ABO mismatched Renal Transplants

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ABO incompatible transplantation

- Why?
- Protocol
- Risks
- Experience abroad
- Experience in UK
- Experience at St George’s
- Conclusions

Why perform ABOI-Tx?

- Increase number of transplants performed
- Live transplants have superior patient and graft function
- Patients want the option

ABOI Patients

- Options
  - Cadaveric list
  - Pair exchange
  - ABOI Tx

ABOI Patients

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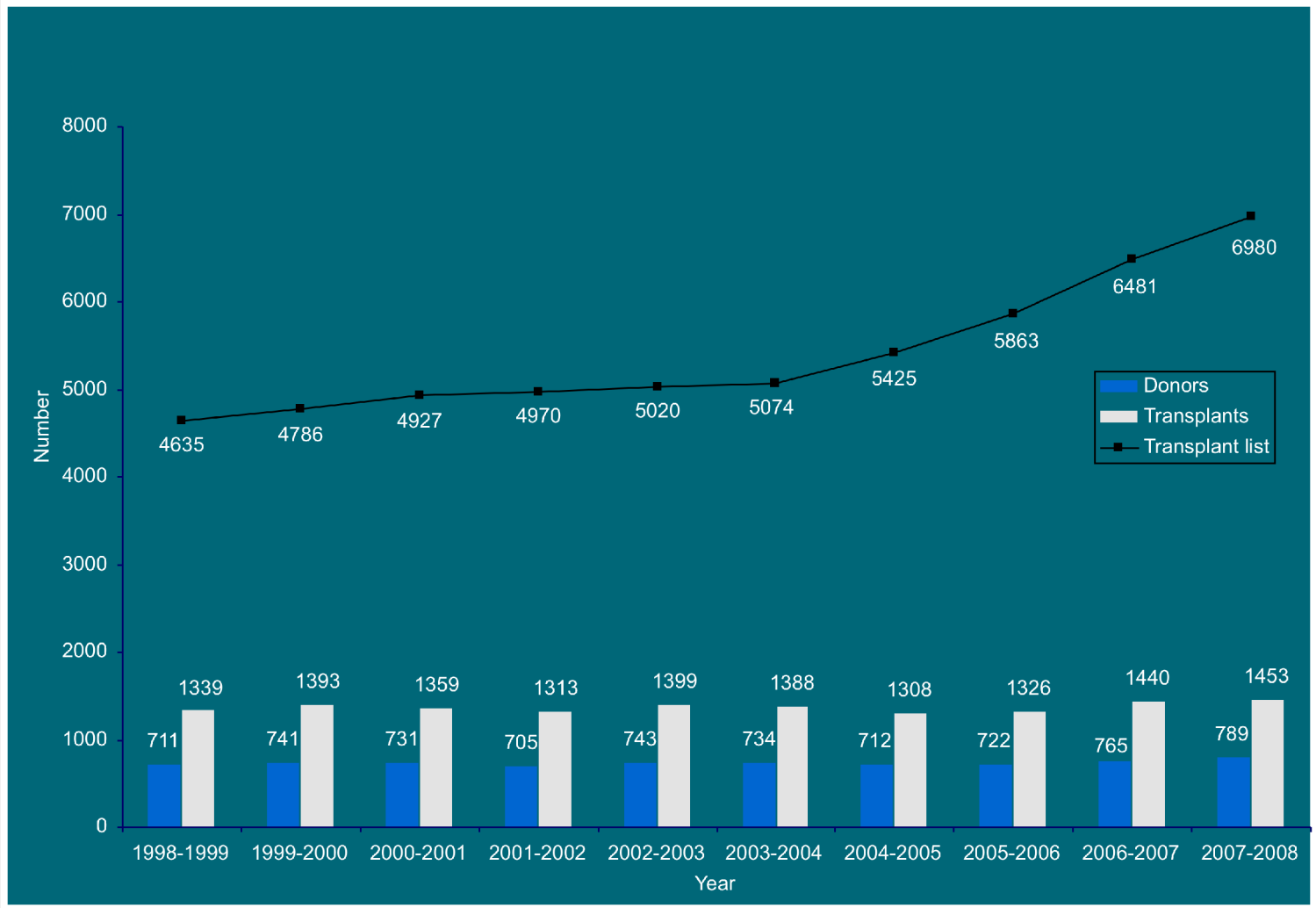
Deceased donor kidney programme in the UK, 1 April 1998 - 31 March 2008
Number of donors, transplants and patients on the active transplant list at 31 March



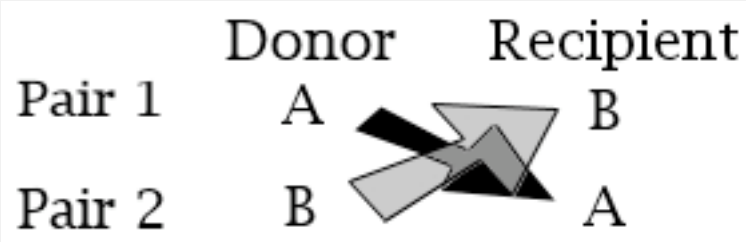
http://www.uktransplant.org.uk/ukt/statistics/statistics.jsp

ABOI Patients

- Options
  - Cadaveric list
  - Pair exchange
  - ABOI Tx

Pair exchange

- Human Tissue Act made paired living kidney donation possible in the UK from September 2006



ABOI Patients

- Options
  - Cadaveric list
  - Pair exchange
  - ABOI Tx

Problem of ABOI Tx

- Hyperacute/early humoral rejection

Protocol

- **Swedish protocol**
  1. Remove cells that produce antibody
     - Drip 1 month before (**rituximab**)
  2. Remove antibody
     - 3-4 sessions of '**immunoadsorption**' before transplantation (remove antibodies against particular blood group)
     - 3 sessions after transplantation
  3. Neutralization of existing antibody
     - **IVIG** given the day before transplant

Rituximab

Rituximab is a novel genetically engineered anti-CD20 therapeutic monoclonal antibody that selectively depletes CD20+ B cells

(Shaw et al, 2003; Johnson & Glennie, 2003)

Rituximab: Mechanism of Action

- Initiates complement-mediated B cell lysis
- Initiates cell-mediated cytotoxicity via macrophages and natural killer cells
- Induces apoptosis

(Clynes et al, 2000; Reff et al, 1994)

Rituximab

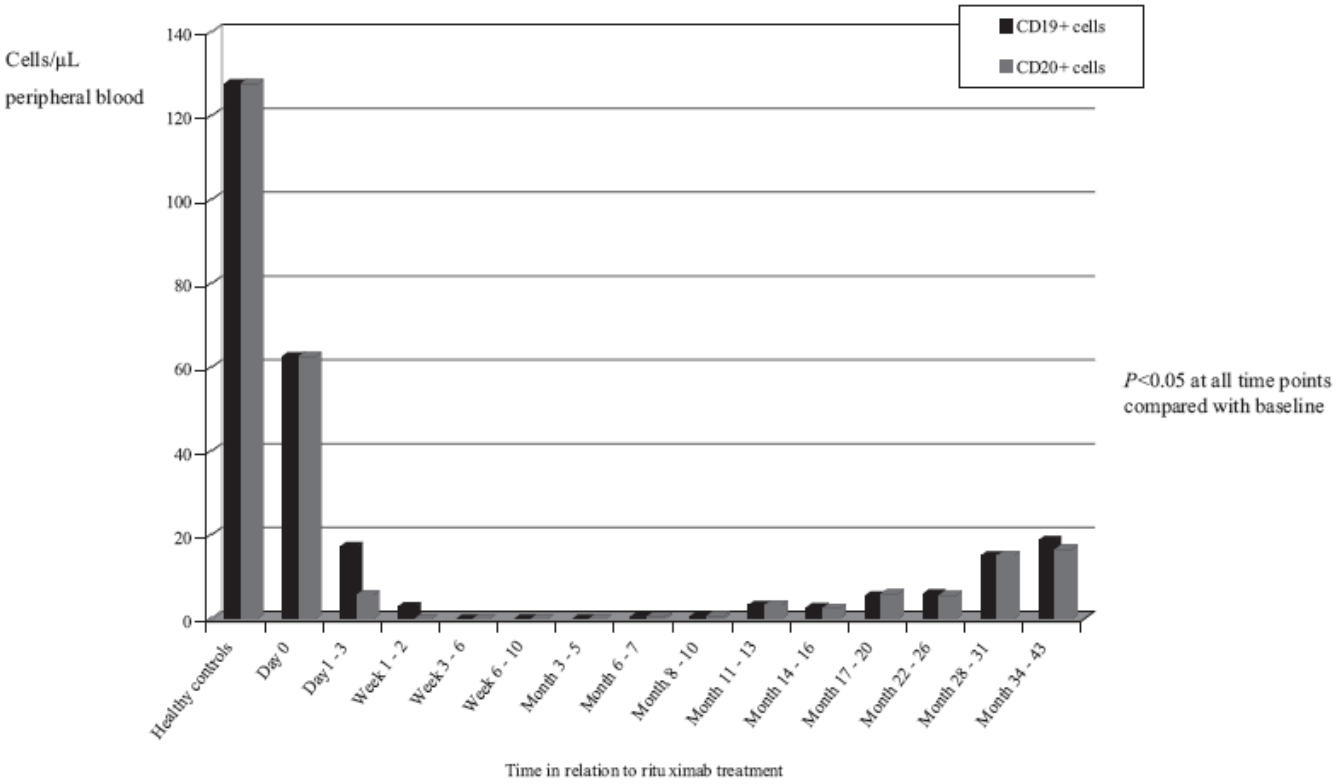


FIGURE 1. Median change in the CD19+ and CD20+ cell count (cells per microliters of peripheral blood) after treatment with rituximab. Immunophenotyping by flow cytometry. A profound and sustained B-cell depletion was observed in kidney recipients treated with single-dose rituximab in combination with tacrolimus, mycophenolate mofetil, and corticosteroids. Day 0=before treatment. Healthy controls = no treatment with rituximab or any other immunosuppressive. Adapted from (*1*).

IVIG

- Pooled immunoglobulin from multiple donors
- How does it work?
  - Neutralization of existing antibody
  - Block the Fc receptors on mononuclear phagocytes
  - Inhibition of expression of CD19 on activated B-cells
  - Inhibition of complement
  - Inhibition of T cells

Policy for transfusion

- **For emergency:**
- Red cells: high titre (HT)-negative red cell units, ABO/D compatible with renal transplant recipient
- Platelets: (HT)-negative platelet units, ABO compatible with renal transplant donor
- Plasma: Fresh Frozen Plasma (FFP), type AB

- **In all other cases:**
- Red cells: washed red cells, ABO/D compatible with renal transplant recipient
- Platelets: platelets in platelet suspension medium (PSM), ABO compatible with renal transplant recipient
- Plasma: FFP, type AB

What are the risks?

- May increase the risk of
  - Rejection
  - Infection
  - Cancer

Experience - Sweden

Implementation of a Protocol for ABO-Incompatible Kidney Transplantation – A Three-Center Experience With 60 Consecutive Transplantations

Gunnar Tydén,[1,4] Johannes Donauer,[2] Jonas Wadström,[3] Gunilla Kumlien,[1] Jochen Wilpert,[2] Thomas Nilsson,[3] Helena Genberg,[1] Przemislaw Pisarski,[2] and Gunnar Tufveson[3]

Background. A new protocol for ABO-incompatible kidney transplantation has recently been introduced. We report here on the joint experience of the implementation in Stockholm and Uppsala, Sweden and Freiburg, Germany.
Methods. The new protocol utilizes antigen-specific immunoadsorption to remove existing ABO-antibodies, rituximab, and intravenous immunoglobulin to prevent the rebound of antibodies, and conventional tacrolimus, mycophenolate-mofetil, and prednisolone immunosuppression. Sixty consecutive ABO-incompatible kidney transplantations were included in the study. The outcome is compared with the results of 274 ABO-compatible live donor transplantations performed during the same period.
Results. Two of the ABO-incompatible grafts have been lost (non-compliance and death with functioning graft). All the remaining 58 grafts had good renal function at a follow-up of up to 61 months. We did not observe any late rebound of antibodies and there were no humoral rejections. Graft survival was 97% for the ABO-incompatible compared with 95% for the ABO-compatible. Patient survival was 98% in both groups. There was a significant variation in preoperative A/B-antibody titer between the centers, with a median 1:8 in Uppsala, median 1:32 in Stockholm and median 1:128 in Freiburg. More preoperative antibody adsorptions were therefore needed in Freiburg than in Stockholm and Uppsala.
Conclusions. The new protocol was easily implemented and there were no graft losses that could be related to ABO-incompatibility. A significant inter-institutional variation in the measurement of anti-AB-antibodies was found, having a substantial impact on the number of immunoadsorptions and consequently on the total cost for the procedure. A standardized fluorescence-activated cell sorting technique for antibody quantification is much needed.

Keywords: ABO-incompatible, Antigen-specific, Immunoadsorption, Rituximab.

(*Transplantation* 2007;83: 1153–1155)

Sweden

TABLE 1. Comparison of graft and patient survival and graft function in ABO-incompatible and ABO-compatible living-donor (LD) transplantations

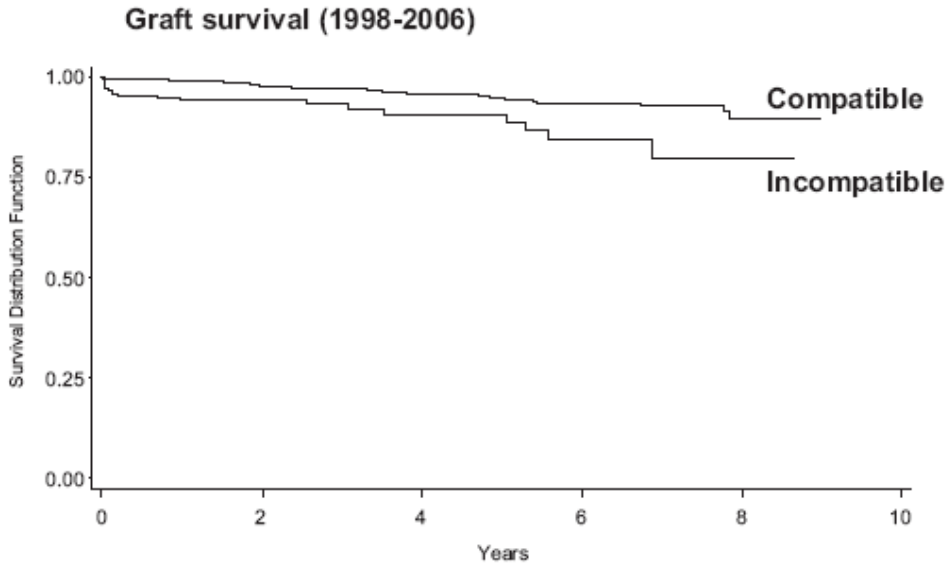
	N	Graft losses	Actual graft survival	Actual patient survival	Actual serum creatinine (μmol/L) mean and range	Follow-up mean and range
ABO-incompatible LD tx	60	1 non-compliance 1 DWFG	97%	98%	127 (42–203)	17.5 (2–61) months
ABO-compatible LD tx	274	7 AHR+2 technical 6 DWFG	95%	98%	133 (53–360)	21.1 (2–63) months

AHR, acute humoral rejection; DWFG, death with functioning graft.

TABLE 2. Demographics of ABO-incompatible kidney recipients, antibody titre before adsorption, and number of pre- and postoperative adsorptions

		Age		IgG antibody titre		Preoperative adsorptions		Postoperative adsorptions	
Center	N	Mean	Range	Median	Range	Median	Range	Median	Range
Stockholm	26	30.8	1–63	32	1–128	4	0–9	3	0–16
Freiburg	21	45.3	21–63	128	8–1024	5	1–12	0	0–6
Uppsala	13	46.3	19–69	8	1–32	4	1–5	4	1–5

Japan



Survival rate					
Compatible	100	97.6	95.7	93.2	89.7
Incompatible	100	94.1	90.4	83.9	79.5
Number at risk					
Compatible	734	551	367	191	53
Incompatible	207	130	74	32	4

FIGURE 3. Graft survival after ABO-ILKT at Tokyo Women's Medical University.

USA

ABO-Incompatible Transplantation: Less May Be More

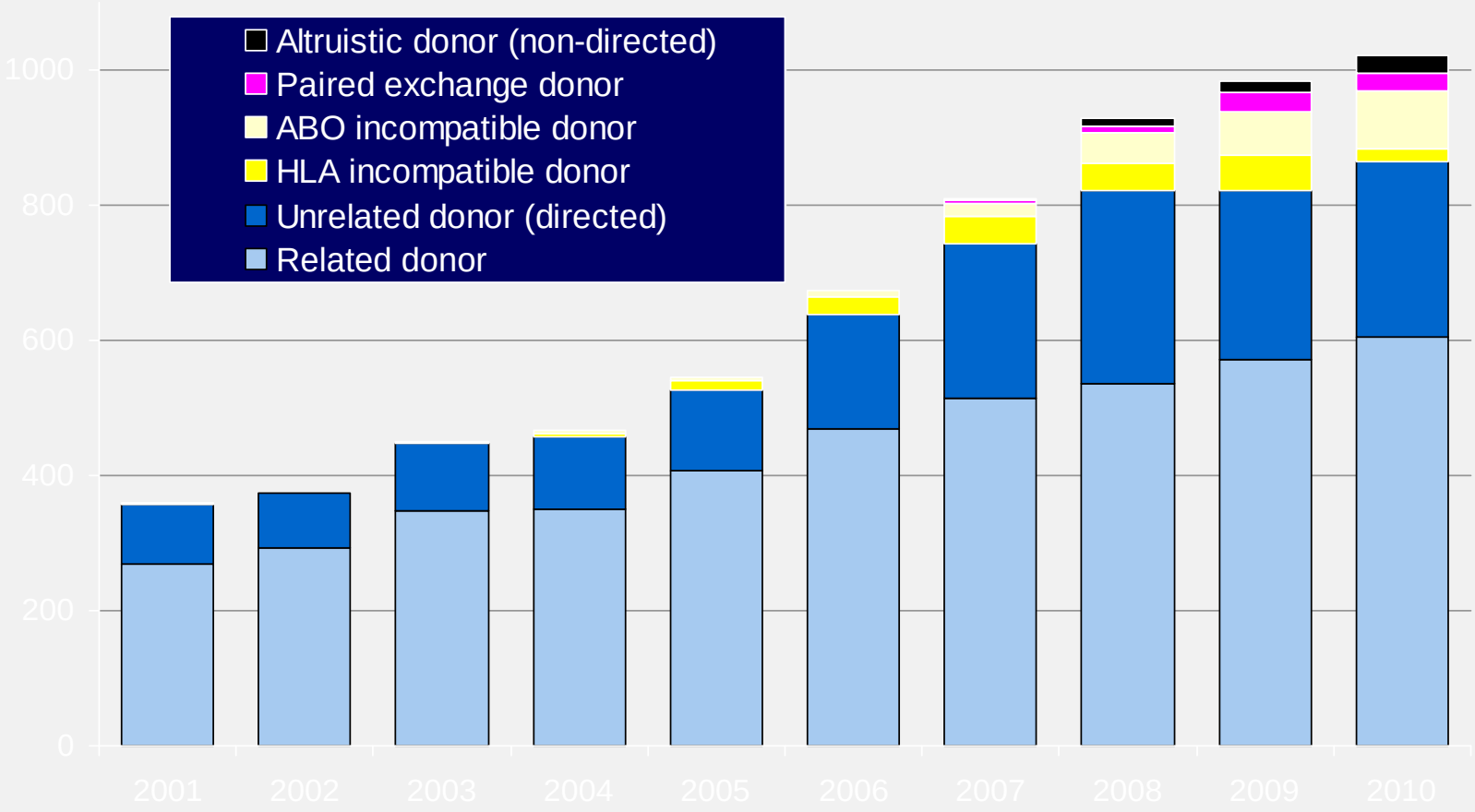
Robert A. Montgomery and Jayme E. Locke

Many have reported success with ABO-incompatible kidney transplantation using B-cell ablative therapies such as anti-CD20 and splenectomy. However, splenectomy and anti-CD20 is associated with an increased risk of infection. We show how ABO-incompatible kidney transplants can be accomplished with a low risk of antibody-mediated rejection and graft loss using plasmapheresis preconditioning, low-dose intravenous immunoglobulin, and standard maintenance immunosuppression. The mean follow up for our cohort of 53 patients is 2 years. The mean creatinine clearance at 1 and 3 years is 58 mL/min and 63 mL/min, predicting excellent long-term function. Only long-term follow up of these patients will render definitive answers, however, these data demonstrate that ABO-incompatible kidney transplantation increases the donor pool by providing live donor kidneys that function promptly with minimal risk of early loss. This can be accomplished with a modest, brief escalation of immunosuppression and at a lower cost to the health care system than maintaining the patient on dialysis

Keywords: Transplantation, Kidney, ABO-incompatible, Immunosuppression, B-cell depletion.

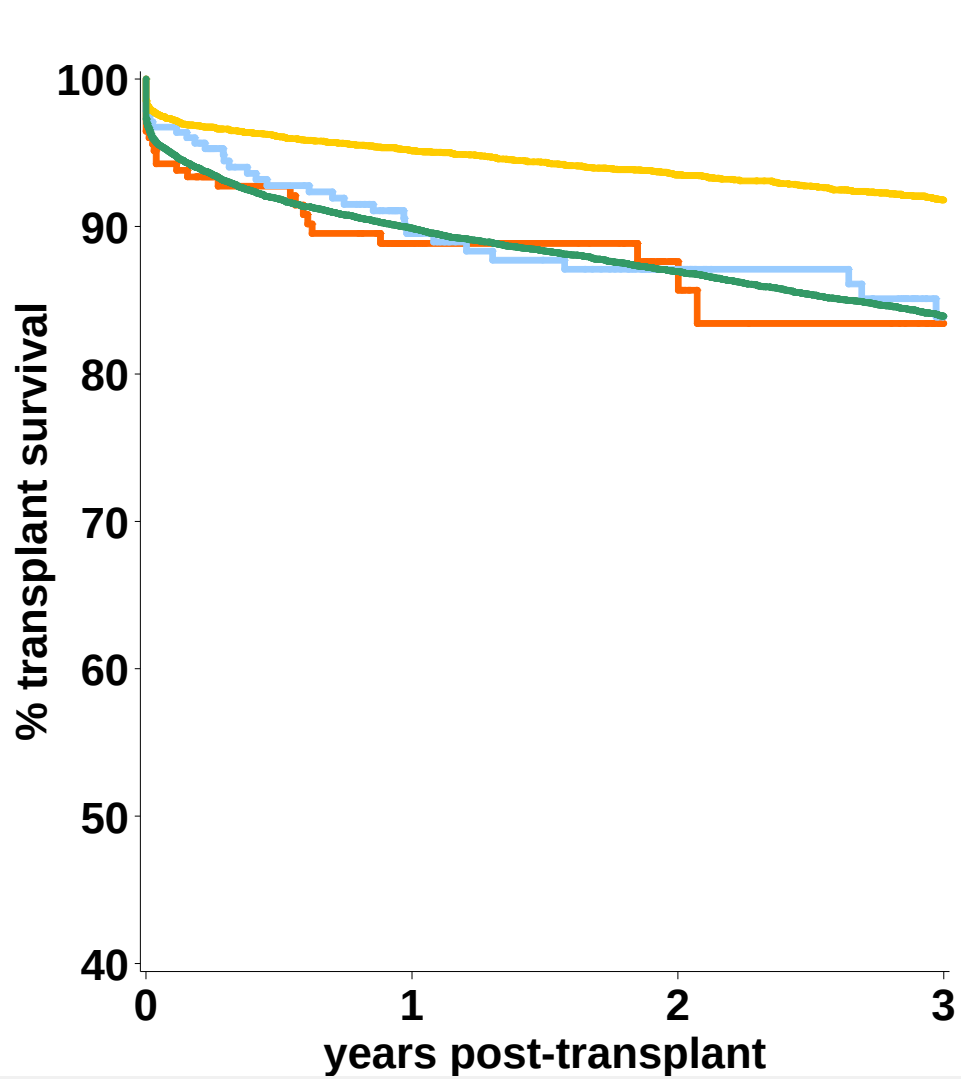
(*Transplantation* 2007;84: S8–S9)

Living donor transplant activity by year



NHSBT 2011

Three-year graft survival (failure or death)



LD 92% (95% CI 91-93%) n=5979
HLAi 84% (95% CI 77-89%) n=276
DD 84% (95% CI 83-85%) n=14071
ABOi 83% (95% CI 74-90%) n=221

ABOi LD vs other LD
Three year transplant survival – $p<0.001$

Cost

Item	Unit Cost	Number	Total Cost
Immunoadsorption Columns	£2,500	7	£17,500
Freight costs	£ 500	1	£ 500
ABO Titres	£ 55	30	£ 1,650
Rituximab	£1,223	1	£ 1,223
IV Ig	£1,225	1	£ 1,225
Histopathology	£ 200	2	£ 400
Increased Length of Stay	£ 500	1	£ 500
Total			**£ 22,998**

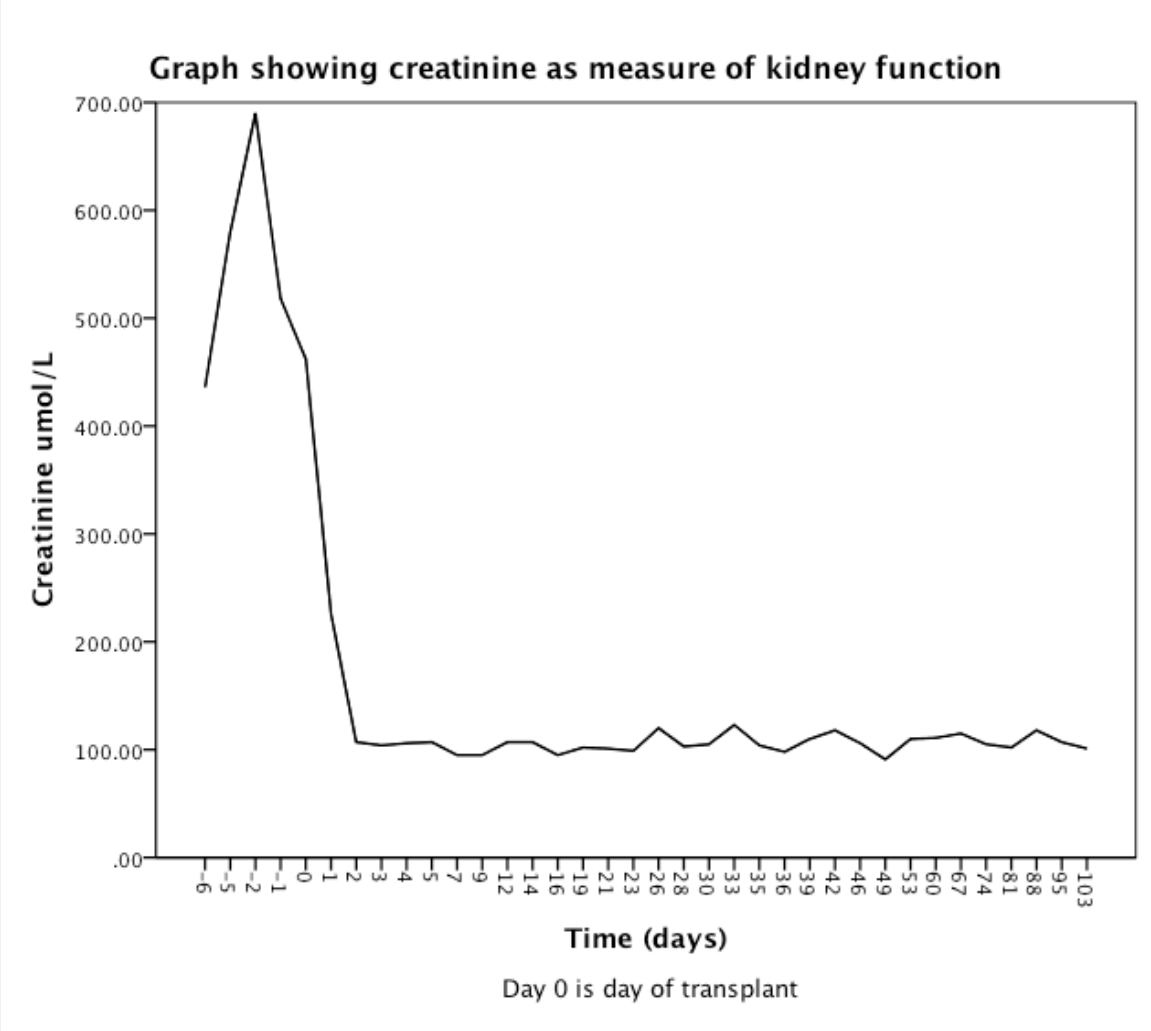
1st ABOI Tx

- 50 yr M , active , independent journalist
- ESRF due to FSGS
- On haemodialysis for 9 months (vascath), native UO of 1 l/day
- PMH: H.T
- Receive an ABOi transplant:

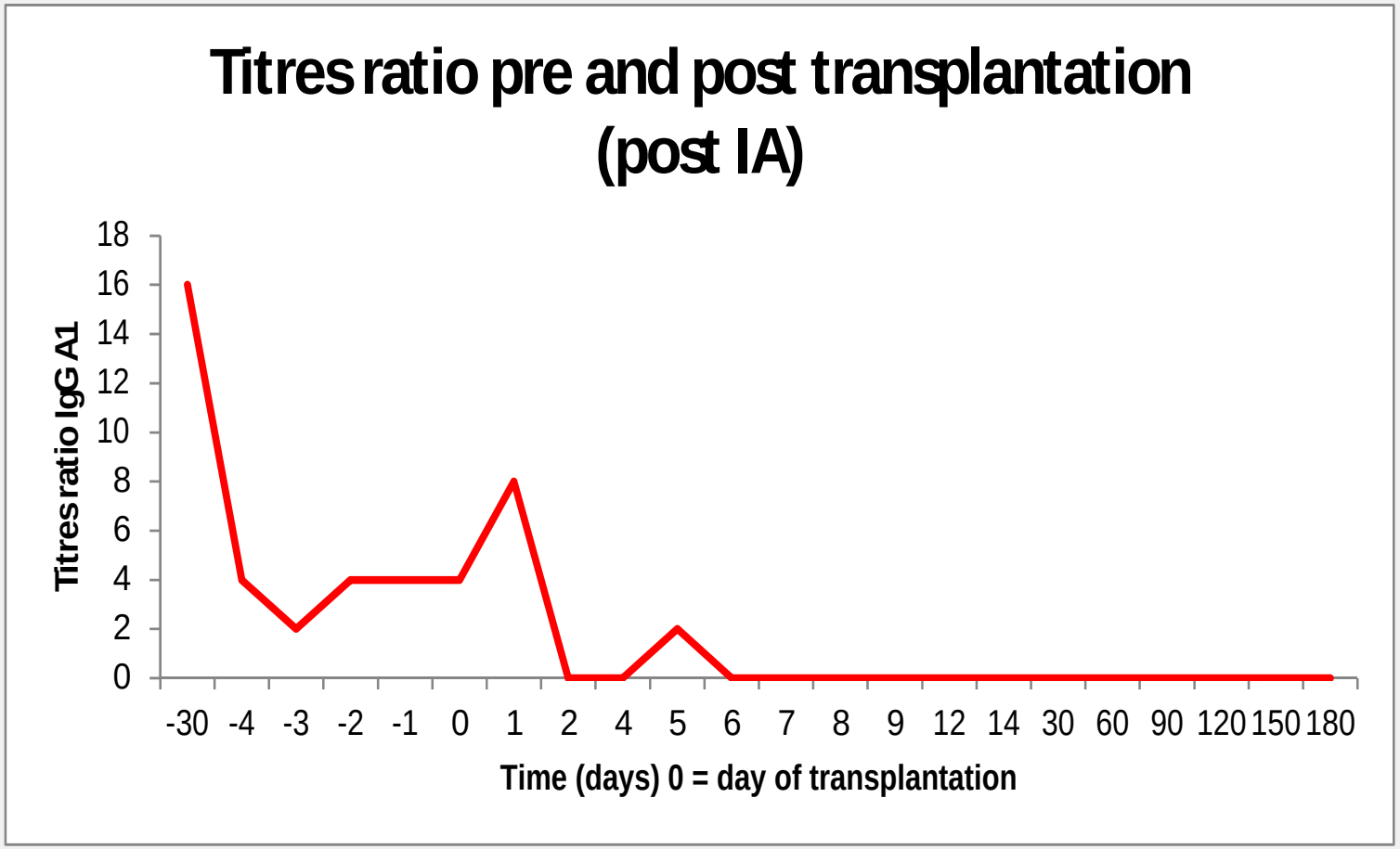
Son (Blood group A) → Father (Blood group B)

(CMV –ve) (CMV –ve)

Creatinine


Graph showing creatinine as measure of kidney function
Creatinine umol/L
700.00
600.00
500.00
400.00
300.00
200.00
100.00
.00
-6
-5
-2
-1
0
1
2
3
4
5
7
9
12
14
16
19
21
23
26
28
30
33
35
36
39
42
46
49
53
60
67
74
81
88
95
103
Time (days)
Day 0 is day of transplant

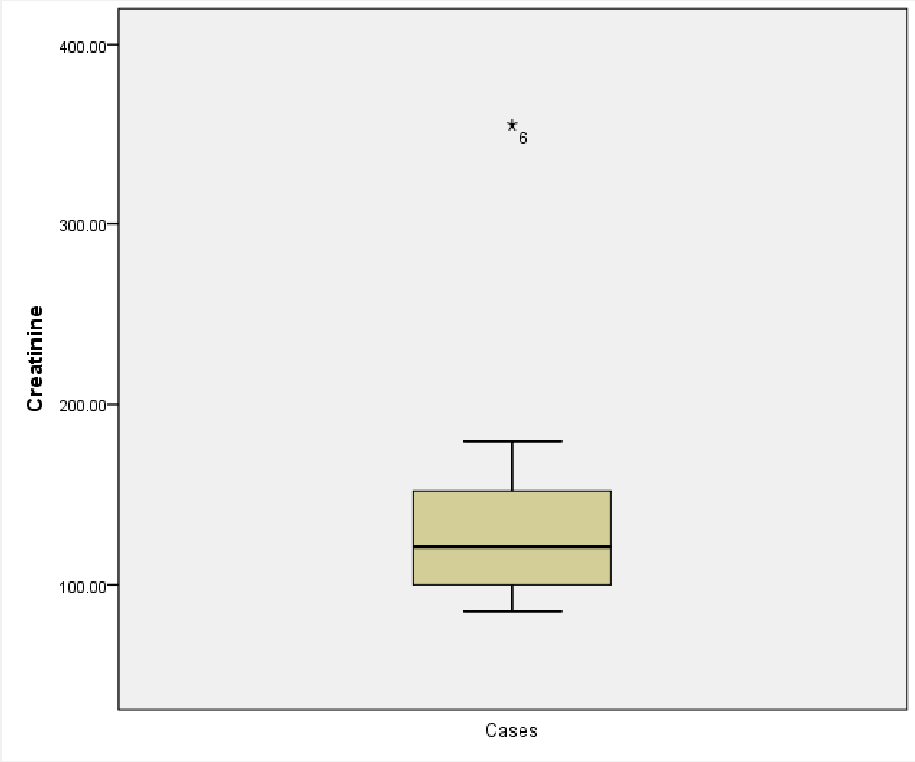
Titres IgGA1



	Age/ Sex	Dialysis	Donor blood group	Recipient blood group	Highest Titres before ritux	Tx date	Rejection episodes	Other complications	Last Creatinine (umol/L)
1	52M	HD	A1	B	1:16	16 Sept 2009	0	No	117 3/2/12
2	50M	PD/HD	AB	O	1:64	3 March 2010	1 Banff 2B Day 5	PE Day 31 Warfarin stopped 6/12	152 27/1/12
3	47F	PD/HD	B	O	1:256	13 October 2010	1 Banff 1A 1 year & 29 days	Lymphocele Drained Dec 2010 BK virus	85 23/2/12
4	53M	Pre	A1B	B	1:2	10 November 2010	1 Banff 2A Day 51	No	100 28/2/12
5	57F	Pre	A1	O	1:32	16 February 2011	0	UTI x1	112 17/2/12
6	57M	Tx/HD	A1	O	1:128	2 March 2011	1 Banff 1a Day 281	Bleeding, re-exploration, ATN	355 21/2/12
7	57M	Pre	A1	O	1:16	30 March 2011	2 Banff 1A Day 5, 59	No	124 20/2/12
8	41M	PD	A1	O	1:64	11 May 2011	0	Bleeding, evac. haematoma, ATN Recurrent FSGS	179 21/12/11
9	68M	PD	A1	O	1:128	14 September 2011	0	Lymphocele Drained Oct 2011	88 22/02/12
10	31M	HD	A	O	1:32	7 Dec 2011	0	No	133 28/2/2012

Summary of results

- 100% graft and patient survival
- Median creatinine 121 (IQR 62)



Conclusions

- ABOI Tx is complicated and expensive but possible
- It is becoming more widely available
- UK results are not as good as abroad
- Very high titre cases should be referred for pair exchange scheme

Acknowledgments

- The huge team
- Immunohaematology lab
- Patients
- PCTs