Blood Group Incompatible Renal Transplantation and Apheresis

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Background

- There is growing interest in transplantation across the blood group barrier to widen the pool of donor kidneys available.

- This can be achieved using a two-pronged approach of

  - desensitisation by either antigen-specific immunoadsorption (IA) or plasmapheresis (PP)
  - and by B-cell depletion therapy

Session Outline

This session will cover:

- A brief review of the theory of ABOi
- Outline of types of apheresis used in ABOi
- Review of the practical aspects of ABO-incompatible renal transplantation in three paediatric case studies

Background

- The greatest barrier to solid organ transplantation is the blood group ABO system.

- If an organ is transplanted which contains non-self A/B antigens, hyperacute rejection will occur causing loss of the graft.

Background

- 1955 - unsuccessful attempt to transplant across the ABO barrier
- 1987 - Alexandre et al, reported successful ABOi, using splenectomy
- Adopted by Japanese to increase living related transplants, in adults and children; heavy immunosuppression used
- Tydén et al in 2003 reported good outcomes in adults using monoclonal antibody (rituximab) rather than splenectomy, immunoadsorption and IVIG.
- First paediatric cases followed in 2005

Antigens

- Nearly all cell plasma membranes express highly specific glycoproteins on their surfaces which act as antigens.
- The antigens expressed on red cell plasma membranes are called agglutinogens (or isoagglutinogens) as they cause agglutination of mismatched red blood cells.
- Plasma also contains preformed antibodies called agglutinins (or isoagglutinins), and individuals possess antibodies against agglutinogens that they do not contain.

Blood Groups

Blood Group	Antigen (agglutinogen)	Antibody (agglutinin)
A (A1, A2*)	A	Anti-B
B	B	Anti-A
AB	AB	none
O	O	Anti-A, anti-B

*A2 cases have lower antigen expression, and are easier to transplant

Antibody Production

- Antibodies are not present in newborns and develop during the first year of life in response to exposure to food and environmental factors.
- Children express lower titres than adults
  - 46% of children on deceased donor list had titres < 1:16

ABO-Mismatching

- If there is an ABO-mismatch preformed antibody binds to blood group antigen structures on the endothelial cells of the transplanted kidney.

- This leads to fixation, binding and activation of complement, leading to endothelial cell inflammation and damage, resulting in microthrombi and micro haemorrhages and possible graft infarction.

Titres

- Antibody titres are measured by direct agglutination (saline method) for IgM and IgG levels by the indirect agglutination method.
- These assays are prone to subjective interpretation as it is a semi-quantitative technique and variation between laboratories occurs.
- Titre measurements by flow cytometry, an alternative newer technique, are associated with greater accuracy and reliability.
- Results are expressed in dilutions, with 1:4, 1:8 or 1:16 being considered safe levels at which to proceed with transplantation (British Transplantation Society, 2011).

Disadvantages of ABOi

- Increased risk of PTLD as increased immunosuppression
- Increased risk of opportunistic infections as increased immunosuppression
- Unknown long-term effects of monoclonal antibody use in transplantation
- Only for planned donation as requires work-up period
- Cost of apheresis?
- Increased risk of bleeding peri-operatively?

Benefits of ABOi

- Increases the donor pool by approx. 40%
- Allows living related donation from ABOi parent

Desensitisation

- Transplantation across the ABO barrier is made possible by the process of desensitisation.
- Firstly, formation of B-cell lymphocytes, which would form antibodies against the donor graft, are inhibited by the infusion of an anti-CD 20 monoclonal antibody, such as rituximab, four weeks before transplantation. This supersedes splenectomy.
- Secondly, circulating existing pre-formed antibodies against the donor's antigens are removed by apheresis techniques such as plasma exchange or immunoadsorption.
- The need for a planned, pre-emptive desensitization programme currently restricts ABOi transplantation to living donation, excluding deceased donor programmes.

Accommodation

- Following ABOi transplantation, most people seem to develop an immunotolerance to the incompatible antigens in the graft and neither reject the graft or develop antibodies against it.
- Those who do develop antibodies against the donor antigens can lose the graft through the processes of rejection.
- There is another group, however, who develop anti-A or anti-B antibodies yet do not experience rejection and this is referred to as accommodation.
- Accommodation - the absence of an antigen-antibody reaction, although antigen is present on the vascular endothelial cells in the graft and there are circulating antibodies.
- The risk of developing acute rejection of the transplanted kidney is greatest immediately following transplantation.

Types of Apheresis

- PP
- DFPP
- Immunoadsorption

Plasmapheresis

- Plasmapheresis (PP) - the removal of plasma from the blood with the replacement of a suitable substitution fluid such as plasma, albumin or colloid (Kumlien, 2008). The term plasmapheresis is used synonymously with plasma exchange (PE).
- Each session of plasmapheresis results in a 20% reduction in antibody levels. When albumin is the replacement fluid, many important physiological substances are not replaced, such as complement, coagulation factors and immunoglobulins; it takes 4-72 hours to return to pre-apheresis levels.
- The indication for plasmapheresis in ABOi renal transplantation is graded category II, grade 1B by the American Society for Apheresis (ASFA) giving it a strong recommendation with moderate quality evidence.

Double Filtration Plasmapheresis

- Double filtration plasmapheresis (DFPP) - plasma is separated from the blood and filtered through a second plasma fractionator to remove specific blood components, such as antibodies and complement factors.
- It is also referred to as cascade filtration. The pore sizes in the membrane determine the selectivity of the process: if the pore size is smaller than that of IgM, then IgM will be retained in the fractionator and not returned to the patient.
- Only a small volume of albumin is removed, therefore only a small amount of substitution fluid is required; coagulation factors are also retained.

Immunoadsorption

- Immunoadsorption (IA) - involves passing the plasma across an immunoglobulin column which removes donor specific anti-A or anti-B IgM and IgG.
- For example, Glycosorb columns (Glycorex, Sweden) contain a synthetic blood group A or B trisaccharides bound to sepharose (a bead-like polysaccharide polymer matrix) and can remove more than 90% of the target isohaemagglutinin without affecting the plasma concentration of albumin, IgG, IgA, IgM or coagulation factors.

Case Study

Double Filtration Plasmapheresis

Case Study DFPP

- 13 year old girl; 34kg
- Diagnosis of dyplasia following twin-twin transfusion
- Creatinine 450 µmol/l, pre-emptive second transplant

- Recipient blood group is O
- Donor (father) blood group is A

- Access via dual lumen tunnelled CVL

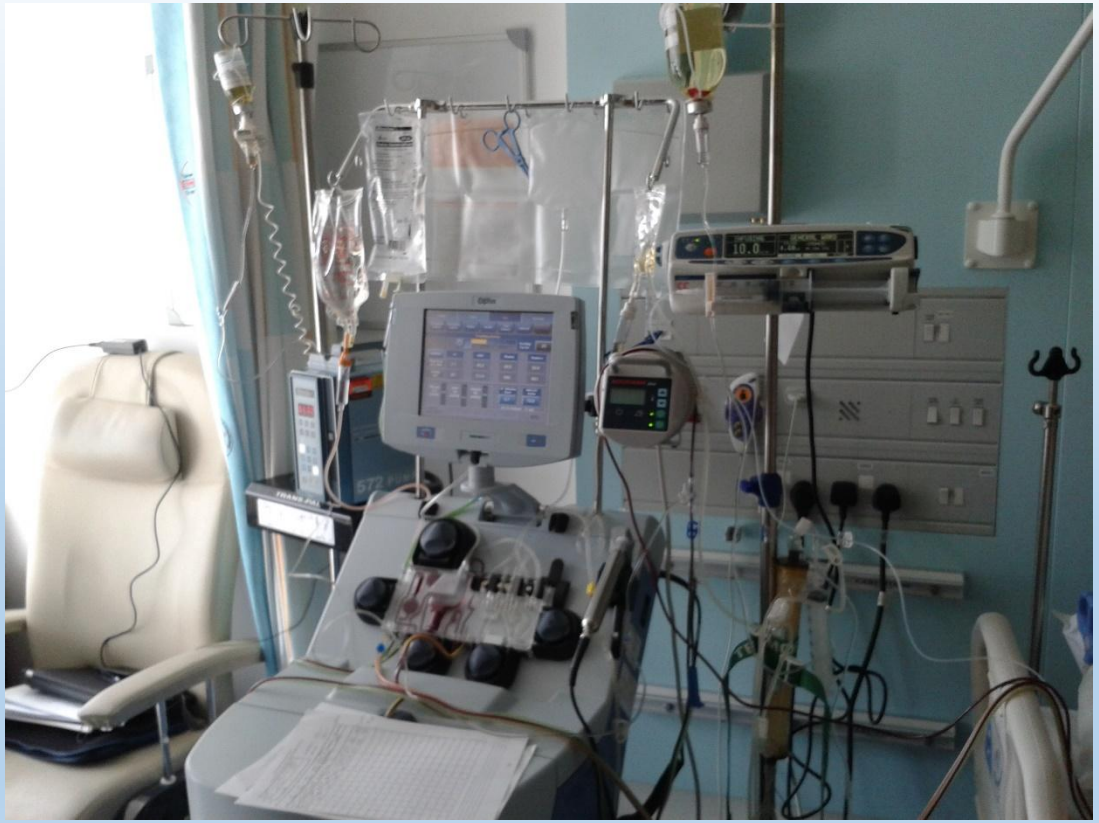
Case Study DFPP cont.

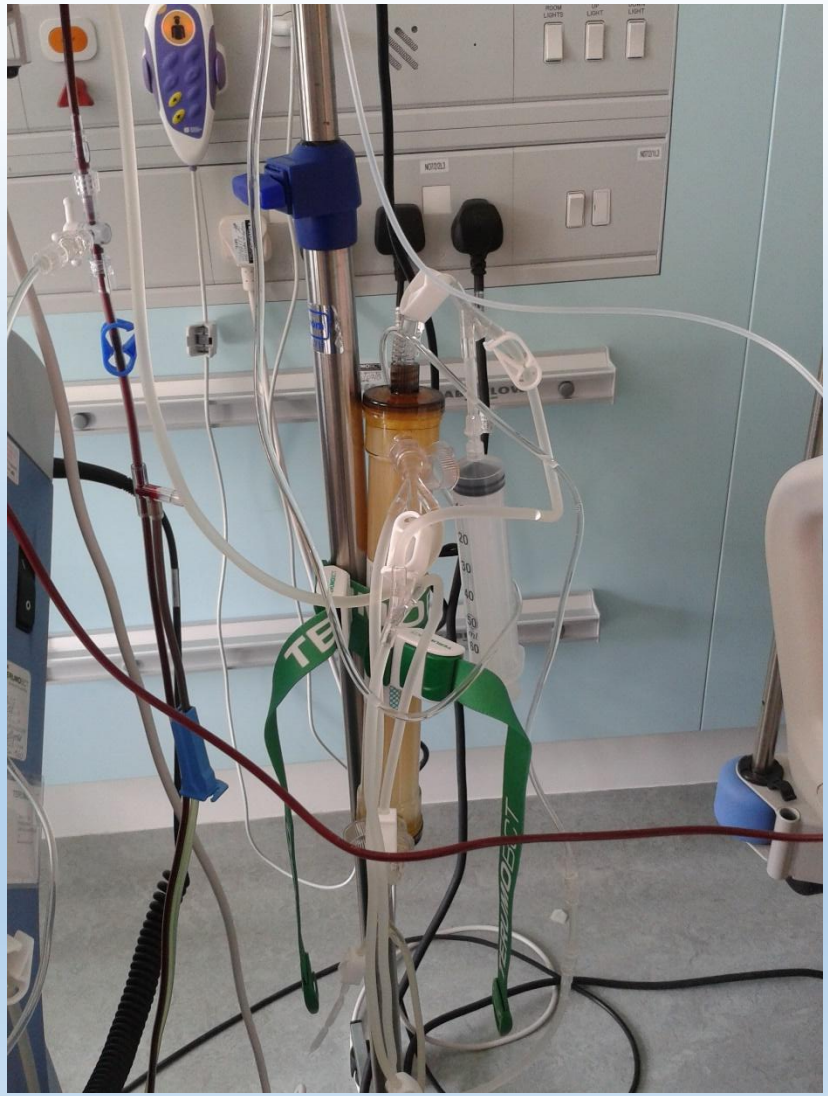
- Day -28 - Rituximab
- Day -5 - MMF and tacrolimus commenced
- Day -3 - day -1 – daily DFPP using Evaflux plasma fractionator
- Day 0 - transplant

Case Study DFPP cont.

- Spectra Optia with secondary plasma device – Evaflux 2A10 fractionator, DFPP
- 3 sessions, on consecutive days prior to transplant
- Volumes:
  - circuit = 145-185 mls
  - blood warmer tubing = 40mls
  - plus plasma prime of secondary circuit approx. 50mls
- HF’s weight 34kg, ECV 217-272mls.
- Circuit primed with saline, and blood warmer used on return line

DFPP





DFPP Plasma Volumes

- 1.5-2 plasma volumes processed:

- Day 1 - 1.5; 164 mins
- Day 2 - 2.0; 194 mins
- Day 3 - 1.5; 130 mins

- ACD-A anticoagulant
- Calcium gluconate 10% infused IV via 3-way tap into distal end of circuit
  - 0.04 mmol/kg/hour; made up to 50-100mls.
- Ionised calcium checked pre and post-procedure

Albumin Replacement

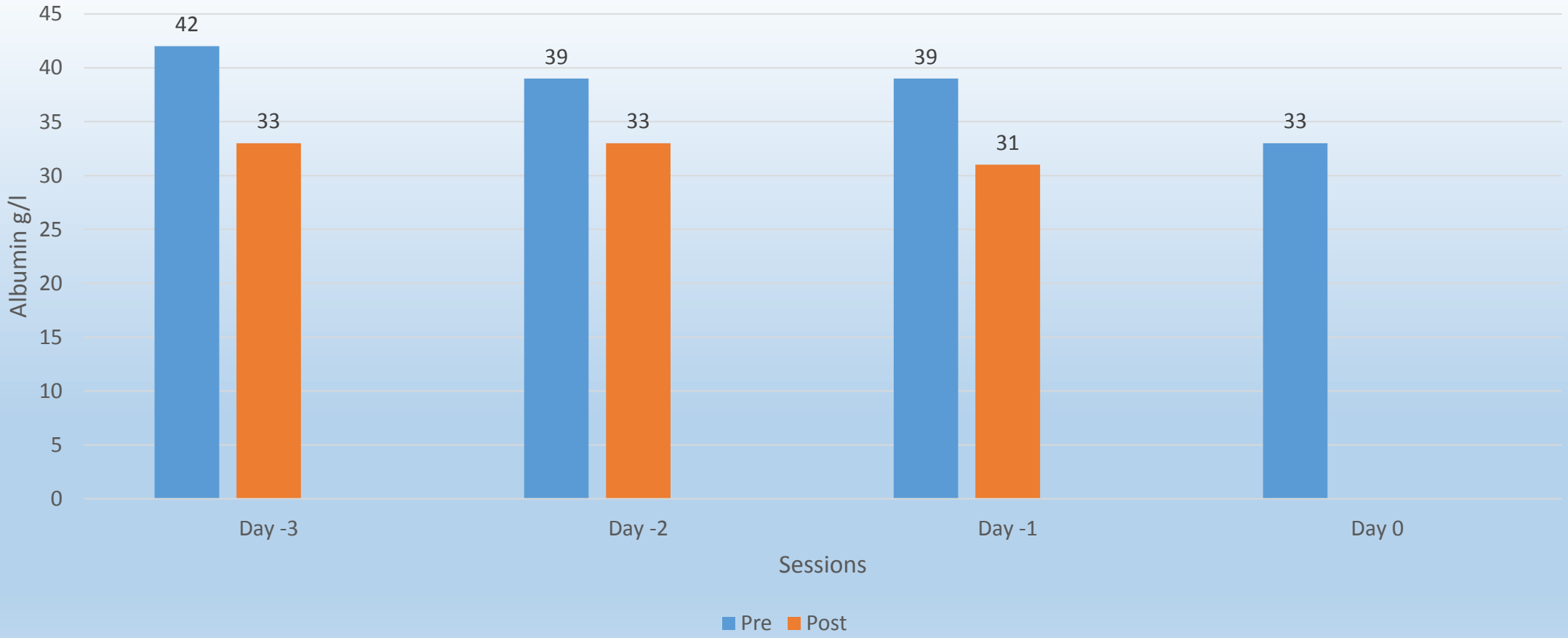
- 20% used to replace plasma proteins lost when the fractionator is flushed
- Aiming for 100mls over the session
- Infused via 3-way tap into venous return line

DFPP - Rinsing the Fractionator

- Max pressures of fractionator are <450mmHg

- Fractionator can be flushed to remove accumulated proteins
- 100mls 4.5% albumin used for each flush
- 3 flushes required for first session and then only 2

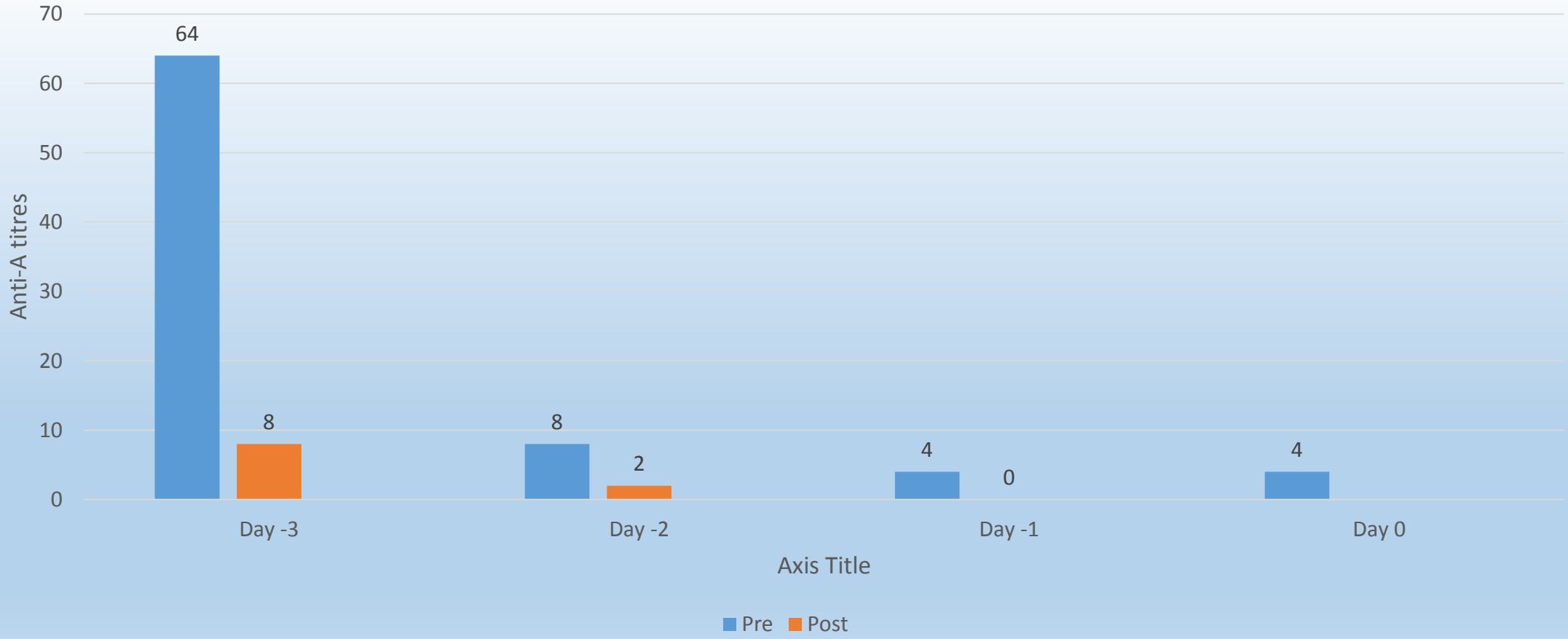
DFPP - Serum Albumin levels



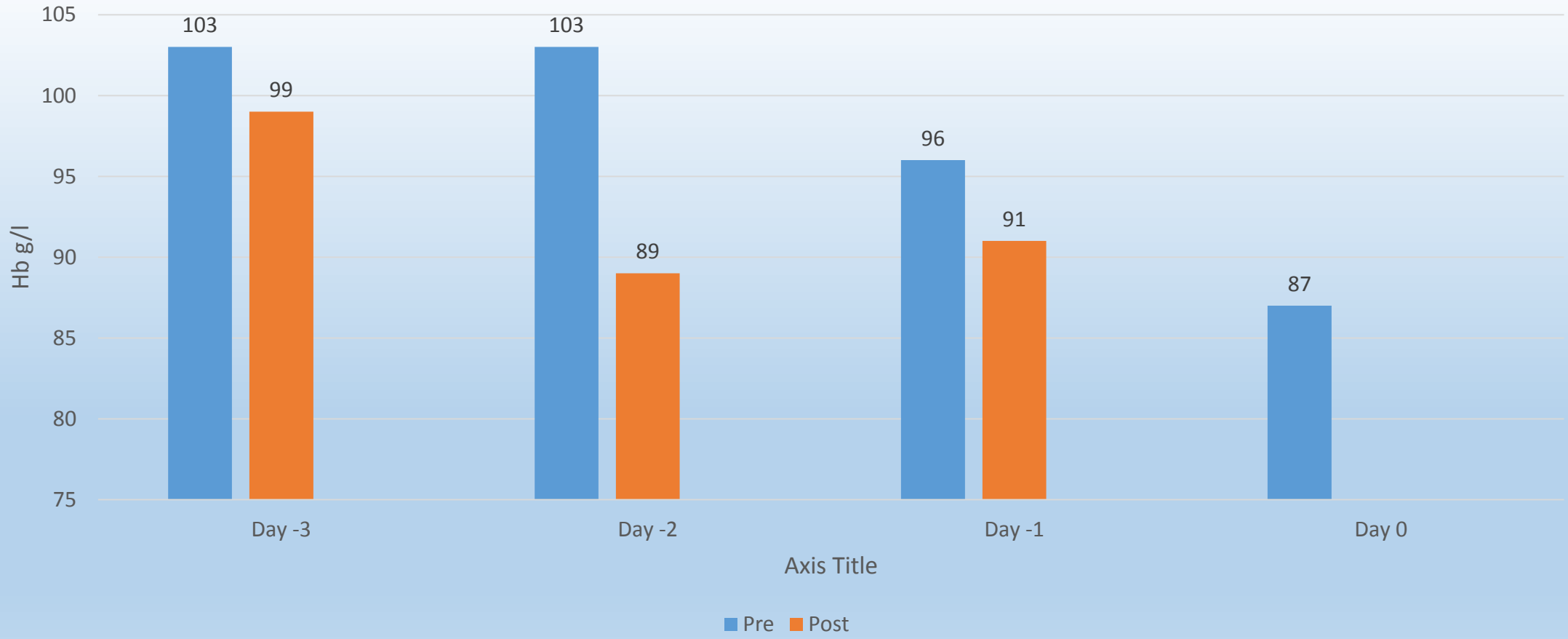
Case Study DFPP - Fluid Balance

DFPP Session	Weight Pre-DFPP (kg)	Weight Post DFPP (kg)	End Procedure Balance	Actual Gain (kg)
1	34.1	34.6	645mls	0.5kg
2	34.0	34.7	754mls	0.7kg
3	34.9	35.1	577mls	0.2kg

DFPP Anti-A Titres



DFPP - Hb Levels



Case Study DFPP - Outcomes

- No further apheresis
- Immediate graft function
- Fall in Hb to 4.5 g/dl; blood transfusion required
- Current creatinine is 70-130 µmol/l
- Anti-A titres remain undetectable

Case Study

Immunoadsorption

Case Study IA

- 9 year old girl; 21kg
- Atypical HUS; 1 failed deceased donor transplant
- On HHD using AVF; on call for several years

- Recipient is group O
- Donor (father) is group A
- Anti-A titres as high as 1:128

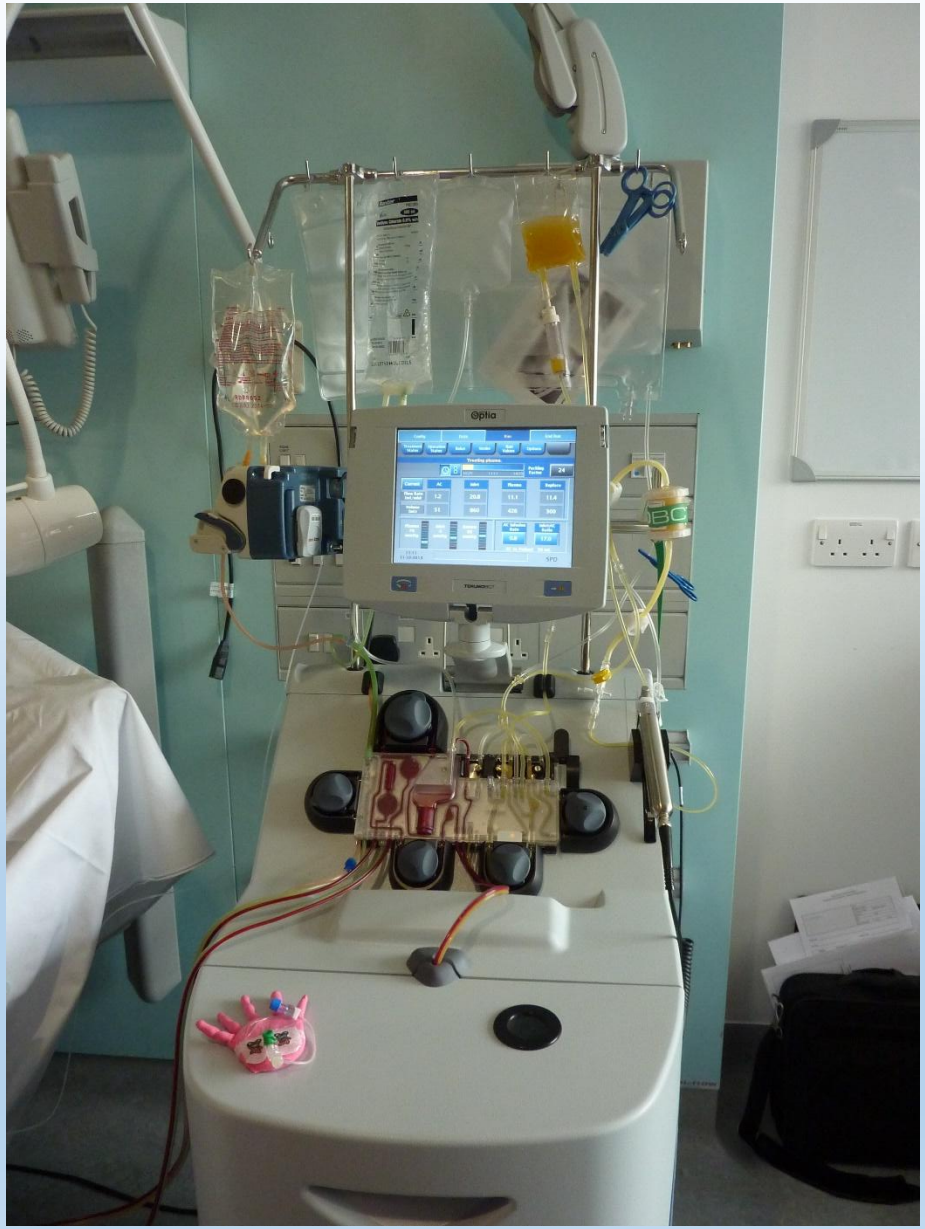
Case Study IA cont.

- Day -28 - Rituximab
- Day -5 - MMF and tacrolimus commenced
- Day -4 - day -1 – daily immunoadsorption using anti-A column
- Day 0 - transplant

IA procedure

- Spectra Optia with secondary plasma device – Glycosorb anti-A column
- Volumes:
  - circuit = 145-185 mls
  - blood warmer tubing = 40mls
  - plus plasma prime of secondary circuit approx. 50mls
- MA's weight 21kg, ECV 135-168mls.
- Circuit primed with 4.5% albumin, and blood warmer not used

Immunoadsorption

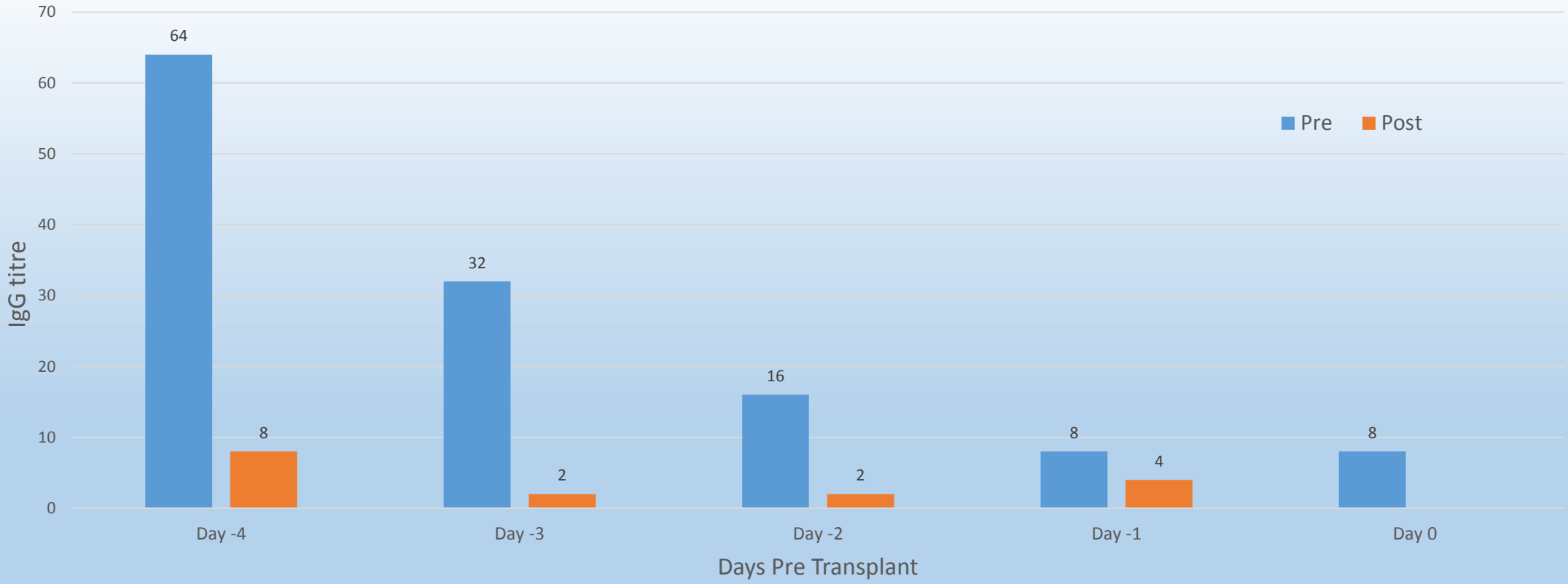


IA procedure

- ACD-A anticoagulant
- Calcium gluconate 10% infused IV via 3-way tap into distal end of circuit
  - 0.04 mmol/kg/hour; made up to 50-100mls.
- Ionised calcium checked pre and post-procedure

- 2.5 plasma volumes treated each day
- 4 hours per session

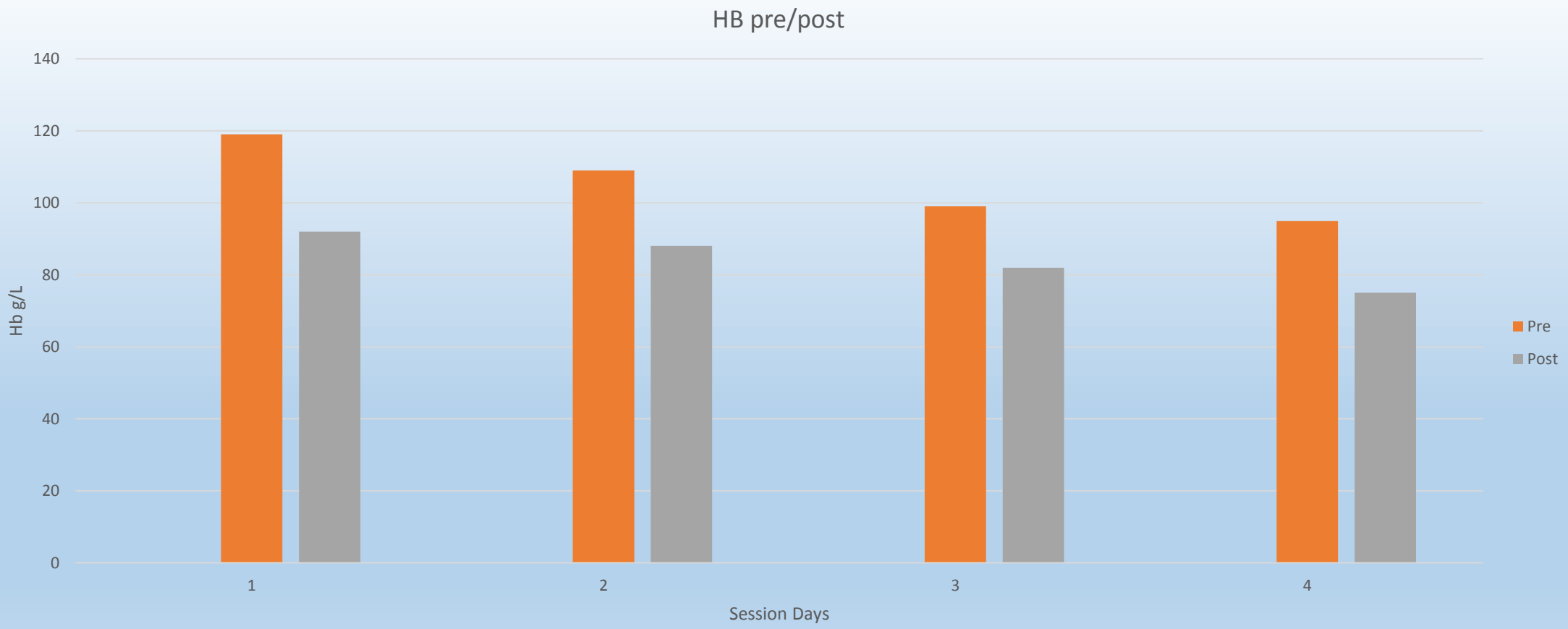
Titres – pre/post IA



Fluid Balance

IA Session	Weight Pre-IA (kg)	Weight Post IA (kg)	End Procedure Balance	Actual Gain (kg)
1	21.5	22.15	491ml	0.65
2	21.4	22.1	381ml	0.7
3	21.6	22.2	404ml	0.6
4	21.5	22.25	554ml	0.75

Hb - pre/post IA



Case Study IA - Outcomes

- Immediate disease recurrence
  - Rise in creatinine
  - Fragments on blood film
  - Drop in platelets/Hb
- Commenced eculuzimab
- No further apheresis
- Blood transfusion
- Creatinine now stable

Case Study IA - titres

- Titres post-operatively between negative and 1:8

Case Study

Rituximab only

No Apheresis?

- If titres are < 1:8 no apheresis is necessary
- B cell ablation using Rituximab only

Case Study

- 14 year old boy
- Steroid resistant nephrotic syndrome, FSGS
- Previous failed living related transplant from father, at age 12

- Recipient is blood group A
- Donor (mother) is blood group B

Case Study cont.

- Antibody anti-B titres ranged from 1:4 to 1:8 pre-transplant
- Decision to proceed with B cell ablation only

- Day -28 - Rituximab
- Day -7 - MMF and tacrolimus commenced
- Day 0 and Day 4 – basiliximab
- Plus corticosteroids

Case Study cont.

- Immediate graft function
- Creatinine at 3 years – 100-140 µmol/l
- No disease recurrence
- Negative anti-B titres

Any questions?

Thank you.