# A multi- disciplinary approach to ABO and HLA incompatible renal transplant

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# Presentation overview

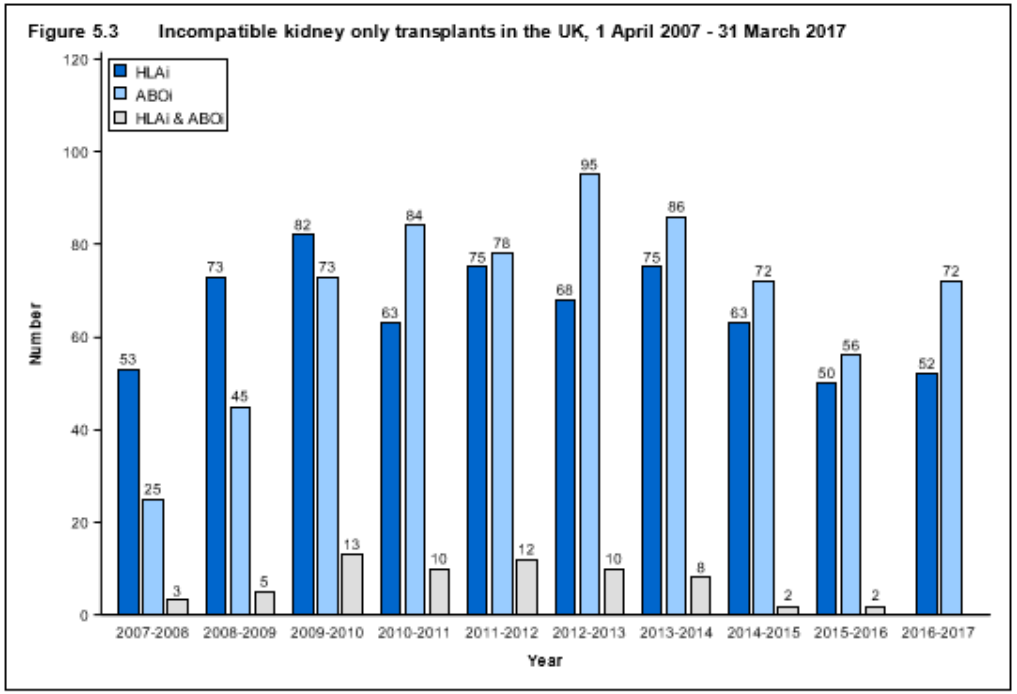
- Patient background
- ABO and HLA incompatible renal transplant
- Desensitisation regimens
- Plasma exchange and haemophilia
- Teamwork involved
- Questions

# Challenges to renal transplantation

- Complicated past medical history
- Highly sensitised- previous transplant/ blood transfusion
- Chances of receiving HLA and ABO compatible transplant 25% at 5 years
- Window of opportunity

# ABO incompatible (ABOi) kidney transplant

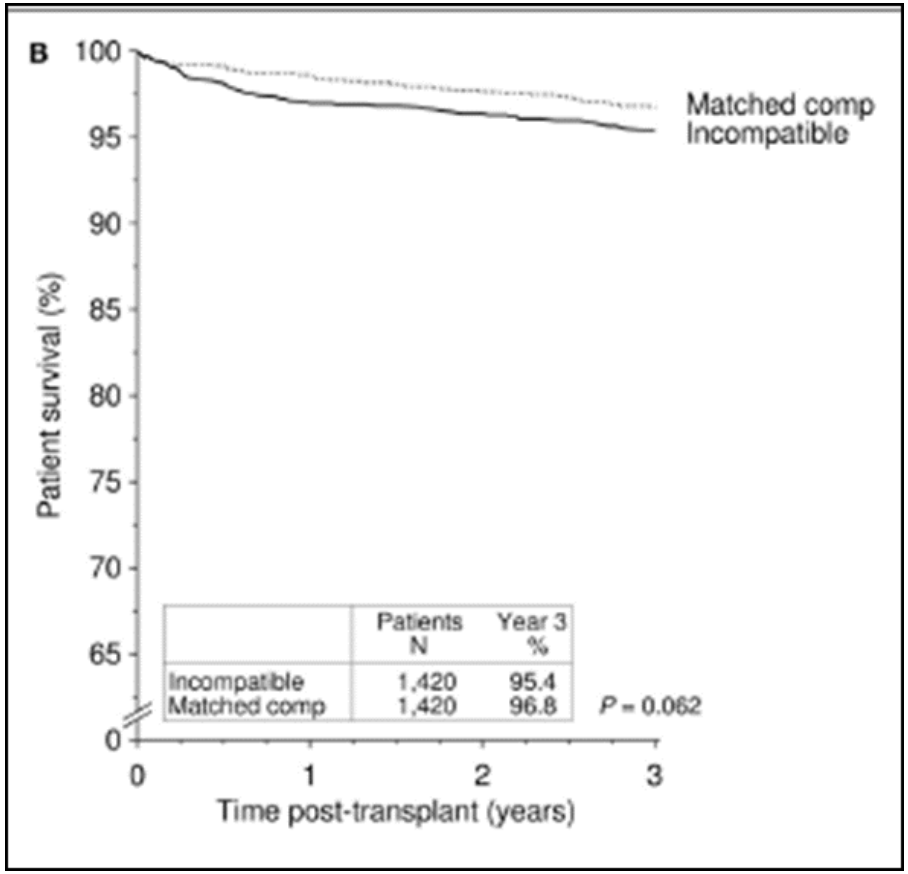
- Early attempts to transplant across ABO groups led to hyperacute rejection.
- In 1987 Alexandre et al introduced an effective desensitization protocol to prevent hyperacute rejection.
- This led to a wider utilization of ABOi kidney transplantations.




Source: Transplant Activity in UK, 2016-2017 NHS Blood and Transplant.

# Current outcomes in ABOi renal transplant

- **Collaborative transplant study**
- 1420 ABO incompatible kidney transplant outcomes.
- Overall graft, death-censored graft, and patient survival were not statistically significant different between the groups.
- ABOi kidney transplant recipients had a higher rate of early infection-associated death.



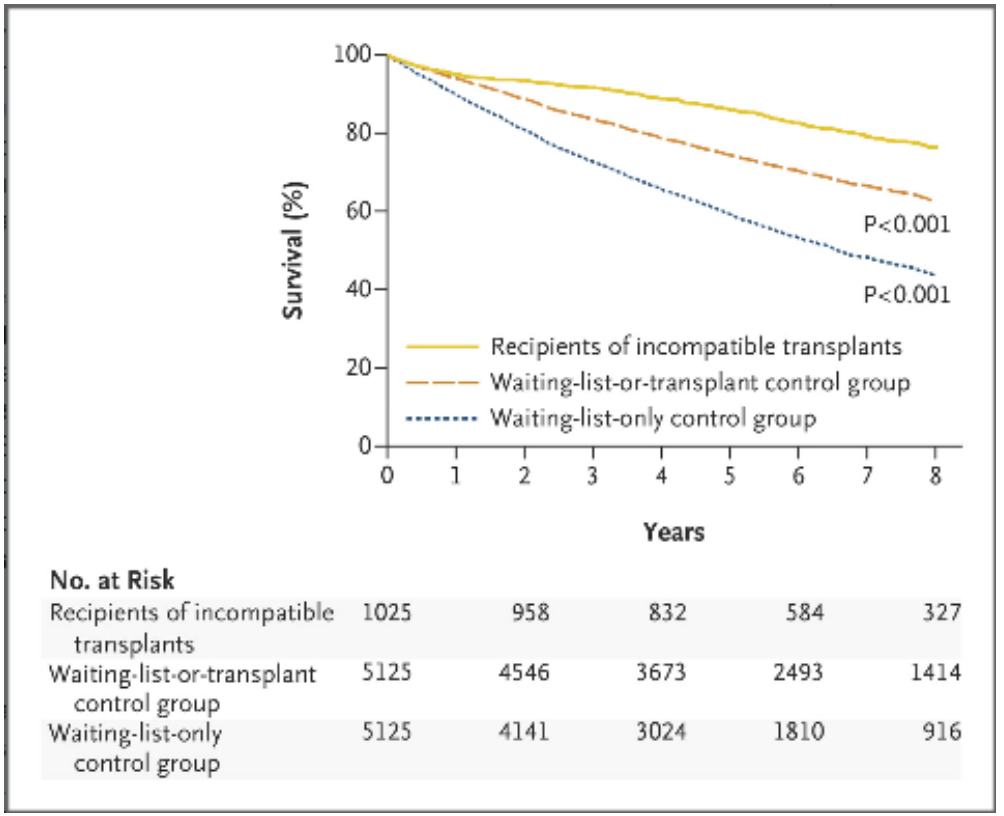

Opelz G, Morath C, Susal C, Tran TH, Zeier M, Dohler B. Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers. Transplantation (2015) 99(2):400–4.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors

- 1025 patients at 22 centre study.
- Higher survival rate in recipients of kidney transplants from incompatible live donors than either control group at 8 years (76.5% vs. 62.9% and 43.9%).
- Survival benefit was significant across all levels of donor-specific antibody (DSA).

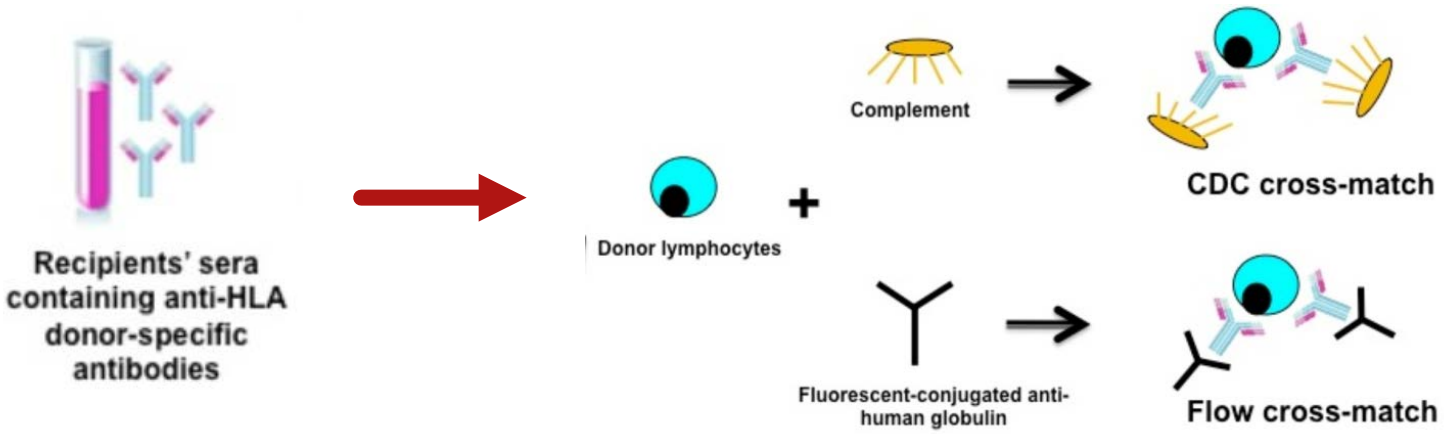



| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Recipients of incompatible transplants | 1025 | 958 | 832 | 584 | 327 |
| Waiting-list-or-transplant control group | 5125 | 4546 | 3673 | 2493 | 1414 |
| Waiting-list-only control group | 5125 | 4141 | 3024 | 1810 | 916 |

Source: Orandi et al. Survival Benefit with Kidney Transplants from HLA-Incompatible Live Donors. NEJM 2016; 374: 940-950.

# HLA antibodies

- There are different techniques for HLA antibody identification.
- **Cell based techniques**
- Complement dependent cytotoxic (CDC) crossmatch
- Flow cytometric crossmatch
- **Solid phase immunoassays**
- Luminex antibody testing

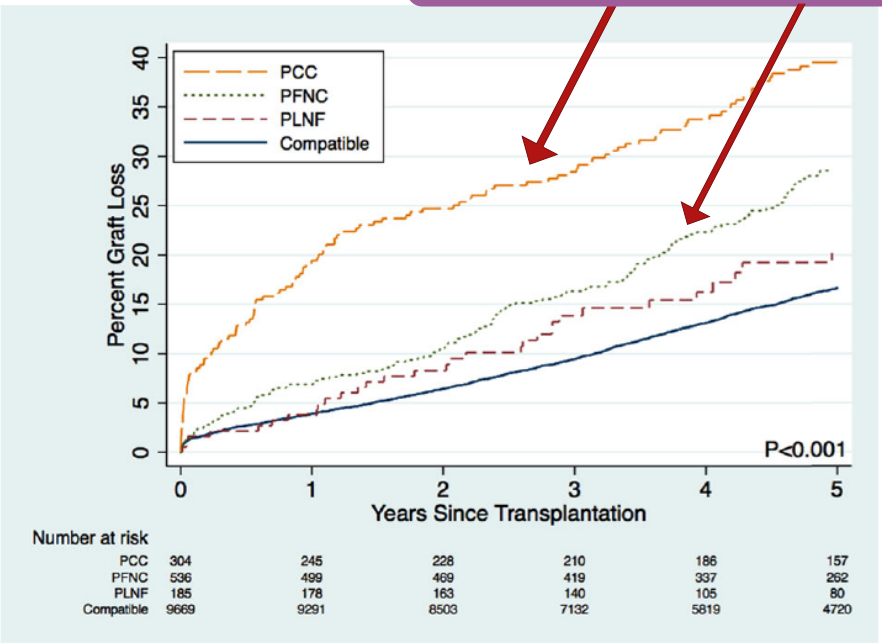


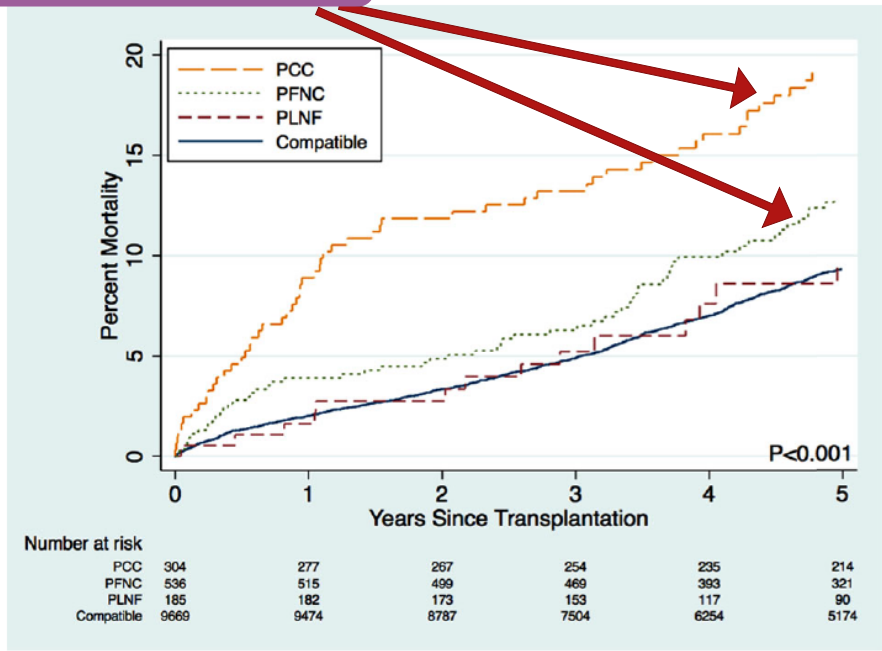
# Quantifying the risk of HLA incompatible kidney transplantation

**% Graft Loss at 5 years**

**% Mortality at 5 years**

Positive flow crossmatch




Source: Orandi, B. J. et al. Quantifying the risk of incompatible kidney transplantation: a multicentre study. American Journal of Transplantation 2014; 14: 1573- 1580.

# Challenges to renal transplantation

- Match on paired exchange
- Blood group incompatibility
  - Donor: blood group B
  - Mr T: blood group O with anti B antibodies (IgG 1 in 16)
- HLA incompatibility
  - A class I HLA donor specific antibody
  - Flow cytometry crossmatch positive result
  - Cytotoxic crossmatch negative
- MDT discussions

# Desensitisation

- Reducing risk associated with HLAi/ ABOi renal transplants
- No agreed current best practice
- Broad approach
  - Reduce/remove circulating antibody
  - Modulate recipients immune system- intravenous immunoglobulin (IVIG)
  - Reduce circulating B cells

# Desensitisation Protocol

- Desensitisation pre-transplant
  - Plasma exchange and IVIG x 5 pre-transplant (day -9, -7, -5, -3, -2)

- Induction therapy
  - ATG 1.5 mg/kg day 0, 1, 3, 4
  - Methylprednisolone 500 mg day 0 and 1
  - Tacrolimus, MMF and prednisolone

# Haemophilia and desensitisation

- A study from the US Renal Data System registry found a two times higher risk of early haemorrhage in ABOi kidney transplant recipients when compared to ABOc controls.
- Found to be significant correlation between the number of pre-transplant apheresis treatments and the peri- and post transplant bleeding risk (de Weerd et al).

# Formulating therapeutic plasma exchange plan for our patient

- How do we manage a patient with Haemophilia A on plasma exchange?
- What would the bleeding risk be?

# Haemophilia A

- Inherited bleeding disorder
- X-linked
- Reduction in clotting Factor VIII
- Mild/moderate/severe depending on FVIII level
- Patients require Factor VIII replacement
  - Bleeding episodes
  - Surgical procedures/invasive interventions

# Bleeding risk

- Vascular access for the patient was his A-V fistula
- Has a high flow rate and pressure could be at risk of major bleeding if Factor VIII not adequately managed.

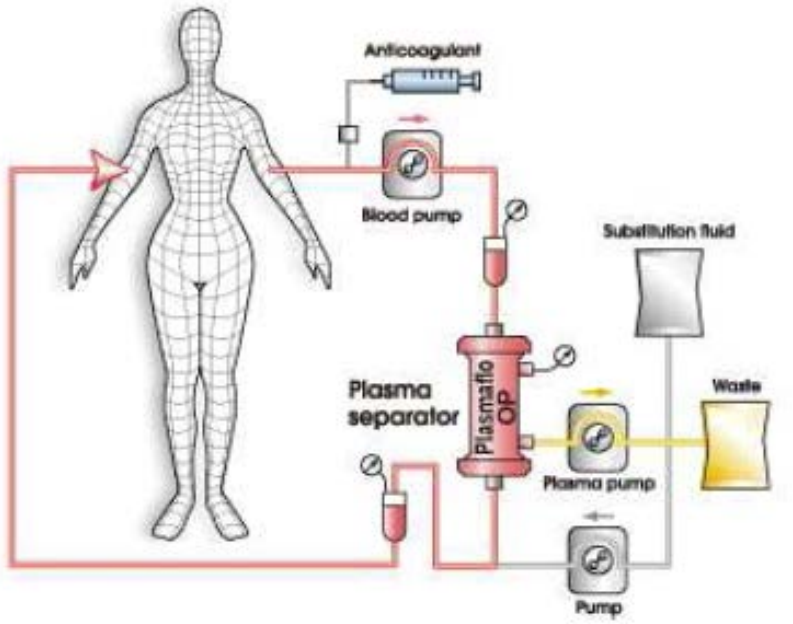
# Goals

- To maintain Factor VIII at safe haemostatic level during therapeutic plasma exchange.
  - **Keep above >40%**
- To minimise bleeding risk and also to have a safe FVIII level at the end of PEX to allow decannulation of fistula
- To maintain a 'normal' coag pre surgery, i.e. patient optimised as possible.

# Questions

- What happens normally to clotting factors during plasma exchange?
- Specifically what happens to Factor VIII?
- Would we be able to check FVIII assays during PEX?
- What will happen to recombinant Factor VIII during PEX?
- As a comparison what happens to patient during dialysis?

# Therapeutic plasma exchange




- Removes large volume of plasma
- Replacement fluid, usually albumin
- Culprit Ab removed as well as other constituents of plasma
- ‘Non selective’

# What happens to clotting factors during PEX?

- During a 1x plasma volume exchange with albumin as replacement fluid
  - Coagulation factor activity decreases and coagulation tests may become abnormal
  - Common to find that intensively exchanged patients may require the use of FFP either during of after plasma exchange due to successive clotting factor depletion

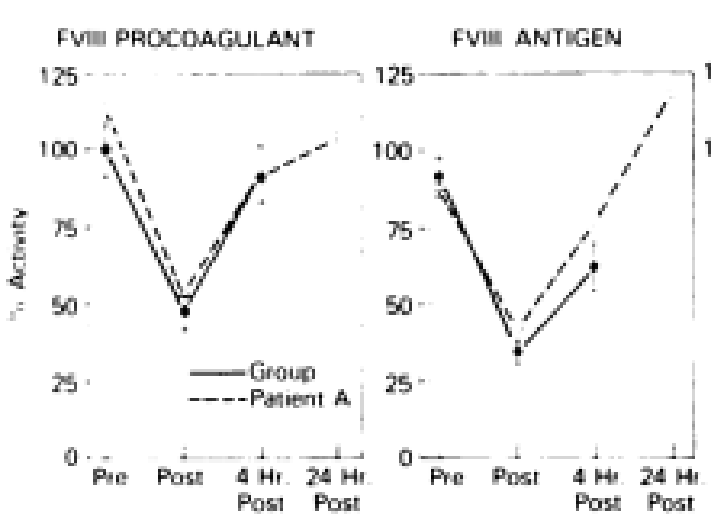
# What happens to clotting factors during PEX?

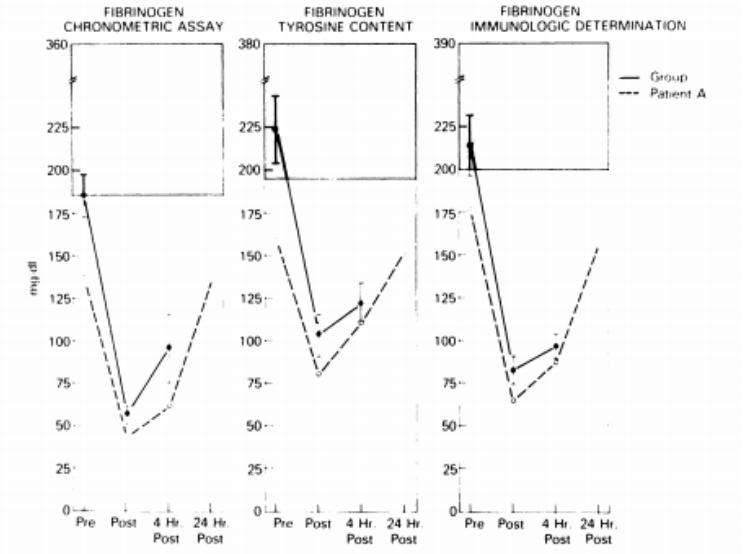
- From studies in the 1980's we know significant declines occur
  - Factor V
  - Factor VII
  - Factor VIII
  - Factor IX
  - Factor X
  - VWF
  - Fibrinogen

# What happens to clotting factors during PEX?

- Activities of FVIII, FIX, and VWF return to normal within 4 hours after TPE.
- The remaining coagulation factors achieve pre-TPE activity levels by 24 hours.
- The exception to this is fibrinogen, which reaches 66% of pre-apheresis levels by 72 hours.

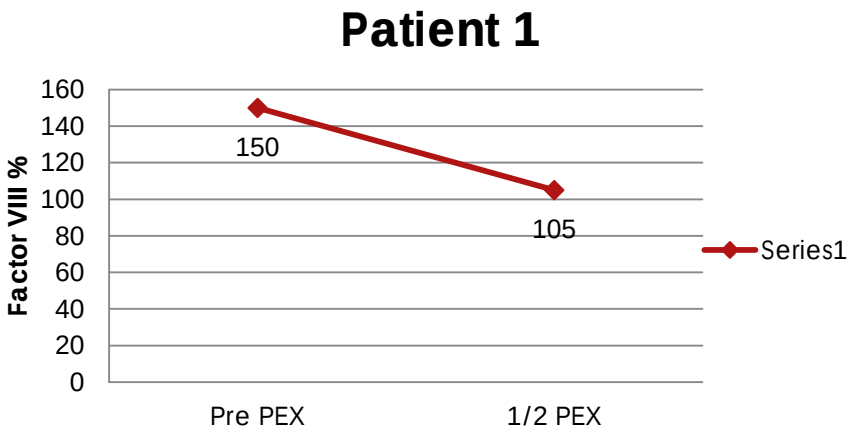
# What happens to clotting factors during PEX?

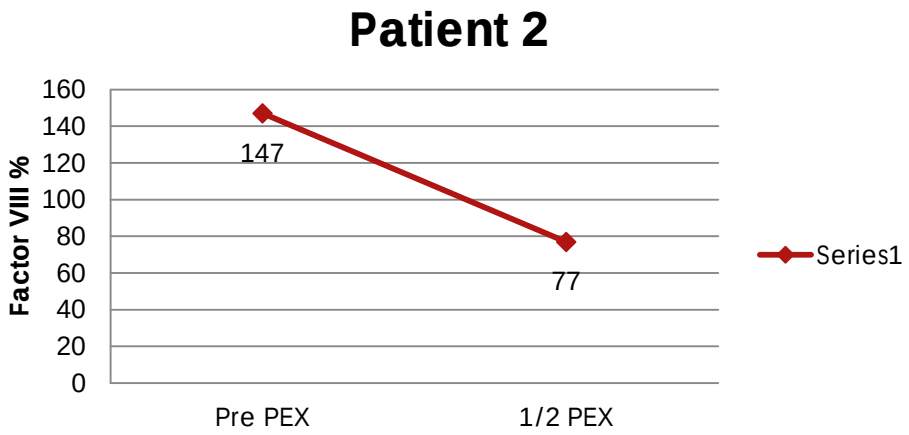


# Would citrate affect the FVIII assay?

- Two patients kindly allowed us to check their FVIII assays pre and ½ through PEX to ensure citrate did not interfere with assaying technique

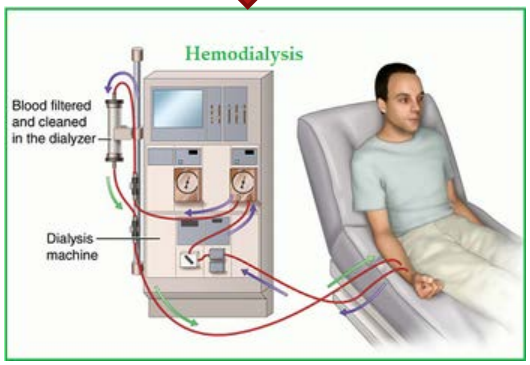


# What happens to recombinant Factor VIII?

- Patient using a product called Advate
- Half life is 12hrs
- Usually twice daily dosing
- According SPC Advate has a molecular weight of 28K DA

# What happens during haemodialysis?




- But there are differences:-
- Dialysis membrane- different pore size
- Electrical charge
- FVIII unlikely to pass through dialysis filter
- FVIII clearance likely to be different in PEX

# Protocol

**Pre PEX**

- Usual 3000 units Advate administered pre dialysis
- Further 2000 units given at end of dialysis

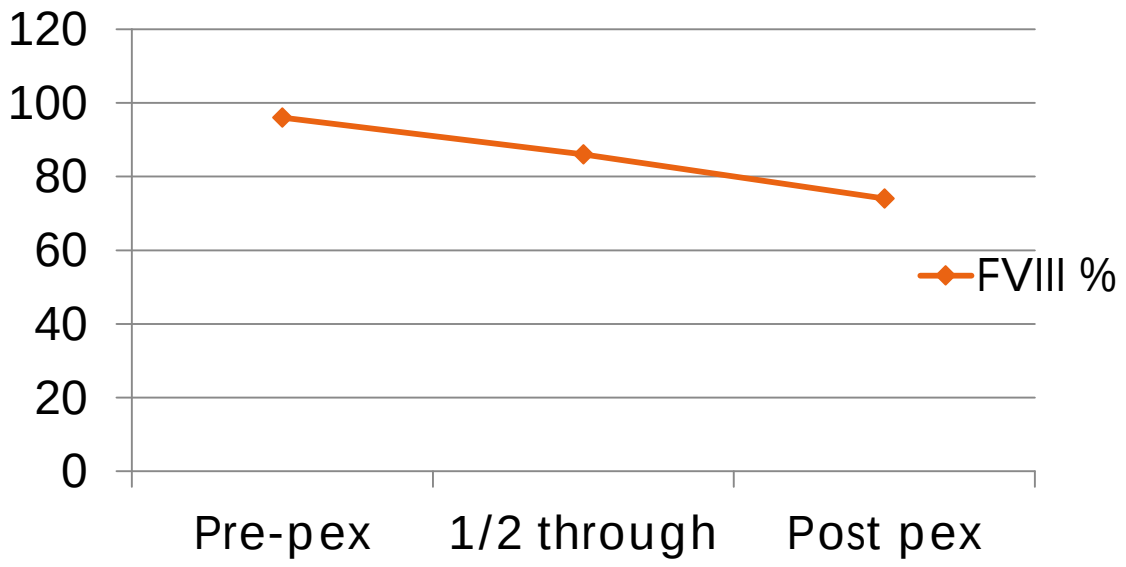
**PEX**

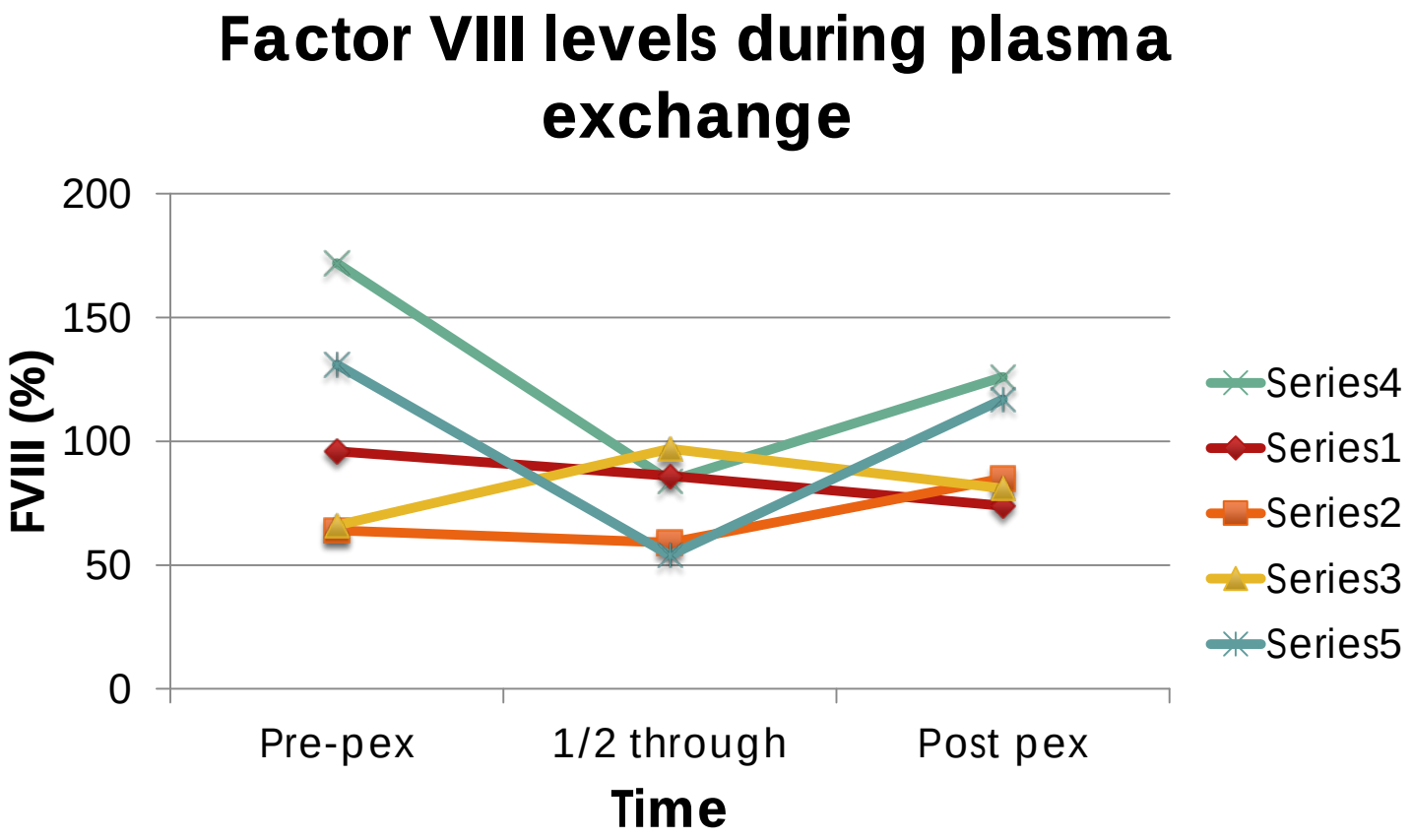
- FVIII levels checked at 15mins, ½ through

**Post PEX**

- 1000 units Advate given pre de-cannulation
- Standard coag sent plus FVIII

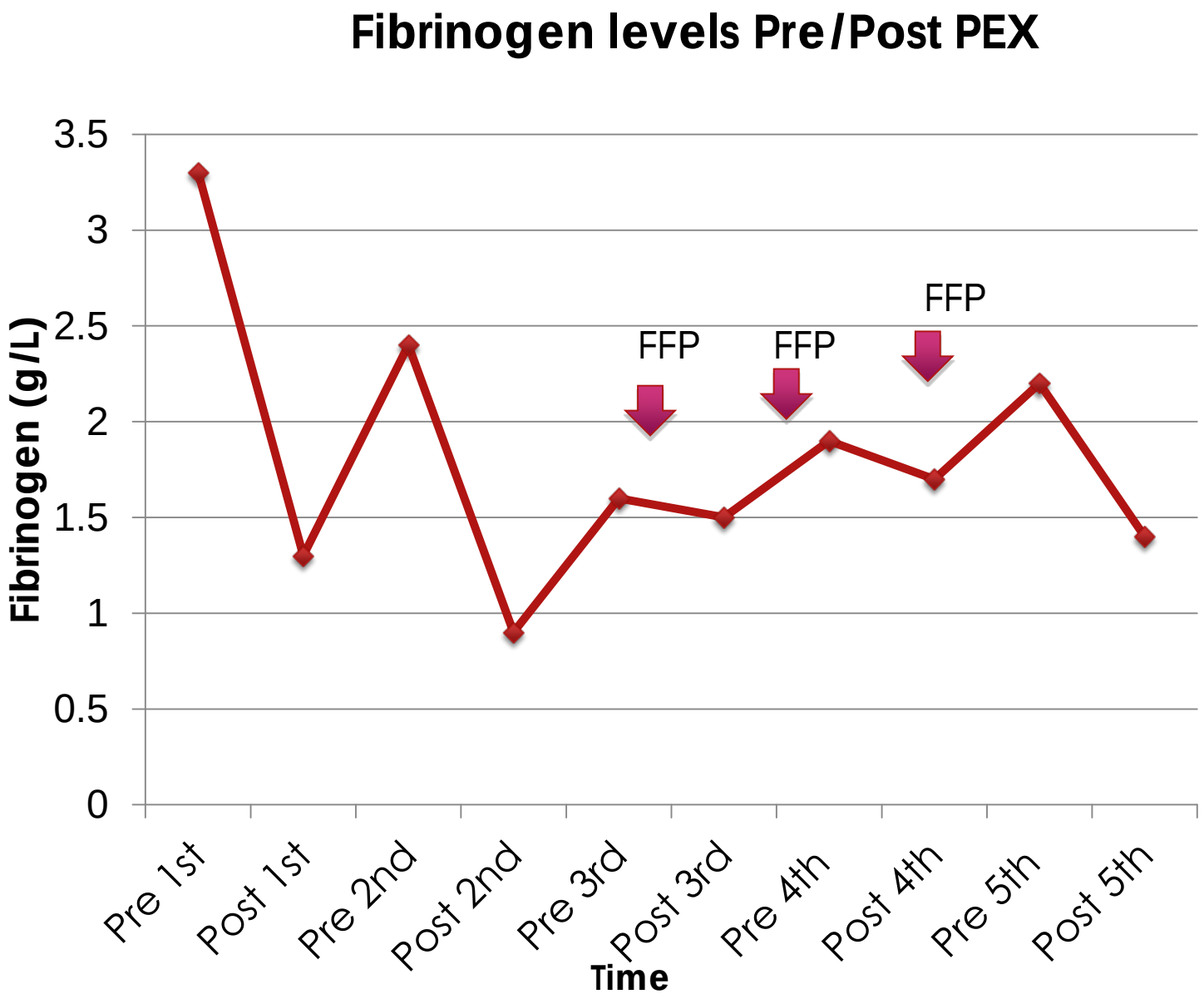
# Patients factor VIII levels with 1st PEX




Factor VIII levels during plasma exchange
FVIII (%)
200
150
100
50
0
Pre-pex
1/2 through
Post pex
Time
Series4
Series1
Series2
Series3
Series5

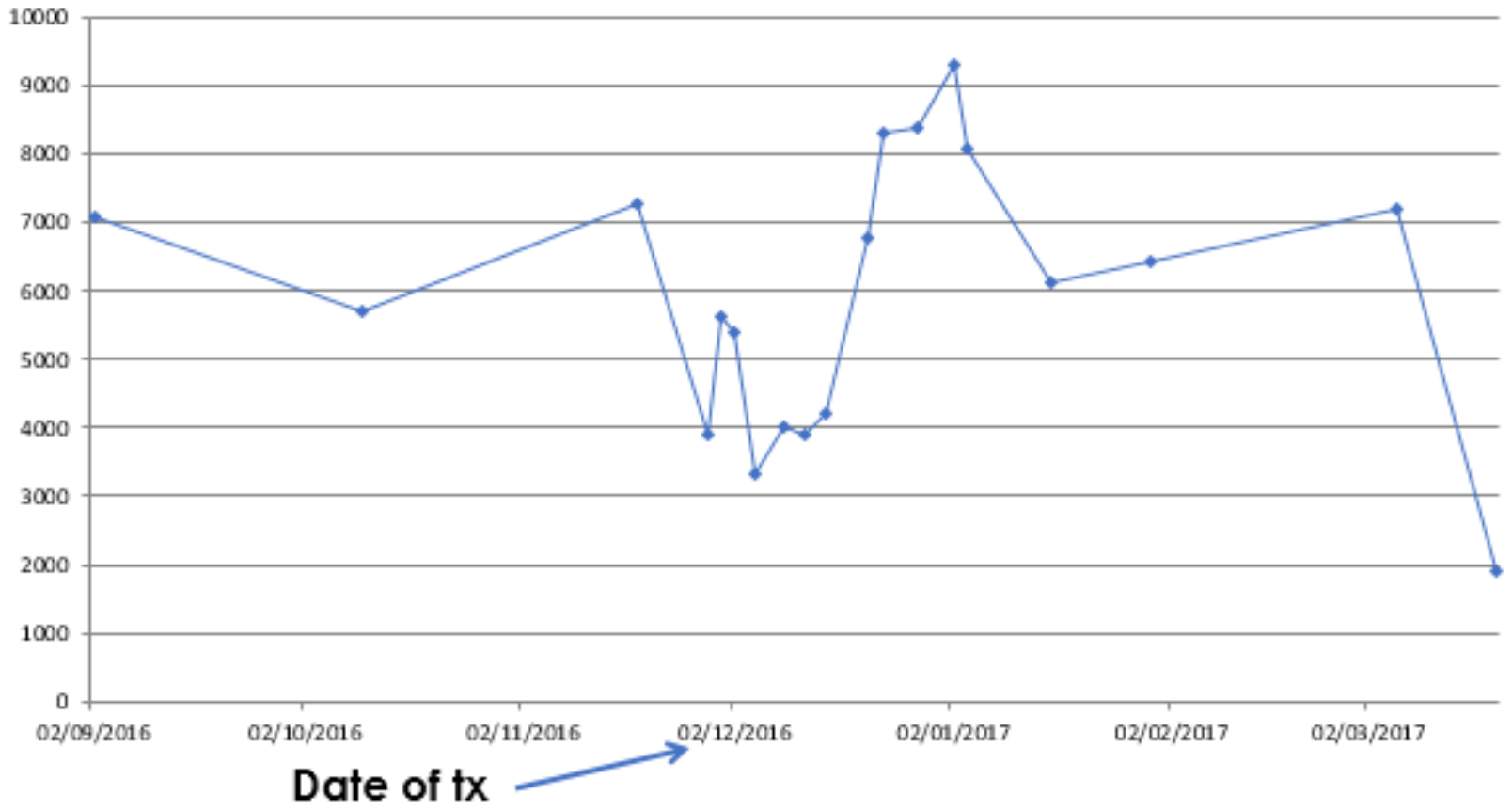
# Protocol continued as per 1st day

- Did notice that increasing amounts of Advate required
- Fibrinogen also dropped
  - Fluid balance


Fibrinogen levels Pre/Post PEX
Fibrinogen (g/L)
3.5
3
2.5
2
1.5
1
0.5
0
FFP
FFP
FFP
Pre 1st
Post 1st
Pre 2nd
Post 2nd
Pre 3rd
Post 3rd
Pre 4th
Post 4th
Pre 5th
Post 5th
Time

# HLA antibody levels

Cumulative MFI- HLA antibody monitoring



# Patient progress

- Renal transplant Dec 2016
- Post renal biopsy haematoma (13 x10 x 13cm) 6 days post surgery- washout in theatre
- Discharged home in time for Christmas
- Decline in graft function March 2017- further renal biopsy- polyoma virus nephropathy with no active rejection

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- De Weerd et al. ABO- incompatible kidney transplant recipients have a higher bleeding risk after antigent- specific immunoadsorption. Transplant Int (2015) 28 (1): 25-33.
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