotypes (3435CC/high pump-activity, CT, TT/low pump-activity) was studied in T cells of 16 healthy volunteers using P-gp-mediated rhodamine efflux (2 hours). The intracellular IL-2 expression in different T-cell populations was measured after PMA/iono stimulation of whole blood by use of flowcytometry, in the presence of 10ng/mL TAC and 40nM verapamil. In addition, the relationship between *ABCB1* SNPs, TAC levels and *ex vivo* induced IL-2 production was studied in 37 TAC-treated renal transplant patients. Results: The mean rhodamine efflux was higher in CD8 T cells compared to CD4 T cells: 40% vs. 16%, respectively ($P<0.001$). In the presence of the P-gp inhibitor verapamil, rhodamine was effluxed by only 0.8% of CD8 T cells (95% CI: 0.3-1.4%), while TAC did not influence the efflux of rhodamine (mean 38%, 95%-CI: 35-42%). In healthy volunteers with the CC genotype 50% (95%-CI: 46-53%) of CD8 T cells effluxed rhodamine which was significantly higher compared to the TT genotype (mean 39%, 95%-CI: 30-46%, $P<0.05$). Blockade of P-gp by verapamil in the presence of TAC decreased the percentage of intracellular IL-2 producing CD8 T cells by 14% suggesting an increased pharmacodynamic effect of TAC through prolonged intralymphocytic accumulation. In TAC-treated renal transplant patients with the CC genotype, verapamil reduced the percentage of IL-2 producing CD8 T cells by 22% whereas no effect of verapamil was found in patients with the TT genotype. Moreover, the ratio TAC C_0 *versus* % IL-2 producing CD8 T cells in CC genotype patients was significantly higher ($P<0.05$) compared to TT genotype patients, showing that in CC-genotype patients, TAC has a smaller pharmacodynamic effect.
Conclusion: Genetic polymorphisms in *ABCB1* influence the P-gp activity of CD8 T cells and the immunosuppressive effect of TAC in kidney transplant recipients.

Incisional hernias after laparoscopic donor nephrectomy: A single center experience

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Background: Due to the shortage of kidneys available for transplantation, an increase in live kidney donation is seen in the last decade. Since its introduction in 1995, laparoscopic donor nephrectomy (LDN) has been successfully implemented in several Dutch transplant centers, leading to a shorter hospital stay, less pain and a better quality of life for donors when compared to the open technique. Although live donor nephrectomy is routinely performed, little is known on the prevalence of incisional hernias (IH) in this population. The aim of the present study was to evaluate the prevalence of IH after LDN, body image and cosmesis.
Methods: Donors who underwent LDN between January 2005 and December 2009 were asked to fill out a questionnaire on their postoperative course regarding possible IH, and a body image questionnaire. The latter consisted of two subscales: the body image scale (BIS) and the cosmetic scale (CS). In total, 519 LDNs were performed in the aforementioned period. Nine donors had deceased due to unrelated causes, therefore 510 donors were available for follow up. Results: A total of 369 subjects (72%) responded, six of these donors had undergone IH correction (1.6%). Three donors had a port-site hernia, 2 had a hernia of the Pfannenstiel incision, and 1 a hernia of an old McBurney incision that was used for kidney extraction. There were no significant differences between the group with and without IH regarding age, gender and BMI. Two donors (33%) with an IH had a postoperative wound infection versus 16 (4.4%) in the other group (p=0.001, Mann-Whitney U). Average BIS-score was 18.9 (5-20), average CS-score was 18.9 (3-24). No significant differences in BIS- or CIS-scores were found between groups. There was no correlation between BIS or CS and gender, age or BMI.
Discussion: To our knowledge, this is one of the largest studies describing the prevalence of IH after LDN. The relation between postoperative wound infection and IH, as has been described earlier, is also seen in this study. Our results show that a low IH rate and good scores on the BIS and CS are achieved after LDN.

Mild Hyponatremia has a Substantial Influence on Clinical Outcome of Patients on the waiting list and after Liver Transplantation

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Background: Waiting list mortality remains high among patients awaiting liver transplantation (LT). Serum sodium levels below 130 mmol/L in patients awaiting LT are associated with an increased waiting list mortality. Aim of this study was to assess the impact of serum sodium levels between 130-135 mmol/L at listing on the waiting list, post-transplant and intention-to-treat survival.
Methods: Data were collected from the transplant databases of 3 transplant centers located in The Netherlands, Germany and the United States. Serum sodium levels, along with other parameters and demographical data were collected at the time of listing for LT. Hyponatremia was defined as a serum sodium level below 135 mmol/L. Mild hyponatremia was defined as serum sodium levels between 130-135 mmol/L. Severe hyponatremia was defined as serum sodium levels below 130 mmol/L.
Results: A total of 1658 patients was included in this study. A strong correlation was found between serum sodium and survival (P=0.001). Waiting list, post-transplant and intention-to-treat survival were all significantly reduced in the mild hyponatremia group, compared to patients with normal sodium levels (P<0.001, P<0.001, P<0.001). This was shown for the entire cohort and for each center separately. There was no significant difference in waiting list, post-transplant, and intention-to-treat survival when comparing patients with mild and severe hyponatremia (P=0.146, P=0.086, P=0.392)
Conclusion: Mild hyponatremia is associated with a significantly worse survival, not only on the waiting list, but also after LT and this decreased survival is comparable to that of patients with severe hyponatremia. Intention-to-treat survival in patients with mild hypoantremia is greatly reduced. Physicians should be more aware of the potential risks of hyponatremia for their patients and consider these risks in their allocation policy.

Importance of HLA mismatches in living and deceased donor kidney transplantation

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Background: HLA mismatches as a categorical variable is known to influence graft survival in deceased donor kidney transplantation. We studied the effect of HLA mismatches in a population with deceased and living donor transplantations.
Methods: All 1821 transplantations performed in our center from 1990 until 2010 were included in the analysis. Univariate and multivariate Cox proportional hazard analyses were performed. Three analyses were performed: HLA mismatches were included as a continuous variable, as a categorical variable (total number of mismatches), and as a binary variable (zero versus non-zero mismatches). Other variables included were year of transplantation, number of previous transplantations, pre-treatment, maximum PRA, current PRA, recipient gender and age, and donor type, gender and age.
Results: 941 patients received a deceased donor kidney and 880 a living donor kidney. There were 494 failures, 337 in recipients of deceased donor kidneys and 157 in recipients of living donor kidneys. In multivariate Cox analysis, donor type and age, current PRA, and recipient age were found to have a significant influence on graft failure, censored for death. Number of HLA mismatches had a significant influence in all analyses. There was no interaction between donor type and HLA mismatches.
Conclusion: Number of HLA mismatches has a significant influence on death-censored graft survival. This holds true for both deceased and living donor transplantation. However, the risk of death-censored graft failure of a 2-2-2 mismatched living donor kidney is comparable to that of a 0-0-0 mismatched deceased donor kidney.

Systematic review and meta-analysis of the relation between Body Mass Index and outcome of laparoscopic donor nephrectomy

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Background: In this era of organ donor shortage, live kidney donation has been proven to increase the donor pool. However, it is extremely important to make careful decisions in including and excluding possible live donors. A Body Mass Index (BMI) above 35 is generally considered as a relative contra-indication for donation. Whether this is justified or not is currently under debate. For this reason, a systematic review and meta-analysis was carried out to compare outcome of live donor nephrectomy (LDN) between high- and low BMI donors. Methods: A comprehensive literature search was performed in the Cochrane Central Register for Controlled Trials, the Cochrane Library, MEDLINE, PubMed and Embase. Reference lists were screened manually for relevant articles. A meta-analysis was performed by using Review Manager version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark). Random-effects models were used. All aspects of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement were followed. Results Out of 529 publications, fourteen studies were selected and reviewed. Eight peri-operative outcome measures were meta-analyzed. Of these, the following demonstrated significant differences in favour of low BMI donors: the mean difference in operation duration was 16.91 minutes (confidence interval (CI) 9.06 to 24.76, $P < 0.0001$), the mean difference in rise in serum creatinine was 0.05 mg/dL (CI 0.01 to 0.09, $P = 0.02$) and the risk ratio for conversion was 1.69 (CI 1.12 to 2.56, $P = 0.01$). Differences in the other outcome para-meters (warm ischemia time, estimated blood loss, length of stay, perioperative complications and decrease in glomerular filtration rate) were not significant. Conclusion: In five out of eight outcome measures no significant differences were found between BMI groups. The clinical relevance of the outcome measures that were significantly different is questionable. Based on these results we conclude that a high BMI alone is no contra-indication for live kidney donation.

Q-methodology to explore attitudes towards adherence in recently transplanted kidney patients

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Background: The rate of non-adherence to medication among renal transplant patients is reported to be as high as 20-37%. The aim of this study was to explore attitudes towards medication and investigate the extent to which these are related to non-adherence. Methods: All consecutive kidney transplant recipients were invited to participate in this prospective study. We report here cross-sectional findings from the first measurement 6 weeks after transplantation. Q-methodology was used: patients were asked to rank-order statements on issues associated with (non) adherence in order of agreement. Factor analysis was used to uncover patterns in the ranking of the statements. The resulting factors represent groupings of patients with the same opinion profile. Respondents completed the BAASIS©-interview, regarding their immune-suppressant medication intake over the last month. Results: 112 renal transplant recipients (19-75 yrs) participated in the study. Results from the first measurement revealed three attitude profiles concerning the post transplant medication regime: (A) Independent & Confident (B) Concerned & Reliable (C) Appearance orientated & Care-free. Patients with attitude A find it important to take their medication exactly every twelve hours. They take good care of their kidney and therefore have no worries about the future. Patients with attitude B were most concerned that their kidney will be rejected, and that they will have to return to dialysis. They are accurate and upset if they forget their medication. Patients with attitude C find their appearance important and don't want their life to revolve around their disease. They experience side effects and do not feel the need to be extra careful with their kidney. The BAASIS©-interview revealed that 19/112 were classified as nonadherent (e.g. missed dose or >2 hours late with medicine taking). None of the profiles were related to nonadherence. Conclusion: Three distinct attitude profiles were detected. Even very soon after kidney transplantation 17% of the patients admitted a certain degree of non-adherence. There was no association of this behaviour with the three profiles we detected with Q-methodology. Attitude towards medication is a potential target for intervention.

The Eurotransplant Donor Risk Index in liver transplantation: ET-DRI (Preferred method to define extended criteria donation?)

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Introduction: In Eurotransplant, extended criteria donation for liver grafts is defined as follows, donor age >65, ICU-stay >7 days, steatosis >40%, elevated BMI, sodium, AST, ALT or bilirubin. Except donor age, none of these criteria have been validated. In 2006 *Feng et al.* developed the Donor Risk Index (DRI) for liver transplantation within UNOS. This DRI is a continuous scoring model including eight donor and transplant factors. Recently, we validated this DRI for the Eurotransplant region. Although this model is a valid tool for scoring donor liver quality, for potential use in allocation, a scoring system tailored to the Eurotransplant region would be more appropriate. OBJECTIVE Objective of our study was to investigate various potential donor- and transplant risk factors and design a risk model that could predict outcome after orthotopic liver transplantation (OLT) for the Eurotransplant region. METHODS This study is a database analysis of all 5 939 liver transplantations from deceased donors into adult recipients from the 1st of January 2003 until the 31st of December 2007 in Eurotransplant. Data were analyzed with Kaplan-Meier and Cox regression models. RESULTS From 5 723 patients follow-up data were available with a mean of 2.5 years. After multivariate analysis the DRI ($p<0.0001$), latest lab gamma-glutamyl transpeptidase (GGT) ($p=0.006$) and rescue allocation ($p=0.011$) remained significant. These factors were used to create the Eurotransplant Donor Risk Index (ET-DRI). Concordance indices were calculated to determine the relation of the two models (ET-DRI and original DRI) with survival. C-indices in our dataset: ET-DRI 0.625 versus (original) DRI 0.614.CONCLUSION The ET-DRI can be used to predict outcome after liver transplantation in the Eurotransplant region. It is based on data of two large datasets (SRTR and Eurotransplant) and has high significant value. Possibly, it could be used for allocation purposes and to define ECD liver grafts.

Are you mother's darling? The NIMA effect

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Background: Exposure of the immune system of a child to noninherited maternal antigens (NIMA) during pregnancy might lead to long lasting down regulation of the alloresponse against these NIMA: the NIMA effect. Therefore graft survival of a kidney from a mother would be superior to that from a father. We tested this hypothesis in our transplant population.
Methods: Between 1981 and September 2011 we performed 1138 living donor kidney transplantations. 250 parents donated a kidney to their child. In 101 transplantations, the donor was the father of the recipient and in 149 the mother donated. Cox proportional hazards analysis was performed studying the effect of recipient gender and age, current PRA, transplantation year, HLA mismatches, donor age, rejection, and donor gender (father/mother) on the risk of graft failure censored for death.
Results: In the period studied there were 60 graft failures (35 in recipients from mother, 25 in recipients from fathers). Acute rejection episodes occurred in 46 recipients of a kidney from mother and 38 recipients of a kidney from father (ns). Cox proportional hazards analysis showed that only donor age and rejection significantly influenced the risk of graft failure censored for death.
Conclusion: In recipients of kidneys from a parent, donor gender did not influence the risk of graft failure or the incidence of acute rejection. The NIMA effect is not detectable in our population of immunosuppressed recipients of a kidney donated by mothers.

Children as donors: a national pediatric intensive care study to assess procurement of organs and tissues

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Objectives: Shortage of size-matched organs and of tissues is the key factor limiting transplantation in children. Empirical data on the procurement process in children is sparse. This study aimed to gain insight into the recognition of potential pediatric donors in The Netherlands and the procurement process.
Methods: A national retrospective cohort study in the Dutch pediatric intensive care units. The records of 683 deceased children were analyzed by two independent donation experts and procurement process data were compared with the national protocol. Results: from 2003 thru 2006, 74 (11%) of the deceased children were found to have been suitable for organ donation and 132 (19%) for tissue donation. Sixty-two (84%) potential organ donors had been correctly identified, parental consent had been obtained and donation effectuated in 26/62 children (42%). Sixty-three potential tissue donors (53%) had been correctly identified, parental consent had been obtained and donation effectuated in 17/63 children (27%).
Conclusion: Recognition of pediatric organ donors by medical professionals is good, recognition of tissue donors may be improved. Efforts to address the shortage of organs and tissues for transplantation in children should focus on the gap between recognition of donors and parental consent. We suggest such studies should not only assess the process itself, i.e. the competencies of the professional staff (micro-level) but also the influence of legislation, societal views on donation by children, and the potential relevance of children's views on donation (macro-level).

Potential donor loss after consent, what are the reasons for non-procurement?

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Purpose: As long as there is a shortage of transplantable organs and a considerable number of patients still die on the waiting list, we have to make great efforts to optimize deceased donation. Medical record reviews of deceased patients in intensive care units (ICU) in The Netherlands have shown that the number of potential organ donors (OD) is 2-3 times higher than the number of actual donors. Refusal by relatives is the main reason of potential OD loss, but also *after* consent potential OD are lost before final organ procurement. In order to clarify and promote best donation practices after consent, we quantified and evaluated the reasons of this loss for different settings.
Material and Methods: Medical records of patients died in the ICU from 72 Dutch hospitals during the years 2007-2010 were reviewed. Data regarding donation were collected in a centrally registered database (MSO). We quantified the number of potential heart beating donors (HBD) and non-heart beating donors (NHBD, < 66 years) who were lost after consent was given by the family. We also compared these numbers for different hospital types and donor regions. Reasons for non-procurement were evaluated.
Results: Among potential OD with consent (199-265 donors per year) procurement was realized in 82%, 93% in HBD and 71% (2007) until 59% (2010) in NHBD. Procurement was 86% in the 7 academic, 79% in the 27 top clinical to 74% in the 38 peripheral hospitals. Eastern donor regions, including Utrecht, showed the highest procurement rates (86-88%) and western regions lower rates (68-79%). Most frequent reasons for non-procurement after consent were medical unsuitability at a later stage (10%) and no cardiac arrest within the time limit of two hours after treatment stop in potential NHBD (5%, 13% of NHBD). But also logistical/clinical problems, withdrawal of a previously consent for donation by relatives, or lack of permission from the coroner were reported.
Conclusion: There is a considerable loss of potential OD in the ICU after the family consented to donate, mainly caused by medical problems at a later stage or no occurrence of cardiac arrest within the time limit for NHBD. Further analyses are needed to find out if changes in donor identification (eg. earlier recognition of medical unsuitability, or change of the 2-hr time limit in NHBD) or donor treatment could increase the donor procurement ratio after consent has been given. Further details might be expected in March 2012.

Illness perceptions and treatment beliefs about immunosuppressive medication after kidney transplantation

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Background: Nonadherence to the immunosuppressive medication regime is a risk factor for poorer clinical outcomes after kidney transplantation. In other patient groups, illness perceptions and indifferent or sceptical attitudes towards medication have been related to nonadherence. The aim of this study was to investigate the illness perceptions and treatment beliefs among kidney transplant patients, and the extent to which these are related to medication adherence.
Methods: Consecutive patients were invited to participate in a face-to-face interview 6 weeks after kidney transplantation. This is the first wave (N=112) of an ongoing prospective study. Adherence was measured using the self-reported Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS©-interview). Beliefs were measured using the Brief Illness Perceptions Questionnaire and the Belief about Medicines Questionnaire. Patients were categorized into attitudinal profiles: Accepting, Ambivalent, Indifferent or Sceptical. Questions were also posed on importance of medication as a personal goal, alignment with other goals and self-efficacy.
Results: Seventeen percent (n=19) of patients were classified as nonadherent (missed a dose or >2 hours early or late). Mean overall adherence rating was 96.4 (77-100). Ninety-eight percent indicated greater necessity for medication than concerns. With regard to attitude profiles, 86% were Accepting (high necessity/low concerns), 13% were Ambivalent (high necessity/high concerns) and 1% were Sceptical (low necessity/high concerns). There were no significant differences in beliefs and illness perceptions between the adherent and non-adherent patients when categorized. However, greater overall adherence was positively correlated with the belief that the graft would last longer, higher personal control, greater necessity of the medication, greater goal importance and goal alignment. Adherence was negatively related to the number of transplant-related complaints.
Discussion: Just 6 weeks after transplantation 17% self reported nonadherence. Patients were generally either accepting or ambivalent about their medication. The way in which patients think about their illness and medication is related to their self-rated adherence behaviour. Illness perceptions and treatment beliefs are therefore important targets for intervention. How beliefs are related to changes in adherence over time will be investigated prospectively in this ongoing study.

Higher organ donation consent rates by relatives of potential uncontrolled donors versus potential controlled donors after death

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Background: Refusal to consent with organ donation is the main cause of the persisting gap between the number of potential organ donors and effectuated organ donors. In The Netherlands, besides donation after brain death, donation after cardiac death (DCD), is common practise. Uncontrolled DCD donors, patients who die after failed resuscitation and controlled DCD donors, patients in whom treatment was discontinued are used. Data on differences in consent rates are limited. Different donor type implies a different setting in which the relatives are approached with the request for organ donation. It is unknown if this setting influences the eventual decision for donation or not. Therefore we compared the consent rate in a uncontrolled and controlled setting.
Methods: 523 potential organ donors between 2003 and 2011 in the 715-bed Maastricht University Medical Centre, The Netherlands were included. Both the patients' registration in national Donor Register (DR) and the relatives' refusal rate in the different groups of donors were retrospectively assessed using data from the donation application database. Results 103 uncontrolled and 420 controlled potential donors were identified. Uncontrolled donors were younger (mean age 52 vs.55 years, p= 0.036) and more often male (69% vs. 52%, p 0.002). The registration rate within the DR was equivalent: 43% of the uncontrolled and 49% of the controlled potential donors were registered. The relatives' consent rate in potential donors who were not registered or placed the decision to relatives, was higher in the uncontrolled donor group (53% vs. 29%, p < 0.001).
Conclusion: Less than 50% of the potential donors were registered in the national Donor Register. Therefore the relatives have an important role in the choice for organ donation. The relatives of uncontrolled potential donors consented more often than those of controlled potential donors.

Cold ischemia time in The Netherlands: Insight in the course of time in the chain of donation and transplantation

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A longer duration of Cold Ischemia Time (CIT) is related to the incidence of Delayed Graft Function (DGF), Primary Non Function (PNF) and a reduced graft survival. To reduce the CIT it is necessary to understand in which part of the process from donation to transplantation the delay occurs. Insight into the loss of time for each process step in the logistics chain is lacking. Benchmarking with surrounding countries show a higher CIT in The Netherlands. To retrieve more information about the Dutch situation, we investigated the average CIT of kidneys that are both donated and transplanted in The Netherlands. Our study is based on all heartbeating (HB) and non-heartbeating III (NHBIII) kidneys that were donated and transplanted in 2009 and 2010 in The Netherlands. The logistics chain with regard to the kidney is divided into 5 steps, with the following time points: start perfusion aorta, nephrectomy time, departure from donor hospital, arrival in transplant center, time of transplant. Per process step, the registered times are charted. In 2009 en 2010 a total of 620 HB and NHBIII kidneys were donated and transplanted in The Netherlands, but only for 517 kidneys the CIT was registered. This included 295 HB kidneys with an average CIT of 15,8 h and 222 NHBIII kidneys with an average CIT of 16,6 hours. If an average CIT per transplant center is calculated, the difference between the center with the shortest and the center with the longest CIT is 6,5 hours. Specification per process step shows an average shipping time of kidneys within The Netherlands of 2 hours. The average time between 'time of arrival' in the transplant center and the 'time of transplant' is 10 hours, with a difference between the two extreme centers of 3 hours.
The limited impact of transport on the total CIT and the time difference between arrival at the transplant center and the eventual transplantation, suggests that there is room for improvement in the donation and transplantation logistics chain, specifically in the transplant center. We are working on further analysis in which we include data from 2011 and the other process steps.

The Clinical Relevance of Luminex-Defined Complement Fixing HLA antibodies in Kidney Transplantation

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Background: Pretransplant risk assessment of graft failure is important for donor selection and choice of immunosuppressive treatment. As detection of C1q fixing donor specific HLA antibodies may identify patients at risk for graft loss, we examined the relation between kidney graft failure and the presence of IgG versus C1q fixing HLA DSA in pretransplant sera.
Methods: Pretransplant sera of 837 crossmatch negative kidney transplantations, performed between 1990-2008, were retrospectively analyzed for the presence of donor-specific IgG and C1q fixing HLA antibodies by luminex single antigen beads. In addition, data from both luminex assays were directly compared including their sensitivity and specificity for correctly predicting conventional complement dependant crossmatch results.
Results: Two-hundred and ninety (35%) out of 837 sera contained IgG-DSA whereas only 30 (4%) sera had C1q fixing DSA. A death censored analysis showed that graft loss was significantly higher in patients with IgG DSA compared to those without HLA antibodies ($p=0.02$). The presence of IgG DSA against only HLA class-I or only against class-II did not result significantly more graft loss compared to patients with non-DSA HLA antibodies. However, the combination of class-I plus –II DSA resulted in a 10yr graft survival of 30% whereas patients without HLA antibodies had a long term graft survival of 72% ($p<0.001$). When patients were separated according C1q DSA status, no significant difference could be found between patients with C1q DSA compared to those without HLA antibodies. A direct comparison between both luminex assays showed that high MFI values on the pan-IgG luminex assay are related to positive signals by the C1q assay. Furthermore, analysis of IgG anti-HLA and C1q fixing HLA antibodies showed a comparable sensitivity and specificity with regard to prediction of crossmatch results.
Conclusions: In crossmatch negative kidney transplantation, the presence of class-I plus –II IgG DSA as detected by luminex in pretransplant sera of kidney recipients is indicative for an increased risk for graft failure, whereas assessment of C1q fixing HLA antibodies has no additive value in this respect.

Successful treatment of allograft rejection after renal transplantation with autologous bone marrow derived mesenchymal stromal cells

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Despite excellent short-term results, long-term survival of transplanted kidneys has not improved accordingly. Mesenchymal stromal cells (MSCs) have anti-inflammatory and anti-fibrotic properties, prevent renal injury in preclinical models, and may constitute a new therapeutic option for allograft rejection and to prolong organ survival. We report results of 5 kidney allograft recipients who received expanded autologous bone marrow derived MSCs because of rejection and/or increased IF/TA in the protocol biopsy compared to the renal biopsy 4 weeks after transplantation. MSCs fulfilled the release criteria and demonstrated *in vitro* immunosuppressive capacities comparable to MSCs from healthy controls. The MSC infusion was well tolerated and there were no adverse events. In 2 recipients of full HLA-DR mismatched living donor kidneys with allograft rejection we performed a surveillance biopsy after MSC infusion. In patient A, the 6-month protocol biopsies showed severe T cell-mediated acute rejection (Banff 1b) and in patient B borderline subclinical rejection with mild IF/TA (Banff <1a). MSCs were infused while immunosuppressive drugs remained unchanged. In both patients, biopsies showed resolution of the interstitial infiltrate and no signs of IF/TA after the MSC infusion. Three patients developed an opportunistic viral infection, despite the fact that maintenance immune suppression was not changed. Patient C developed a BK-virus associated nephropathy 21 weeks after the infusion. In patient D a late primary CMV infection was diagnosed 2 weeks after MSC infusion. In patient E a low grade CMV viral load persisted in the months after MSC infusion, despite reduction of immune suppression. All patients recovered uneventful with antiviral therapy and reduction of immune suppression.
In conclusion, these first clinical observations support the potential of MSCs as novel cell therapy to prevent acute renal allograft rejection and further option to reduce exposure to (nephro)-toxic drugs. The observed systemic immune suppression after MSC infusion implies the need for careful monitoring of opportunistic viral infections.

Machine perfusion or cold storage in deceased-donor kidney transplantation – 3-year follow-up

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In 2009, we showed in an international RCT that hypothermic machine perfusion (MP) of deceased-donor kidneys significantly reduced the risk of delayed graft function compared to cold storage (CS) preservation. We also found that 1-year graft survival was significantly better after MP. As preservation related effects have so far been shown to affect early function only, we decided to extend the follow-up period of our study and investigate whether this substantial graft survival advantage would persist 3 years after transplantation. In our study, one kidney of each included donor was randomly assigned to MP, and the contralateral organ to CS. For the present analysis, all 60 collaborating transplant centers were contacted. Three-year follow-up data were collected from all 672 recipients of consecutive kidneys donated after brain death or after cardiocirculatory death in the main data set, as well as 164 recipients of kidneys donated after cardiocirculatory death in the extended data set. End points were 3-year graft survival, patient survival, and serum creatinine. Overall, 3-year graft survival was better for MP kidneys (91% vs. 87%, adjusted hazard ratio (HR) for graft failure 0.60, p=0.04). Differentiated to donor type, 3-year graft survival after MP was superior to that after CS for kidneys donated after brain death (91% vs. 86%, adjusted HR 0.54, p=0.02), but not for kidneys donated after cardiocirculatory death. The 3-year graft survival advantage after MP was most pronounced for kidneys recovered from expanded criteria donors, (86% vs. 76%, adjusted HR 0.38, p=0.01). Delayed graft function had a profound impact on graft survival of kidneys donated after brain death. Three-year patient survival and serum creatinine were equal in the two study arms.
We conclude that, 3 years posttransplant, graft survival of kidneys donated after brain death remained significantly better after MP compared to CS, especially in kidneys recovered from expanded criteria donors. Delayed graft function was associated with a notably lower graft survival of kidneys donated after brain death. Despite the large reduction in delayed graft function by MP in kidneys donated after cardiocirculatory death that we showed earlier, we found no beneficial effect of MP on graft survival in this subgroup. This could suggest a different type of delayed graft function in kidneys donated after cardiocirculatory death versus those donated after brain death.

POSTERS

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

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Background & aims: Chronic hepatitis C virus (HCV) infection is a leading indication for liver transplantation, but the outcome is often compromised by re-infection of the graft. Several studies have indicated that the use of corticosteroid-based immunosuppression is a risk factor for severe HCV recurrence. The success rate of interferon-a (IFN-α) based antiviral therapy is significantly lower post-transplantation than in a non-transplant setting, but the impact of steroids on the antiviral activity of IFN-α is unknown. Therefore, the aim of this study is to investigate the effect of steroids on the antiviral activity of IFN-α and the impact on the primary IFN-α-producing cells: plasmacytoid dendritic cells (pDCs).
Methods: Our model for HCV replication is a Huh7 hepatoma cell line stably transfected with the non-structural coding sequence of HCV coupled to a luciferase reporter gene (Huh7-ET). Cells were treated with IFN-α in the presence or absence of different doses of prednisolone or dexamethasone. A Huh7 cell line stably transfected with a luciferase gene under control of an interferon response element (Huh7-ISRE-Luc) was used to assess effects on IFN-α signal transduction. To study effects of steroids on pDCs, Huh7-ET cells were co-cultured with pDCs or diluted pDC conditioned culture medium in the presence or absence of steroids and TLR agonist loxoribin.
Results: HCV replication was inhibited by 10 IU/ml IFN-α by more than 99% of control levels. Treatment with increasing doses of corticosteroids did not significantly affect HCV replication. When combining IFN-α with corticosteroids, no interference with inhibition of HCV replication by IFN-α was found. Corticosteroids had no effect on IFN-α signal transduction in Huh7-ISRE-Luc cells. However, when Huh7-ET cells were co-cultured with stimulated pDCs, a significant reduction of HCV replication was found, that was almost completely reversed by steroid treatment. HCV replication was also inhibited by conditioned medium of stimulated pDCs, but no inhibition was observed with conditioned medium when pDCs were stimulated in the presence of corticosteroids.
Conclusion: We found no evidence that corticosteroids interfere with signal transduction and antiviral action of IFN-α. However, corticosteroids significantly affect the antiviral capacity of pDCs, thereby providing an explanation for the observed severity of HCV recurrence by steroids.

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

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Introduction: The need for life-long treatment with drugs that suppress the immune system non-specifically severely impairs the quality of life and patient survival after organ transplantation. Prevention of graft rejection by induction of donor-specific immunosuppression would enable graft survival without generalized immune paralysis. We have recently shown that human plasmacytoid dendritic cells (PDC) after stimulation via Toll-Like Receptor (TLR)-7 or 9 induce the differentiation of CD8+LAG-3+CTLA-4+ regulatory T-cells (Treg) that potently suppress T-cell allo-responses in a donor-specific manner. Interestingly, these CD8+ Treg not only inhibited naïve T-cells, but also allo-reactive memory T-cells, which are resistant to most tolerance induction protocols. The aim of this study was to optimize the yield of CD8+ Treg generated in co-culture with allogeneic PDC.
Results: PDC activated by CD40-ligation induced a 1,4-fold more allogeneic CD3+ T-cell expansion compared to PDC activated by TLR-7 ligation. After co-culture of CD3+ T cells with CD40-ligated allogeneic PDC, 24 ± 5% of CD8+ T-cells (n=4) showed a Treg immunophenotype expressing LAG-3 and CD38, compared to 14± 5% after co-culture of T-cells with TLR7-ligated allogeneic PDC. The yield of CD8+ Treg after co-culture of CD3+ T cells with CD40-activated allogeneic PDC was 2.3-fold higher compared to co-cultures of CD3+ T cells with allogeneic PDC activated by TLR-7 ligation. The capacity of CD8+ Treg generated in co-cultures with CD40-activated PDC was similar to those generated by TLR7-activated PDC.
Conclusion: PDC activated by CD40-ligation are superior to PDC activated by TLR-ligation to induce generation of CD8+ Treg. Donor-derived CD40-activated PDC may be considered as an immunotherapeutic tool to prevent activation of recipient allo-reactive T-cells after organ transplantation.

Optimizing alloantigen presentation as a tool to monitor indirect alloantigen presentation in renal transplant recipients

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T-cell allorecognition, after transplantation, occurs in two different manners: recognition of intact HLA on donor antigen presenting cells (APC, direct pathway), associated with acute rejection, or recognition of donor-derived HLA peptides restricted by self-HLA on recipient APC (indirect pathway) associated with chronic rejection and the occurrence of activated T-helper cells with properties of B-cell help. Current strategies to monitor alloreactive T-cells (MLR and CTLp) are restricted to cells with direct specificity. There are no consistent assays for the monitoring of indirect presentation. In this study we have used a model system to investigate indirect allo-presentation and adapting this model to a clinical setting. Methods: HLA-DR1+/HLA-A2- monocyte derived dendritic cells (moDC), monocytes or PBMCs, were incubated with different concentrations of HLA-A2 monomer/peptide for different time periods. A CD4+ T-cell clone that specifically recognizes HLA-A2 derived peptides in the context of HLA-DR1 was used as readout for HLA-A2 presentation. Supernatants were collected and IFN-γ was measured at different time points, as a marker for T-cell activation. Results: Addition of intact HLA-A2 monomer to HLA-DR1+/HLA-A2- moDC resulted in specific antigen presentation and a dose dependent increase of IFN-γ secretion by the T-cell clone. T-cell recognition occurred only when HLA-A2 was presented in the context of HLA-DR1 (peptide/monomer) indicating a high specificity. Similar results were achieved when monocytes and PBMCs were used. Conclusions: In this study, we have shown that intact HLA-A2 monomers can be used as a specific tool to allow indirect antigen presentation by PBMC,moDC and monocytes and can be used as a clinically applicable assay to monitor indirectly activated T-cells in renal transplantation recipients.

NK cell activation is dependent on HLA-E surface expression and the peptide presented by HLA-E

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Aim HLA-E is a non-classical MHC class I molecule and plays a crucial role in immune surveillance by presentation of peptides to T and NK cells. HLA-E interacts with inhibitory (NKG2A) or activating (NKG2C) receptors on the NK cells. There exist two functional alleles in the population, HLA-E*01:01 and HLA-E*01:03, which differ by only one amino acid. HLA-E expression and genotype has been described to influence patient outcome regarding various cancer types and the outcome in the stem cell transplantation setting. Our aim is to study the impact of the HLA-E polymorphism and the bound peptide on RNA levels, surface expression and NK cell functionality. Methods PBMC from 20 healthy donors homozygous for HLA-E*01:01 or E*01:03 were analysed for RNA and surface expression by Q-PCR and flowcytometry, directly and after incubation with peptides. These PBMC were also used as target cells to study NK cell activation by analysis of the degranulation marker CD107a. Simultneous, the NK cells were stained for NKG2A, NKG2C and KIR to study activation within the various NK cell subsets. Results Our data showed no difference in HLA-E RNA expression between HLA-E*01:01 and HLA-E*01:03, however basal surface expression in HLA-E*01:01 was lower when compared to HLA-E*01:03. In all donors, HLA-E expression was upregulated after 13 hours of incubation with CMV or class I leader peptides. HLA-E surface expression was significantly higher on HLA-E*01:03 homozygous PBMC as compared to HLA-E*01:01. Our data demonstrates that peptide induced HLA-E expression is influenced by both the polymorphism and the peptide. NK cell activation was regulated by HLA-E levels as degranulation of NK cells expressing the inhibitory NKG2A+ receptor was blocked by peptide augmented HLA-E expression, interestingly with exception of C17 peptide. An inhibition of NK cell activation was not found in NKG2A- cells nor upon incubation with a control or the Hsp60 peptide. NK cells expressing the activating NKG2C+ receptor showed increased degranulation after upregulation of HLA-E by HLA-A80 and -B13 leader peptides. Conclusions Our study describes a clear difference in HLA-E surface expression between HLA-E*01:01 and HLA-E*01:03 in PBMC from healthy donors upon peptide incubation. In addition, we showed that NK cell activation is regulated by HLA-E expression levels and by the presented peptide which seems relevant for NK cell responses against virally infected- or tumour cells.

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

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

Aneuploidy in Mesenchymal Stem Cells Cultured for Clinical Application in Solid Organ Transplantation

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Introduction: Mesenchymal Stem Cells (MSC) are of great interest as a cell therapeutic agent in clinical organ transplantation. For clinical purposes, MSC are expanded in vitro. During this expansion, MSC can be at risk for genetic alterations such as aneuploidy. Because this is suggested to be a predecessor of cancer, genetic screening is essential. In the present study we examined the presence and development of aneuploidy in MSC cultures and evaluated the implications of aneuploidy on the applicability of MSC for therapeutic use.
Methods: We isolated and expanded adipose tissue derived MSC from healthy controls and studied the copy numbers of chromosomes using FISH analysis. The occurrence of aneuploidy was studied in cultured MSC from passage 0 till 19 and in proliferating as well as senescent MSC cultures.
Results: Using FISH analysis, tetraploidy was detected in on average 4.7 %(range 1-11.5%) and octoploidy in 0.2 % (range 0.0-0.4%, detected in 4 cultures) of MSC cultures. On average, 94.6 (range 88.5-98%) of the MSC were diploid. Figure 1 shows a representative example of 3 diploid and 1 tetraploid MSC. Percentage of tetraploid cells was independent of passage number and aneuploidy was even detected in passage 0 MSC. However, when MSC cultures reached senescence, tetraploidy dramatically increased to a mean of 18.3% (range 12.3-25.2%). Nevertheless, no transformation of MSC was observed in these cultures. Finally, we observed some tetraploid MSC in metaphases, indicating that tetraploid MSC were capable of cell division.
Conclusion: In conclusion, we found aneuploidy in cultured MSC. The percentage of aneuploidy was independent of passage number and increased when MSC reached senescence. These results indicate that a small percentage aneuploidy in MSC is a natural phenomenon. Therefore, we believe that this should not compromise clinical application.

Serum HLA-G is associated with liver inflammation rather than with liver graft acceptance

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HLA-G is a non-classical HLA class I molecule with immunoregulatory properties and a restricted expression. While in human pregnancy HLA-G has been shown to play a role in promoting maternal immunological tolerance towards the semi-allogenic fetus, its function in solid organ transplantation is still debated. The aim of this study was to determine whether serum HLA-G levels are associated with graft acceptance after liver transplantation (LTX).
Serum HLA-G levels were quantified in a cohort of 28 patients with end-stage liver diseases, both before transplantation and at several time points during the first year after transplantation, and for comparison in 24 age- and gender-matched healthy subjects. While 92% of the healthy subjects had no circulating HLA-G, 86% of LTx-recipients were HLA-G-positive before transplantation. Starting at one month after LTX, serum HLA-G levels gradually decreased. Patients with an acute rejection episode displayed significantly elevated serum HLA-G concentrations compared to non-rejectors during the first two weeks after LTx, which is the time interval during which the acute rejection episodes occurred. Pre- and post-LTx serum HLA-G levels were positively correlated with serum transaminases and bilirubin.
Conclusion: Our data do not support the hypothesis of a tolerogenic role for HLA-G after LTX, but rather suggest that HLA-G expression is associated with states of liver inflammation.

CMV-specific CD8 T cells in lymph nodes: a rare but special breed

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It is believed that the size of the CD8 T cell pool is fixed and that with every new viral challenge the size of pre-existing memory cell population shrinks to make way for the new virus-specific cells. In hCMV-seropositive individuals a large part of the circulating CD8 T cells is directed against hCMV. This prompted us to analyze hCMV-specific CD8 T cells at sites where immune reactions are initiated, i.e. in lymph nodes (LN). LN and paired peripheral blood (PB) hCMV-IE- and pp65-specific CD8 T cells of kidney transplant recipients were analyzed for phenotype and function (granzyme content and cytokine profile) by FACS. Clonal relationships were studied by high-throughput-sequencing of the TCR-Vβ-CDR3 region. Only few hCMV-specific CD8 T cells were found in LN and these contained substantial percentages of CCR7-expressing central-memory-type cells, a phenotype hardly found in blood. In contrast the percentage of CX3CR1-expressing CMV-specific CD8 T cells in LN was significantly decreased. CDR3 analysis revealed that hCMV-pp65-specific CD8 T cells consisted of more clones in blood than in LN. Surprisingly some of these clones were unique for LN. In contrast hCMV-IE-specific CD8 T cells consisted of only few clones that were identical between PB and LN.
Thus hCMV-specific CD8 T cells in LN are not likely to compete for space with other virus-specific cells, indicating that T cell responses to hCMV do not restrain reactions to other viruses. Moreover, the differences in phenotype and CDR3-usage between PB and LN suggest that hCMV-latency may be retained by functionally different clones.

Varicella zoster virus vaccination induces virus-specific class II restricted memory responses in seronegative renal transplant recipients

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Primary varicella zoster virus (VZV) infection causes varicella and may reactivate as herpes zoster. The host immune system, mainly T-cells, is pivotal to control and prevent VZV infection and reactivation, respectively. Consequently, VZV infections in immune compromised patients can be extremely severe with multi-organ failure and eventually death. In our centre between 1999 and 2002, four VZV seronegative adult renal transplant recipients had serious complications of varicella of whom 2 patients died. Therefore, VZV-seronegative patients in our centre on the waitlist for renal transplantation are now scheduled for a two dose VZV vaccination regimen.
The aim of the present study was to determine the VZV-specific B- and T-cell response in seronegative adult renal transplant recipients (n=10) before and after vaccination. Blood was sampled before vaccination and after renal transplantation (mean: 68±30 weeks post vaccination). VZV sero-status was determined by ELISA. $CD3^+$ T-cells and $CD14^+$ monocytes were isolated from PBMC. $CD14^+$ were differentiated into mature moDCs and infected with VZV. T-cells were co-cultured with autologous mock- and VZV-infected moDCs to determine the frequency of VZV-reactive naïve (NA: $CCR7^+CD45RO^-$), central (CM: $CCR7^+CD45RO^+$) and effector memory (EM: $CCR7^-CD45RO^+$) T-cells (i.e. IFN-γ^+) by flowcytometry. Seven of 10 vaccinees seroconverted. No effect was seen on VZV-reactive NA cells and $CD8^+$ CM and EM T-cells. However, the percentage of VZV-reactive $CD4^+$ CM and EM T-cells significantly increased in the 7 VZV seroconverted patients ($p=0.03$) and in one patient who did not responded with an antibody response to the vaccination procedure.
In conclusion, varicella zoster virus vaccination induces, in addition to VZV antibody titres, VZV-reactive $CD4^+$ memory T-cells.

Recovery of VZV-specific T- and B-cell responses by herpes zoster infection after lung transplantation

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Reactivation of varicella zoster virus (VZV) results in herpes zoster (HZ). Compared to healthy individuals, the incidence and severity of HZ is higher in transplant recipients. We questioned whether the VZV immune status of lung transplant patients determines the risk of developing HZ. Ten lung transplant recipients were tested of whom 5 patients developed HZ. All patients experienced varicella during childhood. Blood was sampled before and approximately 6 months after HZ. $CD3^+$ T-cells and $CD14^+$ monocytes were isolated from PBMC. $CD14^+$ were differentiated into mature moDCs and infected with VZV. T-cells were co-cultured with autologous VZV-infected moDCs and subjected to flowcytometric analysis to determine the frequency of VZV-reactive naïve (NA: $CCR7^+CD45RO^-$), central (CM: $CCR7^+CD45RO^+$) and effector memory (EM: $CCR7^-CD45RO^+$) T-cells (i.e. IFN-γ^+, IL-2^+). VZV IgG titres were determined, and the VZV-specific B-cell Elispot was used to quantify the relative number of VZV antibody secreting B-cells. The VZV-specific IgG titre increased in 4 out of 5 patients after HZ, while the antibody levels were similar to those without HZ. In 4 out of 5 patients the number of VZV-specific IgG producing B-cells increased after HZ to higher frequencies than those without HZ ($p=0.06$). No difference in VZV-reactive NA cells were found. The percentage of VZV-reactive CD4 and CD8 CM and EM T-cells increased in all patients after HZ to significantly higher frequencies compared to those without HZ ($p=0.03$).
In conclusion, while immunosuppressed lung transplant recipients are prone to develop HZ, they are perfectly able to mount adequate frequencies of VZV-reactive B- and T-cell memory cells.

Kinetics and characteristics of monocyte subsets in kidney transplant recipients

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Although a major contribution of monocyte-macrophage cell lineage to kidney graft rejection and injury has been documented, it is unclear how the monocyte-macrophage related responses develop after kidney transplantation. Macrophages are present in large numbers in acutely rejecting grafts. Monocyte accumulation in peritubular capillaries is one of the main features of acute humoral rejection. The correlates of innate immunity to graft rejection and survival remain to be elucidated. Here, we analyzed the kinetics and characteristics of peripheral blood monocyte subsets after kidney transplantation. By flow cytometry the phenotypic characteristics of classical (CD14++CD16-), intermediate (CD14++CD16+) and non-classical (CD14+CD16++) monocytes were measured. To study the activation status, cell surface expression of co-stimulatory molecules CD40 and CD80 and MHC class II molecule HLA-DR was determined. Whole blood analysis was performed in a cohort of 22 healthy individuals, 22 renal transplant recipients at the time of transplantation, 9 recipients at 3 months, and 9 recipients at 6 months after transplantation in a cross-sectional approach. Our data reveal that, as a sign of triggered innate immunity, the percentage of CD14/16+ intermediate-non classical proinflammatory monocytes was significantly increased at the time of transplantation compared to healthy individuals (22.3% ± 2.3 and 15.1% ± 0.9 respectively, $p \leq 0.001$). Remarkably, despite potent immunosuppressive drugs, this increase in proinflammatory monocytes, and the concomitant decrease in the classical subset (69.3% ± 3.4 and 74.9% ± 1.5 respectively, $p \leq 0.001$) was retained during the post transplant course when the kidney function was recovered. Although the percentage of CD40 and CD80 expressing monocytes and the level of cell surface expression of CD40, CD80 and HLA-DR within the different monocyte subsets did not differ between kidney transplant recipients and healthy individuals, the percentage of HLA-DR expressing monocytes was significantly increased at the time of transplantation. This reached a minimum at 3 months and was followed by a recovery towards normal range after 6 months.

In conclusion, in kidney transplant recipients the balance in monocyte subsets is skewed towards intermediate and non-classical subsets. This shift could be one of cellular drivers of early post-transplant immunity that may determine the outcome of kidney transplant.

Molecular typing methods for the non-classical HLA-E gene

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Introduction The non-classical HLA-E gene displays limited polymorphism, the nine different alleles encode only 3 different proteins. Two of them, HLA-E*01:01 and *01:03, are present with equal frequencies in the population, whereas the existence of the third one, *01:04, is doubtful. HLA-E might play a role in CMV infection, because a CMV peptide, that mimics the leader peptide of classical HLA class I proteins, can bind to HLA-E and act as ligand for CD94/NKG2 receptors, thus preventing cell lysis. Furthermore, differences in expression levels between the different HLA-E alleles have been reported and a role for HLA-E polymorphism in stem cell transplantation has been postulated. Material and methods To enable routine typing of large cohorts of individuals, three different typing methods were developed. Results The PCR-SSP method uses two different 5' primers and a generic 3'primer that distinguish the non-synonymous difference of HLA-E*01:01 and HLA-E*01:03 at amino acid position 107. The PCR-SSO method is based on the Luminex technology, using different probes for HLA-E*01:01, HLA-E*01:03 and HLA-E*01:04 attached to labelled beads, kindly provided by One Lambda INC, Canoga Park, California, USA. The SBT method is a direct sequencing method based upon PCR amplification and sequencing with specific primers enabling sequencing of exons 1 to 5 and the intervening introns, identifying all synonymous and non-synonymous substitutions.
Conclusion HLA-E diversity can be addressed at the molecular level by differrent approaches. High throughput HLA-E typing of many samples is necessary to understand the influence of HLA-E alleles in SCT and association with diseases enabling conclusions of the contradictory results obtained so far.

The importance of HLA-DPB1 full length polymorphism in stem cell and organ transplantation

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Aim: Despite DP antigens have been shown to be stimulators of the mixed lymphocyte reaction, HLA-DPB1 is not considered in the matching criteria for hematopoietic stem cell transplantation (HSCT). The role of DPB1 matching in HSCT remains inconclusive due to contradictory findings in different studies. The concept of permissible and non-permissible mismatches might clarify these contradictory results. Although several groups have attempted to identify immunogenic epitopes in exon 2 to establish permissive and non-permissive allele groups, the direct correlation between individual exon 2 amino acids and epitopes with DPB1 immunogenicity is still not evident. We hypothesize that polymorphism within the entire molecule, including polymorphic variability in different ethnic groups, is crucial to unravel the function of DPB1 polymorphism. Methods: Using an RNA based approach we sequenced all frequent and available non-frequent DPB1 alleles full length from 148 samples representing 28 different DPB1 alleles from either Black, Caucasian or Oriental origin. Results Our study demonstrates that multiple DPB1 alleles showed additional variation in exon 1, 3, 4 and 5. Moreover, various alleles with identical exon 2 sequences also showed polymorphism in the other exons. Based on the newly defined polymorphisms in exon 4 and 5 one new DPB1 allele was identified. Furthermore, the polymorphisms outside exon 2 were variable in different ethnic populations, which suggest differential evolutionary origins for these alleles.
Conclusions: Ultimately, the combination of full length polymorphism with T-cell recognition of HLA-DPB1 epitopes in stem cell transplantation and antibody specificity in organ transplantation may lead to the definition of functionnally relevant epitopes.

Primary varicella infection and disseminated varicella zoster virus reactivation in renal transplant recipients

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Background: Primary varicella zoster virus (VZV) infection causes varicella and may reactivate later in life as herpes zoster. In immune compromised hosts, both primary VZV infection and reactivation is potentially life threatening.
Aim: We investigated the clinical outcome of renal transplant recipients who developed primary infection with VZV or had reactivation of VZV, comprising disseminated VZV and ocular manifestation of VZV.
Methods: All adult renal transplant recipients of our centre were evaluated for VZV infections between January 2000 and November 2011. In 2003 we started routinely vaccination of VZV-seronegative potential renal transplant candidates. Primary VZV infection was defined as varicella in patients who were documented seronegative for VZV (IgG <0.60AU) and had no history of varicella. Disseminated reactivation is defined as involvement of 4 or more skin dermatomes or visceral or neurological manifestations. Ocular zoster is defined as a complication of involvement of the ophthalmic division of the fifth cranial nerve, confirmed by an ophthalmologist.
Results: We found 24 cases of primary varicella, disseminated VZV reactivation and/or ocular zoster (18 male, 6 female, median age 48.0 years (range 23-76), time after transplantation 10.0 months (0.5-118)). 7 patients (29%) had primary infection (age 34.0 years (23-76)), of whom 2 patients died. 4 of them (57.1%) were born in the tropics. 13 patients (54.2%, age 55.0 years(35-75)) had disseminated VZV reactivation, with skin-eruptions being the most common presenting symptom (11/13, 84.6%), one patient solely had neurological symptoms at time of admission and one patient presented with severe abdominal pain. 3 patients (23.1%) developed multi organ failure (MOF) and died. One other patient had extensive gastro-intestinal VZV-ulcers with bacterial super infection and MOF, but survived, 2 patients had notable accompanying SIADH. 2 patients developed encephalitis but recovered completely. 6 of all 24 patients (25%) had ocular zoster and in 4 this was not accompanied by other organ-involvement. One patient lost vision of one eye.
Conclusion: Both primary VZV as well as disseminated reactivation is associated with considerable mortality and morbidity in renal transplant recipients. We advise to vaccinate VZV seronegative candidates on the waiting list for transplantation to prevent VZV infection.

Pre-transplant parameters predict survival during and after liver transplantation

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Introduction: Prediction of survival in patients after liver transplantation (LT) remains challenging. Several models and parameters have been suggested, all with different cut-off values or points of measurement. Most studies include parameters up to 1-month before transplantation and focus on 1-year survival. Patients however are more interested in staying alive with or without transplantation, or their intention-to-treat survival. In this study we aim at identifying factors that predict survival during LT and post-LT survival.
Methods: Patients transplanted at our center between 2004 and 2008 were analyzed for post-LT survival. The last available routine blood laboratory tests before LT were collected. Blood samples had to be taken in the previous 24 hours before LT to be eligible for analysis. Comparison of means was done with student's t-test. Correlation analysis was done with Spearman's non-parametric test. Survival was assessed using Kaplan-Meier analysis. Multivariate analysis was performed with Cox regression analysis.
Results: In total 220 consecutive patients were transplanted and included for analysis. Univariate analysis showed a correlation between overall survival and the following pre-LT parameters: urea (P = 0.042), Hb (P = 0.007), Ht (P = 0.026), APTT (P = 0.012), patient height (P = 0.026), serum sodium (P = 0.032), albumin (P = 0.043), and creatinin (P = 0.04). Multivariate analysis with all pre-LT laboratory parameters showed that serum sodium, INR, PT and APTT were independent predictors of overall survival after transplantation. In this cohort 5 patients (2.3%) died on the day of transplantation. Creatinine levels were significantly higher in these patients (P = 0.003). No other pre-LT parameters were correlated with intraoperative mortality.
Conclusion: Pre-transplant serum sodium and coagulation factors, mainly APTT, are independent predictors of post-LT survival but not of mortality during transplantation. High serum creatinine is a risk factor for mortality during transplantation.

An overview of unspecified living kidney donors in The Netherlands

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Background: The first anonymous or altruistic donation to a stranger was conducted in 2000 in Rotterdam. The media, the 'Big Donor Show' in 2007, played an important role in the increase of these unspecified living kidney donors over the last years. Here we describe the unspecified living kidney donors who donated from 2000 until now in the 8 kidney transplant centers.
Methods: Data of 120 individuals who donated on an anonymous basis a kidney to a stranger were collected.
Results: The median input per center was 8 donors (range 1-70). The blood type of the donors was 63 times O (53%), 46 times A (38%), 6 times B (5%) and 5 times AB (4%). All donors have donated their kidney between 2000 - 2011 in the transplant centers where they were registered. 51 donors donated directly to a recipient on the wait list and 69 in a domino-paired procedure: 55 made 2 transplants possible, 12 donors donated in a triplet construction and 2 donors in a quartet procedure. So these 69 unspecified donors were enrolled in chain constructions which resulted in 154 kidney transplants. In total 120 unspecified donors made 205 kidney transplants possible.
Conclusion: With 69 chain constructions we have increased the number of kidney transplants by 123% from 69 to 154. Including all unspecified donors in domino-paired procedures would increase the number of transplants even more. All unspecified donors should be enrolled in chain constructions.
Keywords: unspecified donation (*F. Dor et al, Transplantation 2011, 91(9): 935*).

Hepatitis E virus in Renal Transplant recipients in a Tertiary Referral Centre in The Netherlands

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Introduction: Hepatitis E virus is an RNA-virus particularly causing large outbreaks of waterborne acute hepatitis in Asia, Africa and India. In the past years, autochthonous sporadic cases have been described in The Netherlands. Chronic Hepatitis E virus (HEV) infections have recently been described in solid organ transplant (SOT) recipients.
Aim: Determine the prevalence and clinical presentation of HEV-infection in renal transplant (NTX) recipients. Methods: All living NTX recipients of whom between 2009 and 2011 serum or EDTA-plasma was available were screened for HEV infection by real-time RT-PCR. A case of HEV infection was defined as HEV RNA positive and was confirmed either by serology (EIA IgM or IgG) and/or by presence of HEV RNA in sequential sample(s). Chronic infection was diagnosed by retrospective testing of stored samples and defined as HEV RNA positive > 6 months.
Results: In total 574 NTX-patients were screened. Three (0.52%) confirmed cases with a hepatitis E infection were identified. Two of these patients received multiple transplants (1 HTX-NTX and 1 LTX-NTX). In two of the confirmed cases (HTX-NTX and NTX) HEV infection evolved to chronic HEV. These patients had elevated AST and ALT. In the HTX-NTX patient hepatitis is progressive and liver biopsy showed inflammatory activity compatible with viral hepatitis, F2 fibrosis and grade 1 steatosis according to the Brunt classification. In the other two cases, liver enzymes are in normal range at present.
Conclusion: Acute HEV infection in renal transplant recipients occurred in 0.5% of the population studied and can cause severe progressive liver damage. Our study confirms kidney transplant patients being at risk for (chronic) HEV infection and HEV RNA screening must be performed in cases of unexplained hepatitis after renal transplantation.

Unspecified donation in case of nephrectomy for medical reasons

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Unspecified donations (altruistic donations) have been successfully implemented in our live donor kidney transplantation (KTx) program. Amongst them were patients diagnosed with a form of kidney disorder not impairing renal function, but nonetheless required nephrectomy. These kidneys are often suitable for transplantation. As autotransplantation has a considerable risk of complications, and has no benefit for these patients with normal renal function, unspecified kidney donation would be a good alternative. We retrospectively searched all clinical data of our live kidney donation program from 1994-2011. We identified all unspecified kidney donors and their recipients (n=71). Among those, 7 were referred to us as potential donors with pre-existing kidney disorders that necessitated a nephrectomy for medical reasons. We examined clinical course of these donors and graft survival in the recipients. Of 7 patients, 5 had an indication for nephrectomy because of therapy-resistant loin pain, 1 had a renal artery aneurysm, and 1 insisted on a nephrectomy, since she refused a urostomy after iatrogenic ureter injury during a leiomyoma resection. Of the 5 patients treated for loin pain, 1 previously had an infarction of a small part of the kidney, 1 had persistent pain after stone extraction. All laparoscopic donor nephrectomies were performed without major complications (median hospital stay 4 days) and all patients treated for pain were free of complaints after surgery (median follow up 20 months) 7 donors made 9 KTx possible (2 domino paired and 5 straight donations). In the recipients, there was one early death due to cardiac arrest, in a patient with pre-existent cardiac failure. All remaining recipients but one (of which the donor had an infarction in the past) had excellent graft function.
Discussion: The possibility of transplanting kidneys from donors with pre-existing kidney complaints necessitating a nephrectomy, has not been reported previously. Obviously, these potential unspecified donors should meet all criteria for live kidney donors. Our data show that donation as part of the treatment in selected kidney disorders is possible with excellent results in both donors and recipients.

The Utrecht experience on the management of HIV positive kidney transplant patients

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Introduction: Following the introduction of highly active antiretroviral therapy, life expectancy of HIV patients has improved and chronic complications such as kidney failure are seen more frequently. As a result an increasing number of HIV patients is accepted for kidney transplantation. The need for both sufficient immune suppression and HIV control gives rise to problems not encountered in the HIV negative population. Here we evaluate the clinical course and outcome of the Utrecht HIV kidney transplant program which started in 2005.
Methods: We retrospectively collected data up to November 2011 from patient files and the hospital database. The outcomes were compared to those described in international literature. Results are reported as median with their corresponding range. Results: 7 patients were transplanted in our center. All were male, 2 were Caucasian, 3 African and 2 African-American. Age at transplantation was 44 yrs (31-53), with a history of 5.0 yrs (1.5-10.2) of kidney replacement therapy and 7.5 yrs (1.7-18.7) of diagnosed HIV infection. Pre-transplantation CD4 count was >200/mm3 and HIV load < 50 copies/mL in all. Delayed Graft Function was present in 5 patients, with a median of 14 days (12-51). Creatinine at 1, 6 and 12 months was 245 (142-562), 208 (162-215) and 204 (144-365) umol/L respectively. CD4 count at 1, 6 and 12 months was 267 (46-311), 243 (110-661) and 315 (201-628) per mm3. At 12 months 3 viral reactivations (2 CMV, 1 HSV) and 1 Kaposi sarcoma had occurred. One patient showed virological failure due to poor drug compliance. Follow-up was 2 years (1.0-5.9), with a 100% patient and graft survival and a total of 5 acute rejection episodes in 4 patients.
Conclusion: In our cohort we find excellent patient and graft survival with a high rejection rate, which is comparable to reported results (Stock NEJM 2010). Good survival and the absence of serious HIV-related morbidity support the eligibility of HIV positive patients for kidney transplantation.

Intravesical versus extravesical ureteroneocystostomy in kidney transplantation: A systematic review and meta-analysis

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Objective: To determine if an intravesical or extravesical anastomosis in kidney transplantation is to be preferred.
Introduction: From the several techniques for facilitating urinary continuity of the transplanted kidney, the ureteroneocystostomy appears to be most widely accepted and is associated by the least number of complications. Nevertheless, urological complications are still a major problem postoperatively with a reported incidence in up to 30%, associated with significant morbidity, mortality, prolonged hospital stay and high medical costs. There is no evidence to conclude if an extravesical or intravesical approach is superior to the other. This review and meta-analysis was carried out to investigate whether there is a technique for the ureteroneocystostomy that is to be preferred.
Methods: Comprehensive searches were conducted in PubMed, Embase and the Cochrane Library. Reference lists were searched manually. The methodology was in accordance with the PRISMA statement.
Results: Two randomized controlled trials and seventeen cohort studies were indentified. Based on the meta-analysis, the relative risk (RR) of stenosis was 0.67 (confidence interval (CI)) 0.48-0.93, p=0.02), RR of leakage was 0.55 (CI 0.39-0.80, p=0.001), RR of total number of urological complications was 0.56 (CI 0.41-0.76, p=0.0002) and RR of haematuria was 0.41 (CI 0.22-0.76, p=0.005) in favour of the extravesical anastomosis group.
Conclusion: Based on these results there is evidence in favour of the extravesical ureteroneocystostomy technique for decreased urological complications in kidney transplantation.

Elimination of calcineurin inhibitors in paediatric renal transplant recipients

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Objectives: There is a growing number of reports on the use of everolimus in paediatric renal transplant recipients with calcineurin inhibitor (CNI) intolerance or chronic allograft nephropathy. We report the outcome of this alternative immunosuppressive regimen at our centre.
Methods: In 5 out of 41 renal transplant patients aged 7-14 years CNI were partially (n=1) or fully (n=4) replaced by everolimus 4 months to 8.5 years following transplantation. Concomitant immunosuppression consisted of mycophenolate mofetil (n=4), prednisolone (n=2) and low dose cyclosporine A (n=1). Indications included chronic fatigue and headache (n=2), encapsulating peritoneal sclerosis (n=1), intracranial hypertension with papillary oedema (n=1) and presumed chronic allograft nephropathy with refractory arterial hypertension (n=1). The follow-up period was 4-8 months. The target everolimus trough level was 4-9 µg/l.
Results: The mean dose required to achieve the everolimus target level was 1.5 mg/m² (range 1.2- 2 mg/m²). The mean eGFR at everolimus commencement was 68 ml/min/1.73m² (range 39-110 ml/min/1.73m²). In one child we observed an improvement in eGFR from 43 to 67 ml/min/1.73m² and reversal of papillary oedema whereas in the remaining 4 children the eGFR remained stable, but there was an improvement in the severity of complaints in 2 patients. None of the children had acute rejection and there were no infectious complications during the follow-up period. The mean cholesterol level increased from 4.84 to 5.25 mmol/l. No other adverse effects of everolimus were reported.
Conclusions: We observed a clear short term benefit of CNI replacement in one out of 5 children in eGFR and a clinical improvement in 2 children. We conclude that this immunosuppressive regimen can prove beneficial in the long term due to the lower risk of nephrotoxicity and chronic allograft nephropathy. Further studies are required to establish the role of everolimus in paediatric renal transplantation with regard to the indications and outcome.

Design of a simplified medication regimen in renal transplant patients by using tacrolimus OD (ADVAGRAF®)

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Background: Adherence to the immunosuppressive therapy is of great importance for a successful outcome after renal transplantation. In most transplant centers, tacrolimus forms the cornerstone of the immunesuppressive treatment. In tacrolimus-treated patients, the introduction of tacrolimus OD (ADVAGRAF®) potentially allows to simplify the treatment regimen in such a way that the total medication intake can be limited to one or two convenient time points per day (e.g. early in the morning and late in the evening). This simplification can be expected to increase treatment satisfaction and adherence.
Objective: To establish the percentage of tacrolimus-treated renal transplant patients in whom a simplified treatment regimen, including the use of tacrolimus OD, can be realized.
Patients and methods: The records of all patients who received a renal transplant between August 2006 and August 2010 in our center and still had a functioning graft were evaluated. We selected all patients treated with tacrolimus. Subsequently, we evaluated for every drug of the entire regimen whether this could be taken once daily (either early in the morning or at bedtime). This allowed us to calculate the percentage of tacrolimus-treated patients in whom medication intake can be limited to one or two convenient time points per day ('simple regimen').
Results: Between August 2006 and August 2010, 368 patients received a renal allograft that was still functioning, and 231 of these patients used tacrolimus. 31 of these patients used mycophenolate mofetil BID and they were excluded for further analysis. For 151 of the remaining 200 tacrolimus-treated patients (76%), it was possible to design a simple medication regimen. The main reason for which a simple regimen was not possible, was the use of antihypertensive drugs that could not be prescribed once daily (n= 22, 11%). In an additional 27 patients, the use of other drugs taken at multiple time points per day, like phosphate binders, prohibited a simple regimen.
Conclusion: In the majority of our tacrolimus-treated renal transplant patients, the introduction of tacrolimus OD allows the design of a simple medication regimen in which all drugs are taken at one or two convenient time points per day. Hence, opportunities to improve treatment satisfaction and adherence seem to be present.

Long-term outcome of renal transplantation in patients with a urinary conduit,a case-control study

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Introduction: To study the short- and long-term outcomes of kidney transplantation in patients with a bladder augmentation or substitution compared to patients with a kidney transplantation in a normal functional bladder.
Patients and Methods: Between January 2000 and March 2011, 13 patients received 16 grafts into a reconstructed urinary tract. We performed a retrospective case-control study and matched each patient to four controls for donor and recipient gender and year of transplantation.
Results: Short- en long-term complications of kidney transplantation occurred in 12 patients, varying from urinary tract infections to medical hospitalization with or without surgical or radiological intervention. In 5 patients a percutaneous nephrostomy drain was placed followed by surgical re-intervention. Three patients had a graft failure as a result of chronic rejection and the patients were re-transplanted. There was no graft loss as a result of surgical complications or related to the reconstructed urinary tract. One-year patient and graft survival was 100%. After five years all patients were alive and seven of the nine grafts (77.8%) were functioning. Mean follow up time was 4,3 years. Among the controls, 55 grafts were transplanted in 52 patients. Ten patients underwent a percutaneous nephrostomy placement. Five patients needed a surgical re-intervention. In three rejection proceeded and transplantectomy was performed. Three patients underwent second kidney transplantation. One patient had a failing graft after 7½ years post transplantation and became dialysis dependent.
Conclusion: Kidney transplantation in patients with a reconstructed urinary tract has an increased complication rate. Nevertheless, the long-term results are comparable to patients with a normal urinary bladder.

Treatment of chronic humoral rejection with Intravenous Immunoglobulins (IVIG)-a case series

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Introduction: Chronic humoral rejection (CHR) after kidney transplantation (kTx) is a major cause of graft failure and difficult to treat. We describe 4 cases of CHR treated with IVIG (4x 0.5 g/kg) and Solumedrol (SM, 3x 1 g). Prednisone and cellcept, if not already given, was added to the immunosuppressive regimen.
Cases: Patient A, 49 year non-immunized (NI) male with ESRD due to M. Wegener, received a living unrelated kTx, HLA mismatch (HLAmm) 1A0B1DR. He had no acute rejections and was stable on tacrolimus (tac) monotherapy for 10 years. Because of slow rise in creatinine (from 186 to 235µmol/l) in combination with proteinuria (0.8g/d) a renal biopsy (bx) was performed showing CHR C4d positive. Donor-specific antibodies (DSA) testing (Luminex) was positive (DQ2). After treatment with IVIG and SM creatinine decreased to 196µmol/L and proteinuria disappeared.
Patient B, 29 year NI old male with ESRD due to hydronephrosis had a living related kTx (HLAmm 0A1B1DR) without acute rejections and was stable on tac monotherapy for 10 years. Over a period of 8 months his creatinine increased from 157 to 200µmol/l in combination with proteinuria up to 0.6g/d. Bx showed CHR, C4d positive. DSA were inconclusive. After treatment with IVIG and Solumedrol creatinine and proteinuria remained stable.
Patient C, 61 year immunized female (ESRD: chronic interstitial nephritis) received a NHB kTx (HLAmm 0A0B1DR) with 2 borderline tubulointerstitial rejections in year 1 and was stable on tac monotherapy for 5 years. Over 6 months her creatinine increased from 220 to 300µmol/l together with severe proteinuria (4.4g/d). Bx was compatible with CHR, C4d and DSA were negative. Despite treatment with IVIG and SM creatinine and proteinuria worsened.
Patient D, 68 year NI male with ESRD due to glomerulonephritis received an ABO incompatible living kTx (HLAmm 1A2B1DR) without rejection. Being on tac and cellcept, 1.5 years later he had a rise in creatinine from 137 to 220µmol/l and proteinuria up to 0.35g/d. Bx showed CHR, C4d was positive, DSA was positive against DR53. He was treated with 1 session of plasmapheresis, IVIG and SM. His creatinine stabilized at 182µmol/l and proteinuria at 0.3g/d.
Conclusion: Although uncontrolled, our data suggest that treatment with IVIG and SM may be beneficial in patients with CHR. Controlled data are needed to better elucidate the potential of IVIG and steroids.

Case report: Unilateral right-sided pleural effusion in a renal transplant recipient: Beware of extrarenal manifestations of ADPKD

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic renal disease that leads to end-stage renal disease (ESRD). In the Eurotranplant data of the last decade 8.3% of the recipients have ADPKD as original renal disease. Besides ESRD, ADPKD can cause a broad variation of symptoms. In this case-report we describe a serious complication of ADPKD in a renal transplant recipient.

A 67 year old female patient presented 12 months after an uncomplicated postmortal renal transplant with slowly progressive abdominal discomfort, dyspnoea and unilateral right-sided pleural effusion. There were no (clinical) signs of decompensated heart disease or infection. Laboratory results showed a creatinine of 190 umol/L (MDRD 24) and serum albumin was 43 g/L. Analysis of the pleural fluid showed an LD of 30 u/L (serum LD 124 U/L), no leucocytes and the pH was 7.78. Hence it was regarded as transsudate with negative cytology and cultures. Pleural drainage was unsuccessful. On MRI no direct connection between abdominal and pleural cavity was found and only small amounts of intra-abdominal fluid were seen, without signs of portal venous thrombosis at that time. Because of supposed increased intra-abdominal pressure due to enlarged native kidneys, and knowledge of the mechanism of pleural effusion in CAPD, bilateral nephrectomy was performed. Afterwards the pleural effusion disappeared, but massive ascites production emerged. At this point imaging did show signs of mass-effect on the intra-hepatic blood vessels and compression of the inferior caval vein. Moreover there was evidence of thrombosis of the posterior right portal vein. Liver function at that time was still uncompromised, shown by markers of liver syntheses. The patient was stabilised by means of hemodialysis to lower hydration state and institution of parenteral nutrition and anticoagulation, thus preparing her for combined liver and kidney transplantation. This was performed successfully after dialysis for 9 months. Post transplant she had an uneventful course and was released after 23 days with good renal and hepatic function and mild abdominal discomfort.

This case showed that ADPKD can in rare cases lead to pleural effusion because of high intra-abdominal pressure due to ascites. Although the formation of ascites and thrombosis in the inferior caval vein have been described before as complications of ADPKD, pleural effusion has not been described before as a first presenting symptom.

Idiopathic giant esophageal ulcer and leukopenia after renal transplantation: a late complication of rituximab?

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Introduction: Ulceration in the gastrointestinal tract is frequently seen in immunocompromised patients such as transplant recipients. We present a case with a rarely reported cause of esophageal ulceration which occurs simultaneously with leukopenia.
Case: A 45-year-old male, who had received a renal allograft, was admitted because of a giant esophageal ulcer coinciding with leukopenia. An extensive workup revealed no explanation for either the ulcer or the leukopenia. Our final diagnosis by exclusion was an idiopathic giant esophageal ulcer and late-onset neutropenia as a consequence of rituximab induction therapy given during the transplant procedure. The patient fully recovered after treatment with prednisone. After 4 months the ulcer and leukopenia relapsed with again complete cure after high dose prednisone. The pathogenesis of late-onset neutropenia after administration of rituximab and idiopathic giant esophageal ulceration is poorly understood. Idiopathic giant esophageal ulcers are mainly seen in immunocompromised patients and are especially described in patients with AIDS. The simultaneous occurrence and recurrence of leukopenia and esophageal ulceration suggests mutual involvement. Some have postulated that an imbalance in CD4 and CD8 positive lymphocytes as consequence of rituximab administration might cause late-onset neutropenia. Like in our patient, this imbalance in lymphocyte subpopulations has also been observed in the biopsy specimens of idiopathic giant esophageal ulcers.
Conclusion: Rituximab induces a shift in lymphocyte populations, which might cause both late-onset neutropenia and idiopathic giant esophageal ulceration. Hence, the peri-operative administration of rituximab was the most likely cause of the relapsing leucopenia and the coinciding idiopathic giant esophageal ulcer.

Als de papieren status elektronisch wordt

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Achtergrond: Bron documentatie bij klinisch wetenschappelijk onderzoek is bij wet bepaald. Brondocumenten van onderzoek dat valt onder de Wet Mensgebonden Onderzoek (WMO) moeten 15 jaar na het beëindigen van een studie bewaard worden. Vanaf juni 2011 is onze afdeling overgegaan op het elektronisch patiënten dossier systeem (ELPADO). Papieren statussen worden nu ingescand en vervolgens vernietigd. Wij vroegen ons af of ingescande gegevens van proefpersonen voldoen als bron documentatie. Moeten de papieren statussen alsnog bewaard blijven tot 15 jaar na einde van studie?
Methode: Om antwoord te krijgen op deze vraag benaderden wij: de Medisch Ethische Toetsingscommissie (METC) in het Erasmus, Centraal Commissie Mensgebonden Onderzoek (CCMO), Team ELektronische PAtiënten DOssier (ELPADO), Inspectie van Volksgezondheid (IGZ), het Ministerie van Volksgezondheid, Welzijn en Sport (VWS) en de afdeling juridische zaken Erasmus MC.
Resultaten: Onze METC had geen antwoord op de vraag en verwees ons naar de CCMO. Advies gevraagd bij het ELPADO team, die beloofde dit uit te zoeken bij IGZ. Inmiddels contact gehad met de CCMO, die ons adviseerde ook IGZ te benaderen. IGZ antwoordde het ELPADO team dat de ingescande gegevens niet voldoen, maar schreef ons dat ingescande gegevens wel voldoen. Daarom opnieuw advies gevraagd aan METC en juridische zaken: Situatie blijft onduidelijk, dus vooralsnog dienen papieren dossiers bewaard te worden.
Conclusies: Deze zoektocht is gestart in april 2011, nu december 2011 hebben wij nog geen definitief antwoord op onze vraag. Er zijn nog geen wettelijke bepalingen en richtlijnen omtrent het bewaren van source documenten en ingescande gegevens van proefpersonen die deelnemen aan WMO plichtig onderzoek. Wij vragen ons af hoe er in andere ziekenhuizen met deze kwestie wordt omgegaan.

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