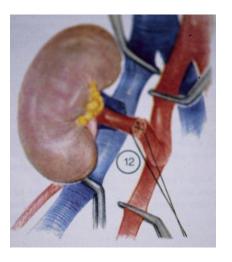
Living Donor Kidney Transplantation The Donor & The Recipient



Jonathon Olsburgh

Consultant Urologist & Transplant Surgeon







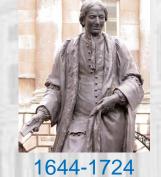
The Department of Medicine, Faculty of Science, University of Mauritius







Guy's Hospital 1721 - 1725 "The Hospital for the Incurables"







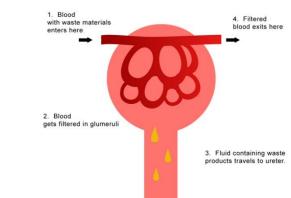
Living Donor Kidney Transplantation The Donor & The Recipient

- Kidney Transplantation
 - History, UK perspective & Guy's Hospital perspective
- Recipient Medical Aspects
- Surgical Aspects of Kidney Transplant
- Living Donation
- Donor Medical & Psychological Aspects
- Surgical Aspects of Donor Nephrectomy
- Questions



Renal Function

- eGFR (e)stimate:
 - serum creatinine, age, sex & race
 - abbreviated (4 point) MDRD equation
 - not validated for children or in pregnancy
 - significant errors at extremes of body type
 - e.g. malnourished, amputees, body builders
 - racial differences- 20% higher in Afro-Caribbean black patients
- Formal GFR
 - EDTA or DTPA GFR



Chronic Kidney Disease (CKD) stages

Stage				
	eGFR	Description	Monitoring	Management
1	90+	Normal function but evidence of structural abnormalities	Annual	BP control, ACE if proteinuric
2	60-89	Mildly reduced kidney function	Annual	BP control, ACE if proteinuric
За	45-59	Moderately reduced kidney function	6 monthly/Annual	BP control, ACE if proteinuric, CVS risk management
3b	30-44	Moderately reduced kidney function	6 monthly	BP control, ACE if proteinuric, CV risk management
4	15-29	Severely reduced kidney function	3-4 monthly	Prepare for Dialysis, Transplantation, Anaemia, CKD-MBD and CV risk management
5	<15 or on dialysis	Very severely reduced kidney function (end stage kidney disease)	Frequently	Dialysis, Transplantation, Anaemia, CKD-MBD and CV risk management

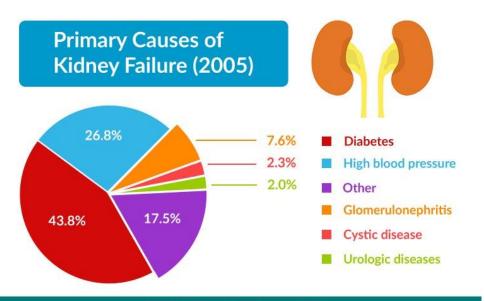
Suffixes P= significant proteinuria T= transplanted

D= on dialysis



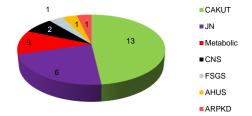


Causes ESRD



© TheDiabetesCouncil.com





Underlying Aetiology	Number of Children	Percentage (%)		
Posterior urethral valves (PUV)	40	53.3		
Dysplastic kidneys	15	20		
Prune belly syndrome	6	8		
Neuropathic bladder	4	5.3		
Idiopathic	2	2.7		
Other	8	10.7		

VACTERL association, horseshoe kidney, duplex system, vesicoureteral reflux (VUR) and cloacal anomaly.

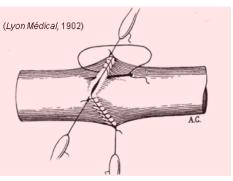


History

- 1902 Ullman
 Carotid
- 1906 Carrel & Guthrie
- 1906 Jaboulay
 Brachial / Femoral







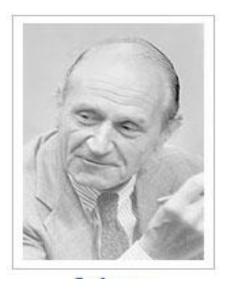
The Transplantation of Organs NY Med J 1914

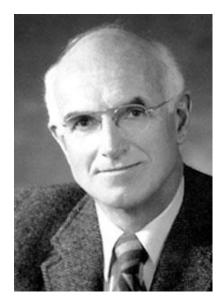
History

- 1933 Voronoy
- Human-femoral



- 1951 Kuss
- Human-abdominal





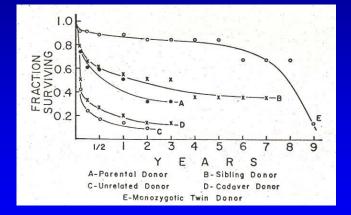




December 23rd 1954: Dr Joseph Murray 1st successful kidney transplant Identical twins - Ronald & Richard Herrick Brigham & Women's Hospital – Boston, USA **1957-61 6-MP & azathioprine synthesised** (Elion & Hitchings). Worked in dogs (Calne) but initial results awful in humans.



1963: Starzl azathioprine + steroids



40 cases





1970 Cyclosporine isolated from fungus *Tolypocladium inflatum* Sandoz (Basel). 1976 J. F. Borel discovered its immunosuppressive activity 1978 R Calne – 1st Human transplant use <u>"Cyclosporin A in patients</u> receiving renal allografts from cadaver donors" *Lancet* 1979;2 (8104-5): 1323-1327

Where do kidney donors come from?

Living donors

- related/unrelated
- paired exchange scheme
- altruistic
- ABO incompatible

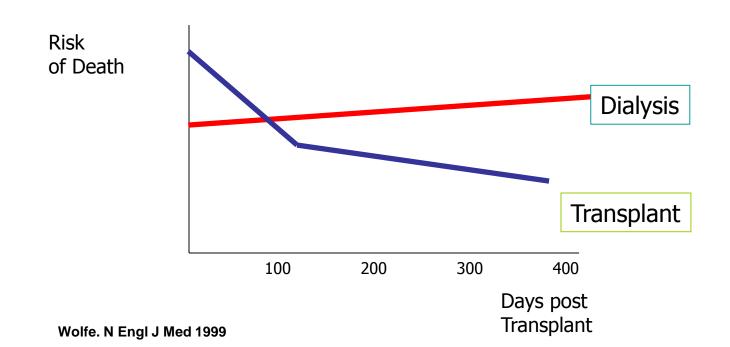




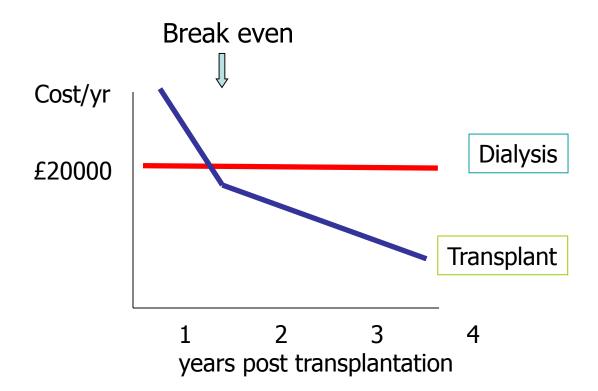
Non heart-beating donors donation after cardiac death (DCD)

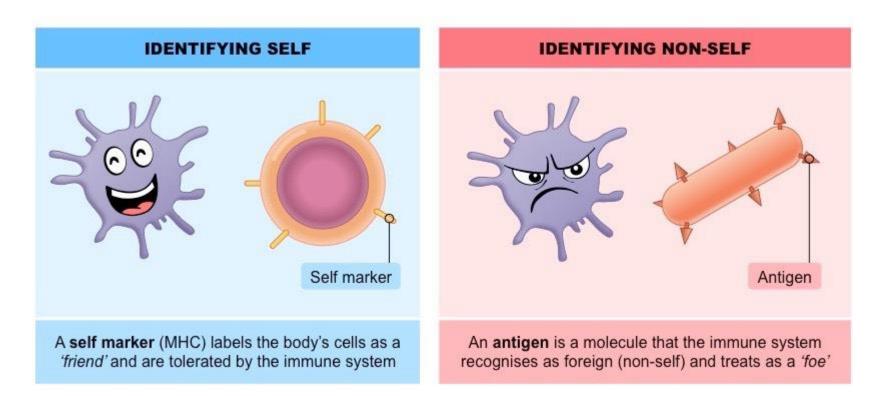
Heart-beating donors donation after brain-stem death (DBD)

Transplantation adds years



Transplantation is economical





Human Leucocyte Antigen = Major Histocompatibility Complex

The Clinical Conundrum

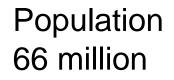
Immunosuppression Under Over **NODAT - Diabetes** Acute rejection Infection-CMV, BK, UTI Nephrotoxic Chronic rejection Malignancy-PTLD, Skin

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UK Transplant

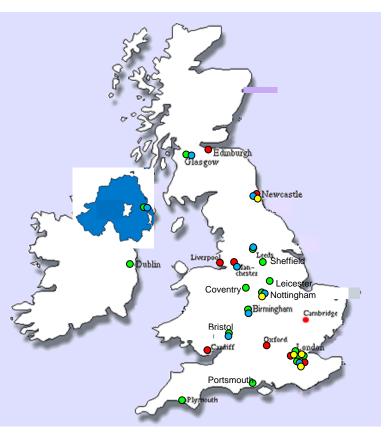
- Adult Kidney Centres = 23
- Kidney & Pancreas Centres = 8
- Paediatric Kidney Centres = 9
- Transplant Urology at 6 centres



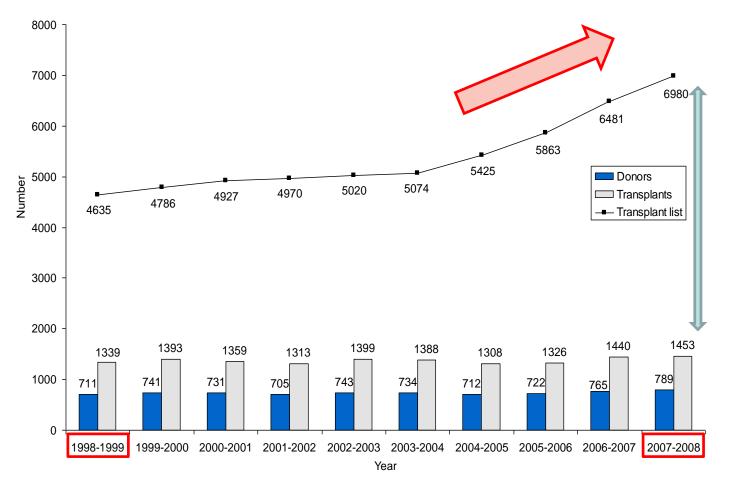
2018-2019

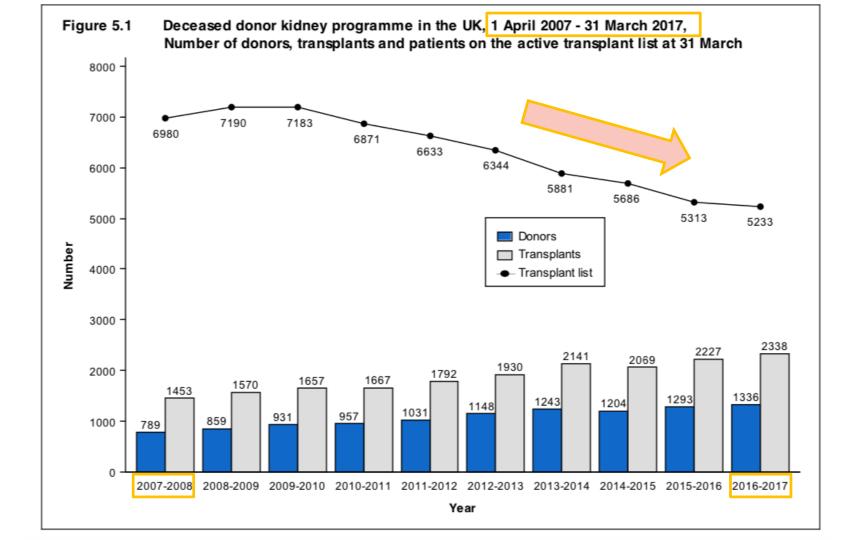
3594 Kidneys Transplanted





UK Deceased donor kidney programme, <u>1 April 1998 - 31 March 2008</u> Number of donors, transplants & patients on active transplant list





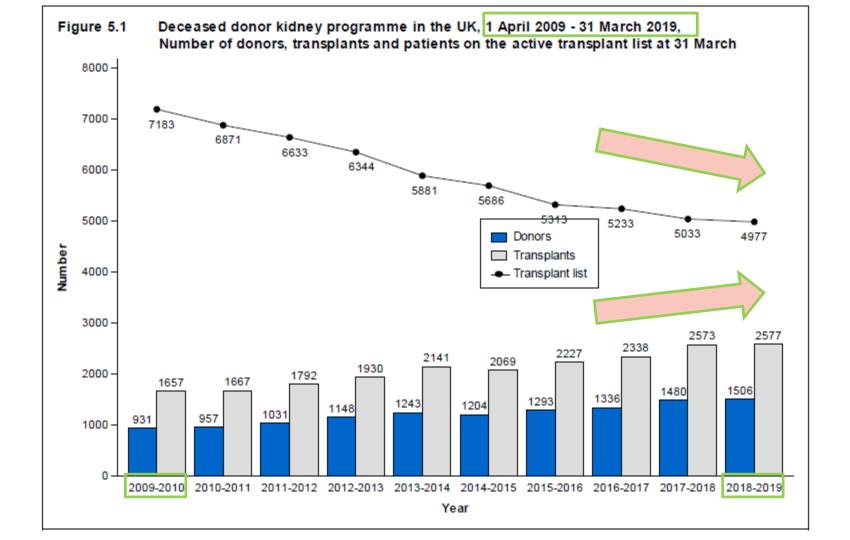
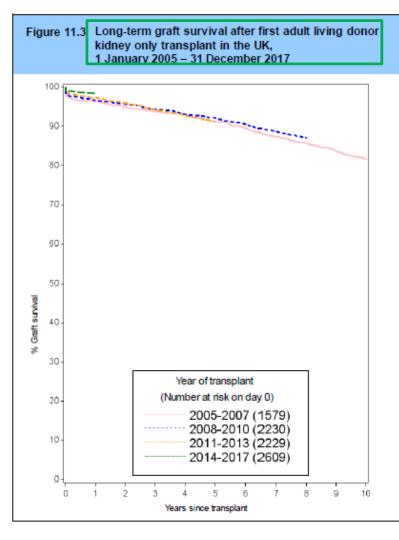


Table 2.5	able 2.5 Number of transplants reported as functioning at 31 March 2019					
		Functioning transplants ¹				
Kidney		39700				
Pancreas		2000				
Cardiothorac	ic	4000				
Liver		10500				
Intestinal		100				
ALL PATIEN	TS	54500				
¹ Approximate number of patients with a functioning transplant being followed up Multi-organ transplants (excluding intestinal transplants) are counted in each organ Excludes those patients known to be lost to follow-up						

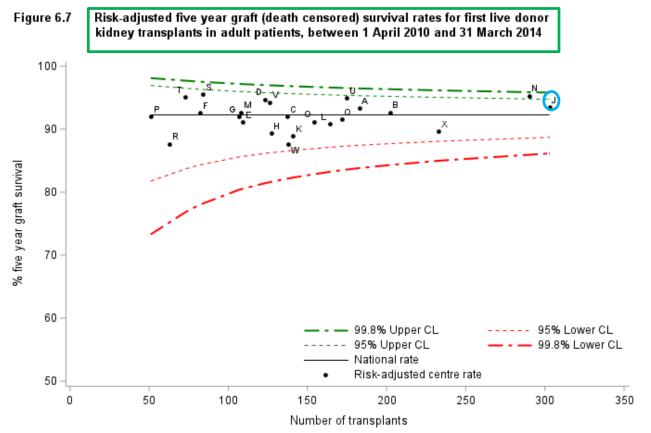


Outcomes

Table 11.5	Graft surviv	al afte	r first adul	t living	g donor kie	dney t	ransplant		
Year of transplant	No. at risk on day 0	On	% Gra e year		vival (95% o year		dence inte 'e year		n year
2005-2007 2008-2010 2011-2013 2014-2017	1579 2230 2229 2609	96 97 97 98	(95-97) (96-97) (96-98) (98-99)	95 96 96	(94-96) (95-96) (95-97)	91 92 91	(90-93) (91-93) (90-92)	82	(80-84)

Table 11.6	ble 11.6 Patient survival after first adult living donor kidney transplant								
Year of transplant	No. at risk on day 0	On	% Pati e year		rvival (959 o year		idence int e year		n year
2005-2007 2008-2010 2011-2013 2014-2017	1579 2230 2228 2609	99 99 99 99	(98-99) (98-99) (99-99) (99-99)	98 98 98	(97-99) (97-98) (97-99)	96 94 95	(95-97) (93-95) (94-96)	90	(88-91)

NHS Blood and Transplant



Source: Annual Report on Kidney Transplantation 2018/19, NHS Blood and Transplant



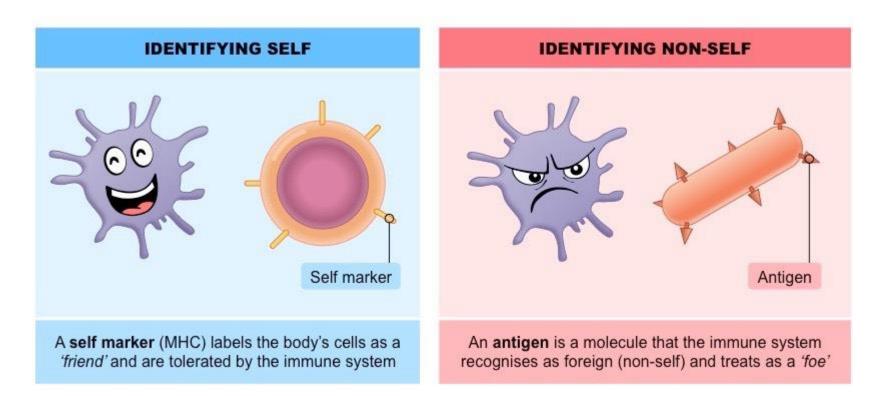
Optimise the donor organ

Optimise the transplanted organ

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Optimise the recipient

I III IIII IIII IIII KING'S HEALTH PARTNERS



Human Leucocyte Antigen = Major Histocompatibility Complex

Donor-Recipient Matching in Kidney Transplantation

Principle	Rationale
ABO compatibility	Avoids hyperacute rejection
Best HLA match (HLA-DR > HLA-B > HLA-A)	Reduces risk of acute rejection May improve graft survival Prevents allo-sensitisation
No preformed anti-donor HLA antibodies (negative cross-match)	Avoids hyperacute rejection
Minimise cold ischaemia time	Reduces allograft injury

HLA "Mismatches"

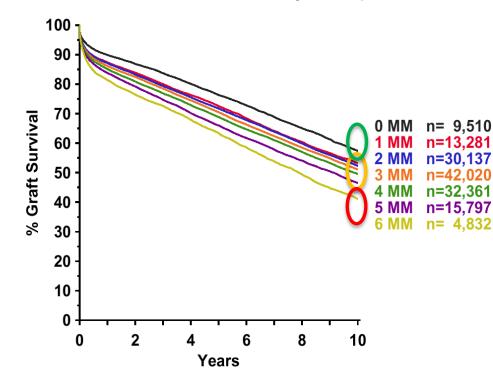
Convention describes relationship between donor and recipient HLA type as "mismatches" 6 potential mismatches (2A, 2B, 2DR) e.g: 1,0,1 = A 1 matched, B both matched, DR 1 matched

e.g: 0,1,0 = A both matched, B 1 matched, DR both matched

0,0,0 = A, B & DR all matched

HLA-A+B+DR Mismatches

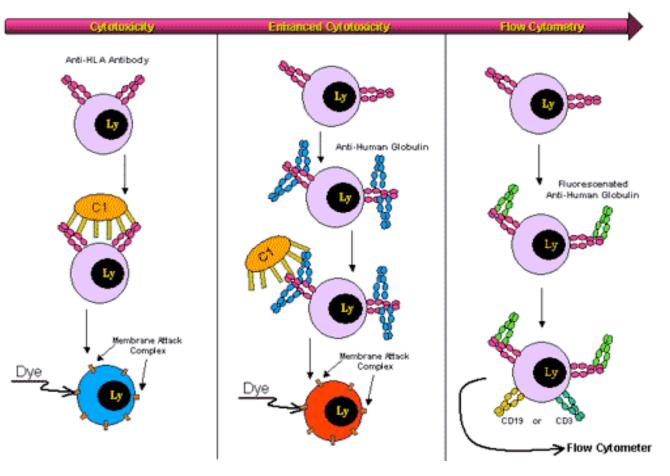
Deceased Donor, First Kidney Transplants 1985-2009



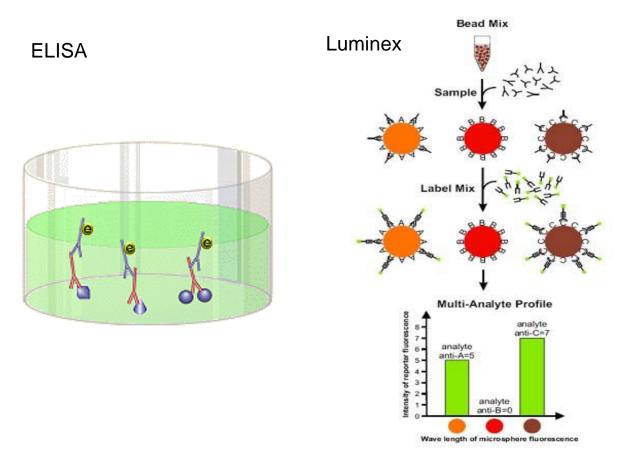
HLA match is less important with living donors

Degree of	Unadjusted 5yr survival by donor type						
HLA MM	Extended criteria donor donor		Living donor				
0	60%	74%	87%				
1	53%	71%	80%				
2	57%	71%	80%				
3	52%	70%	79%				
4	52%	70%	79%				
5	50%	66%	81%				
6	47%	65%	79%				

Cell-based HLA antibody screening



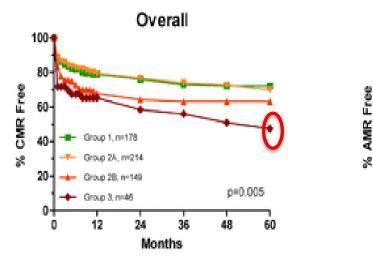
Solid phase immunoassays for HLA antibody screening

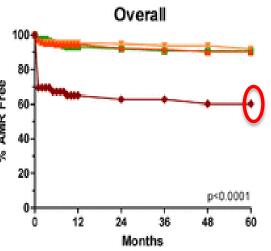


Donor-specific HLA antibody leads to increased rejection

D

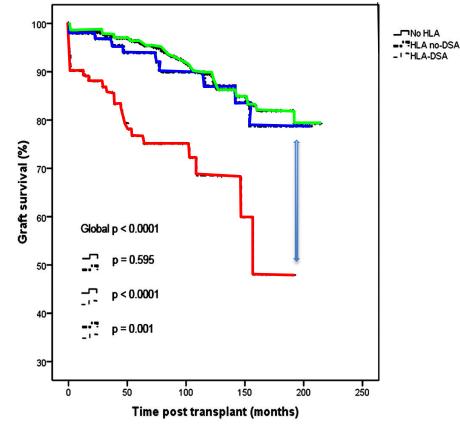
A Cell Mediated Rejection-Free Survival Antibody Mediated Rejection-Free Survival





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Donor-specific HLA antibody leads to poorer graft survival



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Stratification of Immunological risk

- "Low risk"
 - non-sensitised patient receiving minimally HLA mismatched organ in the absence of current or historical donor reactive antibodies

• "Intermediate risk"

- sensitised patients with HLA antibodies (but not donor-specific)
- or chance of prior donor sensitisation (even in absence of current antibody)
- Husband to Wife
- Child to Mother
- Previous transplanted organ

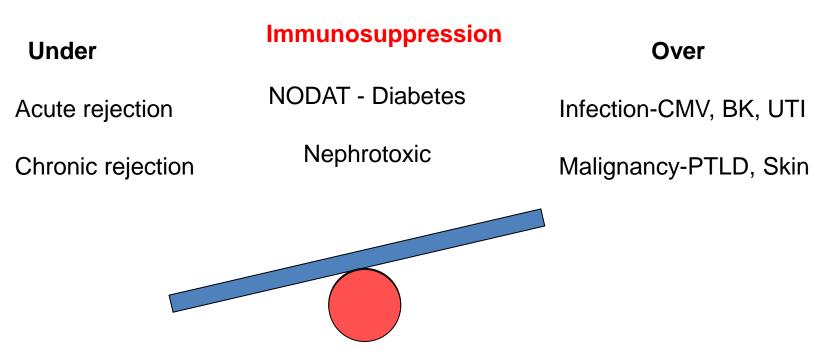


Stratification of Immunological risk

• "High risk"

- patients who are cross-match **negative** by flow-cytometry but who have a **current** or **historic** donor-specific antibody which arose following exposure to this antigen from a previous solid organ transplant or pregnancy (these patients require augmented immunosuppression)
- "Very High risk" HLA Antibody incompatible
 - patients who are cross-match **positive** by flow-cytometry are deemed
 HLA Antibody incompatible (these patients require measures to remove the DSA pre-transplant plus augmented immunosuppression)

The Clinical Conundrum



Immunosuppression - basic principles

• Acute rejection risk & graft loss highest in the first three months

 \Rightarrow immunosuppression is at its highest during this period

• **serious side effects** of immunosuppressive therapy (i.e. infections and malignancy) correlate with total immunosuppressive burden

 \Rightarrow immunosuppression taper to maintenance level by 6 to 12 months



Principal side effects of immunosuppressive therapy

Corticosteroids	Ciclosporin	Tacrolimus	Azathioprine	Mycophenolate mofetil	Sirolimus
Hypertension	Nephrotoxic effects	Nephrotoxic effects	Marrow suppression	Diarrhoea gastrointestinal upset	Hyper lipidaemia
Glucose intolerance	Hypertension	Hypertension		Cytomegalovirus infection	Thrombo- cytopenia
Dyslipidaemia	Glucose intolerance	Glucose intolerance			Poor wound healing
Osteoporosis Poor	Dyslipidaemia	Insulin- dependent diabetes mellitus			Lymphocele
wound healing	Gum hyperplasia	Dyslipidaemia			
	Hirsutism				

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Induction immunosuppression

- Monoclonal antibodies
 - Basiliximab (anti-IL2 receptor)
 - Alemtuzumab (anti-CD52) (CamPath)

- Polyclonal antibodies
 - Anti-thymocyte globulin ATG (rabbit)

Immunosuppression Protocol

- Induction:
- Basiliximab (Simulect[®]) 20mg IV administered by anaesthetist pre-operatively (day 0) and on day 4 post-operatively on the ward.
- Tacrolimus (Adoport[®]) 0.05mg/kg PO 1 hour pre-operatively.
- Methylprednisolone 1g IV administered by anaesthetist pre-operatively
- Maintenance:
- Tacrolimus (Adoport[®]) 0.05mg/kg orally BD adjusted according to trough tacrolimus levels.
- Mycophenolate mofetil 500mg orally QDS.
- Prednisolone 20mg orally OM for 2 weeks, then 15mg for 2 weeks, then 10mg for 4 weeks then 5mg OM and continue for 6 months then review.

Tacrolimus levels

Low risk: Trough 3-7ug/l Standard & High risk: Trough 10-12ug/l for 2 months then 8-10ug/l

Preventing drug toxicity

- Steroid sparing regimens, and steroid avoidance
- Reduce calcineurin inhibitor dose after early post transplant period
- Calcineurin inhibitor avoidance
- Single drug regimens

• Higher rates of acute rejection

"Symphony Study 2007"

The NEW ENGLAND JOURNAL of MEDICINE

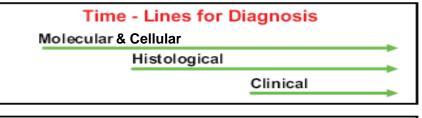
ORIGINAL ARTICLE

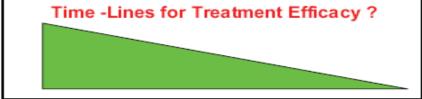
Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

Henrik Ekberg, M.D., Ph.D., Helio Tedesco-Silva, M.D., Alper Demirbas, M.D., Štefan Vítko, M.D., Björn Nashan, M.D., Ph.D., Alp Gürkan, M.D., F.A.C.S., Raimund Margreiter, M.D., Christian Hugo, M.D., Josep M. Grinyó, M.D., Ulrich Frei, M.D., Yves Vanrenterghem, M.D., Ph.D., Pierre Daloze, M.D., and Philip F. Halloran, M.D., Ph.D., for the ELITE–Symphony Study*

> **Tacrolimus levels** Low risk: Trough 3-7ug/l

Rejection: A Time-Line Model





Rationale: early intervention

Molecular and cellular surveillance strategies anticipate histological and clinical rejection.

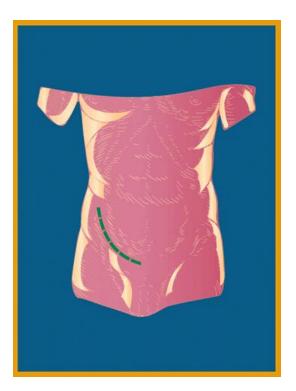
D Anglicheau & M Suthanthiran Transplantation 2008; 86: 192

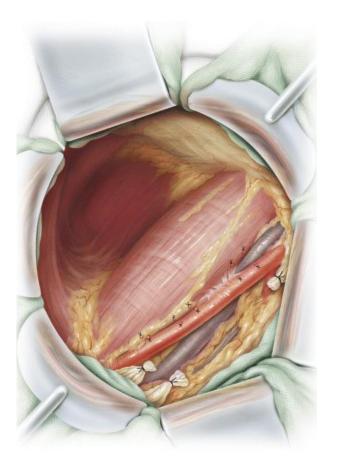


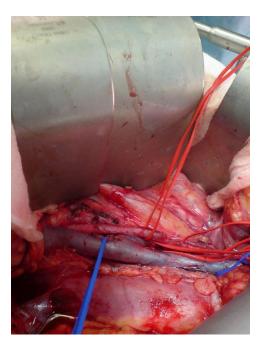


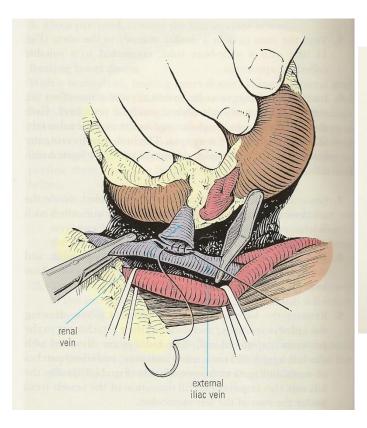
3 anastomoses and that's it

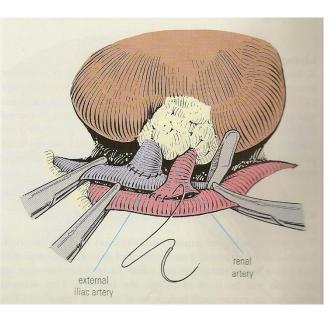
Incision

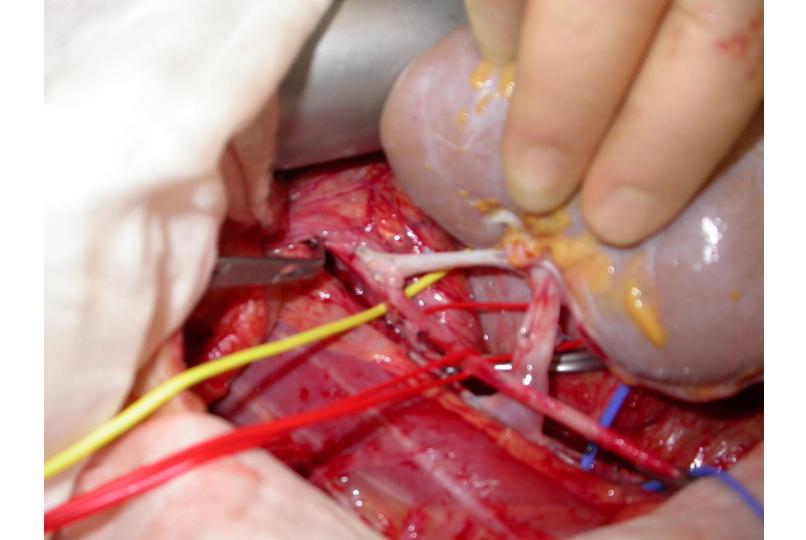


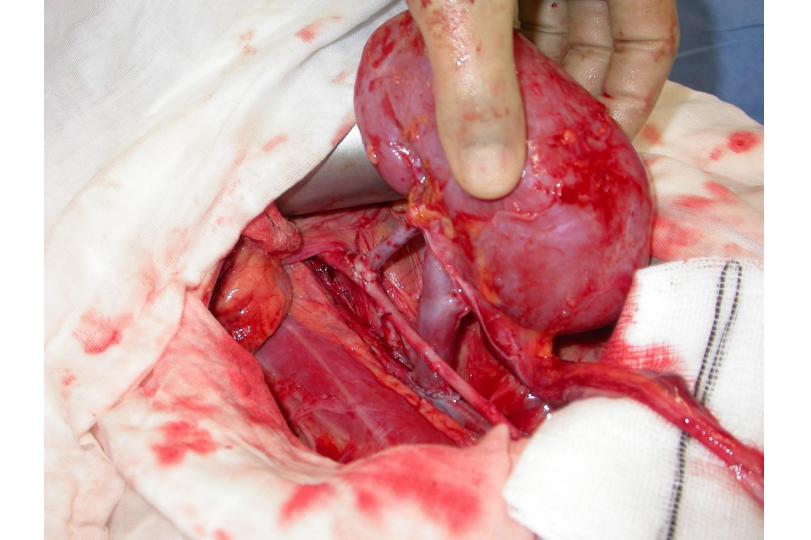




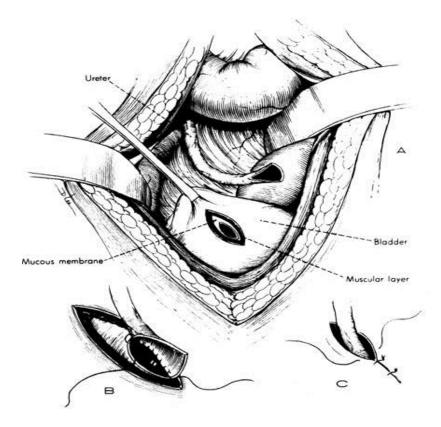






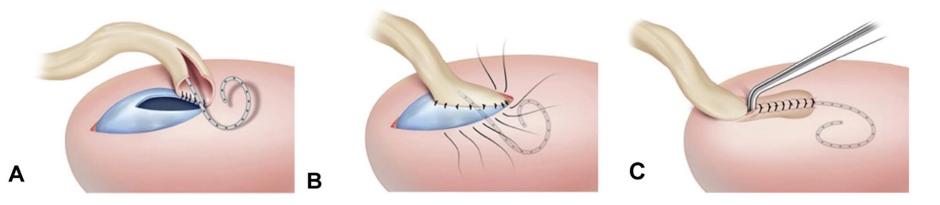


Extravesical / Onlay – Lich-Gregoir interrupted / continuous



Ureteric anastomosis – standard approach

Ureter to bladder – Lich-Gregoir (Campos-Friere)
 – Role of Transplant Ureteric JJ stent



Urology, Volume 3, Issue 3, March 1974, Pages 304-308

Geraldo de Campos Freire, Gilberto Menezes de Góes, J. Geraldo de Campos Freire



Early post op issues

- Fluid balance: can have high UO 4 litres/24 hours
- Bleeding: Haemoglobin & drain output
- Arterial/Venous thrombosis 1%

Suspect if sudden fall in UO (take care to account for any native output) Gross haematuria Graft tenderness Management- urgent Doppler/ Surgical exploration

• Urinary leak: 1%-2%

Unexplained abdominal pain, decreased UO, increased drain volume.

Rise in serum creatinine, check drain fluid creatinine

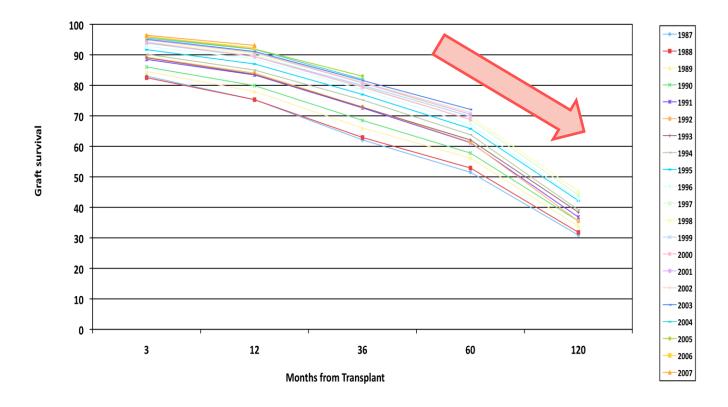
Management- catheter/surgical

• Recurrent 1' FSGS- urinary protein creatinine ratio

Prophylaxis

- Arterial Thrombosis aspirin
- sc heparin only if increased risk venous thrombosis
 e.g. anti-phospholipid syndrome
- Peptic ulcer Rantidine or PPI
- Infection
 - PCP: Co-trimoxazole, Dapsone, Pentamidine nebs
 - CMV: Valgancyclovir if Donor positive to Recipient negative
 - TB: Isoniazid/pyridoxine

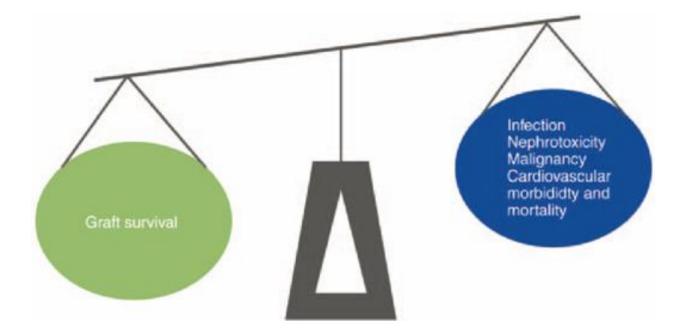
Late graft loss remains problematic



OPTN/SRTR 2009 Annual Report

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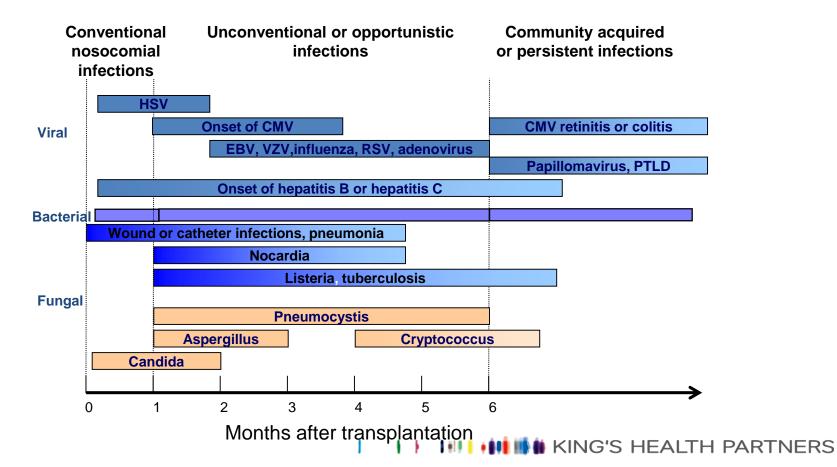
Getting the balance right



Post-transplant infection - general principles

- Common community-acquired AND rarer opportunistic infections
- Fewer symptoms, muted clinical findings, delayed clinical presentation
- Drug resistance more common
- May need urgent treatment
- Potential drug interactions
- Drug levels only crudely estimate immunosuppressive burden
- Focus on disease prevention: prophylaxis and vaccination

Timeline of post-transplant infections



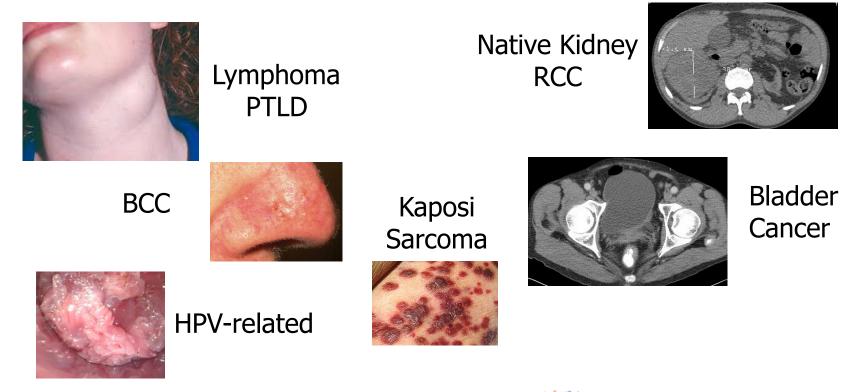
Viral Infections post-transplant

• Community-acquired (e.g. common respiratory viruses)

• Latent viruses (e.g. HSV, CMV, VZV, hepatitis B and C, papillomavirus, and polyomavirus)

• Donor-derived (e.g. CMV, EBV, hepatitis B & C, HIV, rabies)

Post-transplant malignancy



Post-transplant malignancy

Cancer Site	No. Cases	Expected No.	Ratio
Nonmelanoma skin	127	5.1	24.7
Thyroid and other endocrine	30	2.1	14.3
Mouth, tongue, and lip	22	1.6	13.8
Cervix, vulva, and vagina	39	3.6	10.8
Non-Hodgkin lymphoma	25	2.4	10.3
Kidney and ureter	32	3.5	9.1
Bladder	26	4.7	9.1
Colorectal	38	10.5	3.6
Lung	30	12.5	2.4
Brain	10	4.1	2.4
Prostate	11	5.2	2.1
Melanoma	7	4.1	1.7
Breast	15	13.6	1.1

Birkeland et al Int J Cancer 60:183-189, 1995

Recurrent renal disease

- 3rd commonest cause of graft loss
- FSGS
- Membranous GN
- MCGN type 1 and 2
- IgA
- Diabetic nephropathy
- HUS

Summary points

- Increasing effectiveness of transplantation allows many more patients to be considered, **but** ongoing shortage of donors
- Outcomes living donor kidneys much better than deceased donor kidneys
 - Optimise Donor
 - Optimise Organ
 - Optimise and Monitor Recipient

Summary points - 2

Improvements in managing early acute rejection have **not** led to impressive long-term improvement in graft and patient survival

Strategies to minimise rejection include immunological matching and identification / avoidance of preformed anti-donor HLA antibodies

• Immune-suppression still corticosteroid & calcineurin inhibitor-based, in spite of side effects

• Main side-effects - increased risks of infection, malignancy & diabetes

Guy's and St Thomas' NHS NHS Foundation Trust

Living Donation



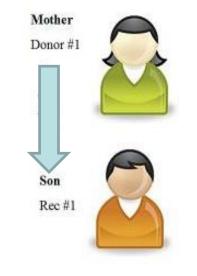
Living Donation

• Relative / friend / colleague

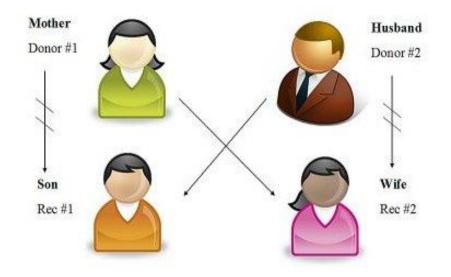
- Strangers...
 - Altruistic
 - "Good Samaritan"
 - Unspecified



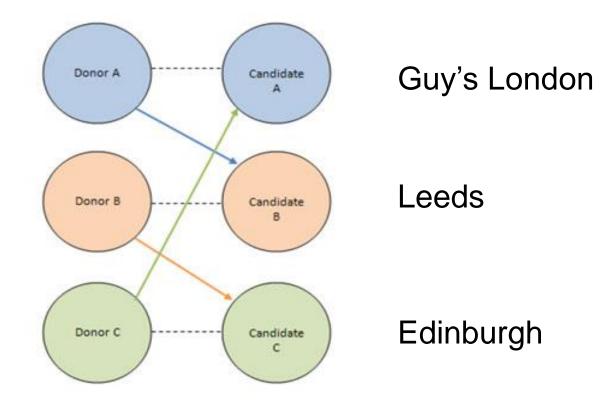
Living Donation – Standard Direct Donation



Living Donation – Paired Exchange

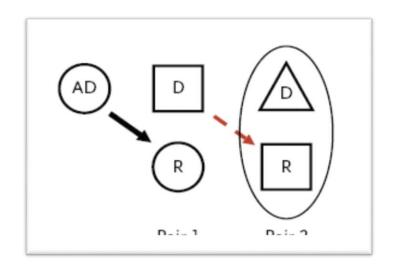


Living Donation – National Kidney Sharing



Living Donation – Domino Chains

- Altruistic donors
- Therapeutic nephrectomy
- Human Tissue Act





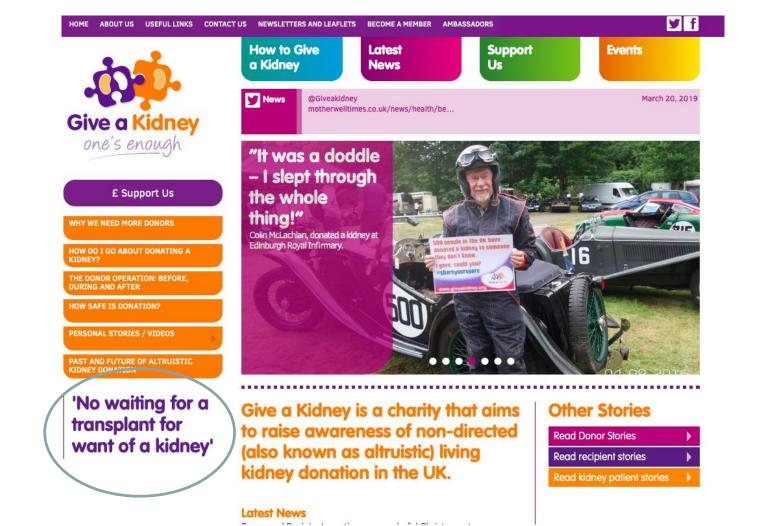


Altruistic (non-directed) Donors

- Controversial!
 - Challenges traditional views on medical ethics
 - Where does the benefit lie?
- Issues
 - Troubles some transplant professionals
 - Is illegal in some parts of the world
 - Assumption of psychopathology

Non-directed Donors

- However...
 - Around 80 people do this each year in the UK
 - 9% of living donor programme nationally
- Very motivated group of individuals
 - They have their own charity...



Altruistic Donors

- Outcomes:
 - Very positive
 - No significant difference with people donating to someone they know
- There are some differences...
 - Demographics
 - Altruistic behaviours
 - Fits in with lifestyle

Altruistic Donors

- Getting the transplant community on board
 - Improved in recent years
 - · Need to address issues / concerns
 - 1. Psychopathology
 - 2. Motivations
 - 3. Outcomes
 - 1. Who will donate?



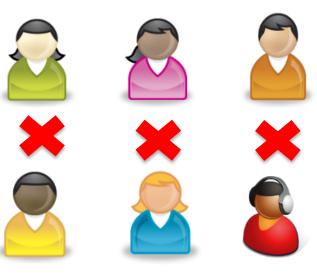
Understanding Barriers and Outcomes in Unspecified (altruistic) Kidney Donation

- 2. Who may get screened out and why?
- 4. What is a living donor kidney worth?
- What is the best way to use these kidneys?
 - Hit the jackpot!
 - Donor chains

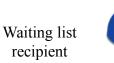


Non-directed

donor



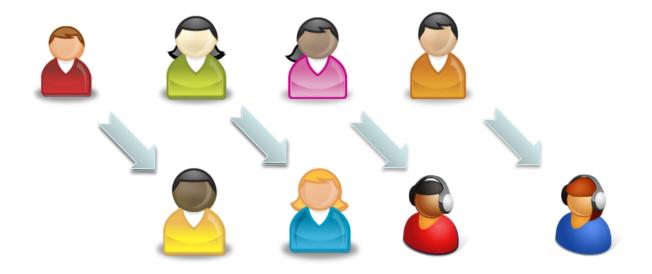
Incompatible donor-recipient pairs



Often very difficult to transplant

- Highly sensitised
- May otherwise not be transplanted

Non-directed Donors



2009 HEROES AMONG US AWARDS



1 non-directed donor = 20 kidney transplants

Non-directed Donors

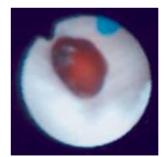
- Making a massive contribution to the waiting list
- UK has largest kidney exchange programme in Europe
 - Surge in 2018
 - 48% donated as part of a chain in 2018

- 33 donors
 - 82 transplants
 - Combination of short and long chains

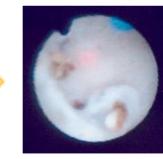
Donor Stones - Bench URS







Before Fragmentation



After Laser Fragmentation



Hand Assisted Laparoscopy Donor Nephrectomy



Technique

- Transverse / midline 7cm
- 2 x 12mm ports







- Donor Safety
- Donor QOL; Pain; LoS; Cosmesis
- Recipient outcome
- Reproducible across department
- Ability to train / teach

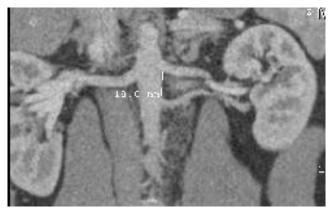
Risk is with Recipient not Donor

- Energy source -Thunderbeat
- Dissect colon medial
- · Gonadal vein to renal vein
- Thunderbeat / Ligasure gonadal + adrenal veins
- Mobilise kidney
- Ureter divided at pelvic brim clips
- A / V articulated linear stapler

Left HALDN

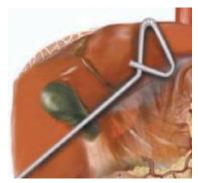
Right side

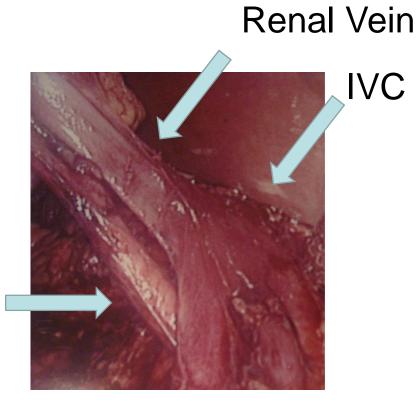
- Why right?
- Single R v multi L RA
- Split function
- Stone / Benign mass



2 Renal Arteries to Left 1.8cm apart 1Renal Artery to Right

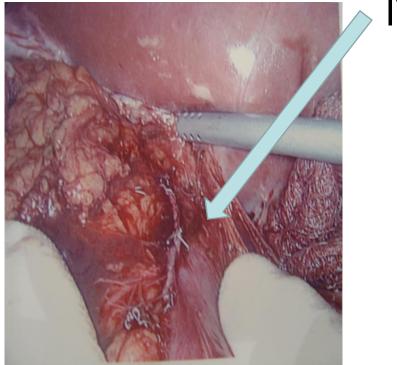
- Potential problems
- Short renal vein
- Liver retraction
 - Extra 5mm port





Renal Artery

Right HALDN



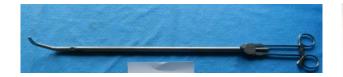
IVC

Right HALDN

Energy Sources



Lap Emergency Trolley









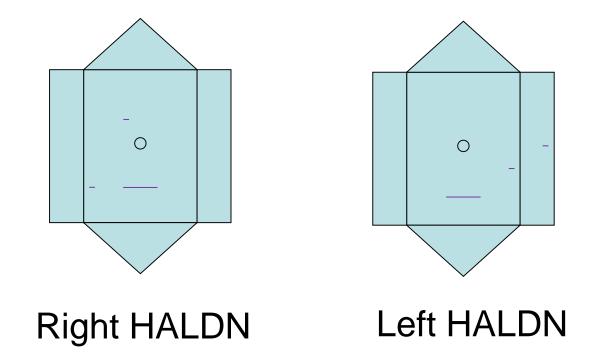
"First do no harm"

- Donor safety paramount
 - Major intraoperative risk bleeding
 - Friedman 2006 2 lap donor fatalities non-locking clips RA
 - Bowel diathermy injury
 - Oyen 05
- Minimise donor morbidity
- Maximise recipient outcome

Risk is with Recipient not Donor

Patient preference

Cosmesis – where do they want the scar?



HALDN v Other techniques

- Donor Safety
- Donor QOL
- Recipient outcome
- Reproducible across department
- Ideal for training

- Mini-open
- Pure Lap
- Retro Lap
- Robot-assist Trans Lap



Costs - The bigger picture?

Theatre time

HALDN: 180 min

Re-usable equipment

Lap stacks etc; Lap instruments

Consumables

	£		£
Thunderbeat	387	Harmonic	407
Stapler	294	Ligasure	411
Stapler reload x2	244	Hemolock	24
Gelport	281	Fibrillar	60
Trocars x2	67	Dermabond	22
Sucker	93	TOTAL	1500

Hospital stay: 2-4 days (culture) Time back to work: 3 v 6 weeks ?



Pain management

- 20mls 0.5% levo-bupivicaine between peritoneum and fascia
- LA wound infiltration skin / ports
- LA Infusion pump 0.125% L-BP
- Fentanyl PCA low background & demand
- Paracetamol iv / po
- +- 3 days Ibuprofen with PPI cover

Training







50 years of Renal Transplantation at Guy's - the early years

1962 Acute HD & PD Aug 1966 long- term HD

Richard Batchelor (1931-2015) tissue typing and matching (trained by Peter Gorer) May 1967 1st transplant Nov 1968 1st paediatric transplant

Frank Ellis & Michael Joyce Mick Bewick 1968; Geoff Koffman & John Taylor 1970/80s

1976 500 Tx in SE region (421 DD; 79 LD) 1979 1000 Tx (820 DD (DCD); 180 LD)





Cameron & Ogg













Pioneering



American Journal of Transplantation 2017; XX: 1–10 Wiley Periodicals Inc. © 2017 The American Society of Transp and the American Society of Transplant doi: 10.1111/

Prophylactic Ureteric Stents in Renal Transplant Recipients: A Multicenter Randomized Controlled Trial of Early Versus Late Removal



Transplant Urology



Robotics



EVNP



HIV transplants





3D printing





Living Donor Kidney Transplantation The Donor & The Recipient



Kidney Transplantation

History, UK perspective & Guy's Hospital perspective **Recipient Medical Aspects** Surgical Aspects of Kidney Transplant Living Donation **Donor Medical & Psychological Aspects** Surgical Aspects of Donor Nephrectomy Questions



Thank you



