

Plasmapheresis and Desensitization

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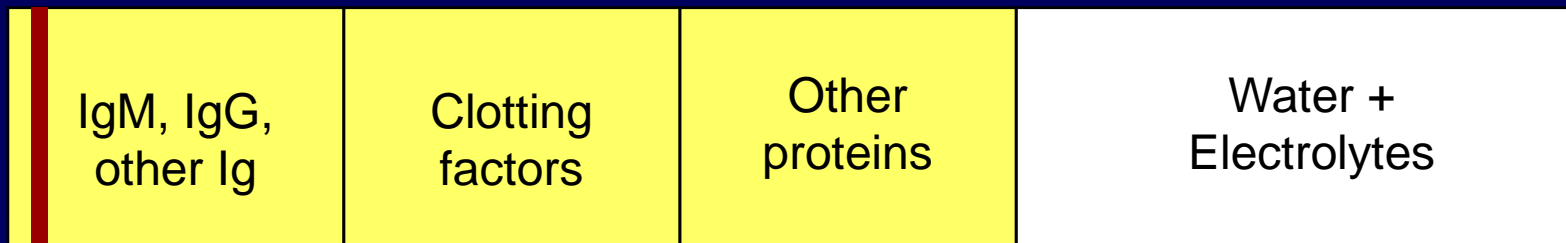
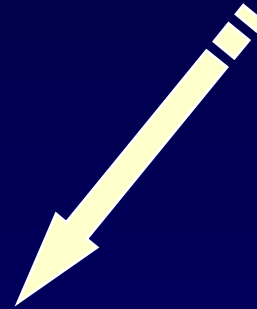
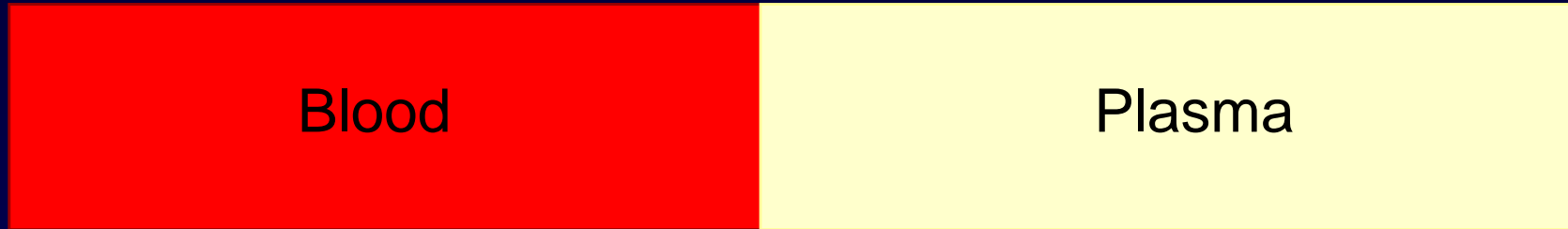
What is plasmapheresis?

- Removal of plasma and replacement with certain components of plasma
- Goal is usually removal of a toxic plasma protein
- In practice, all plasma proteins are removed
- Either use a filter or a centrifuge system

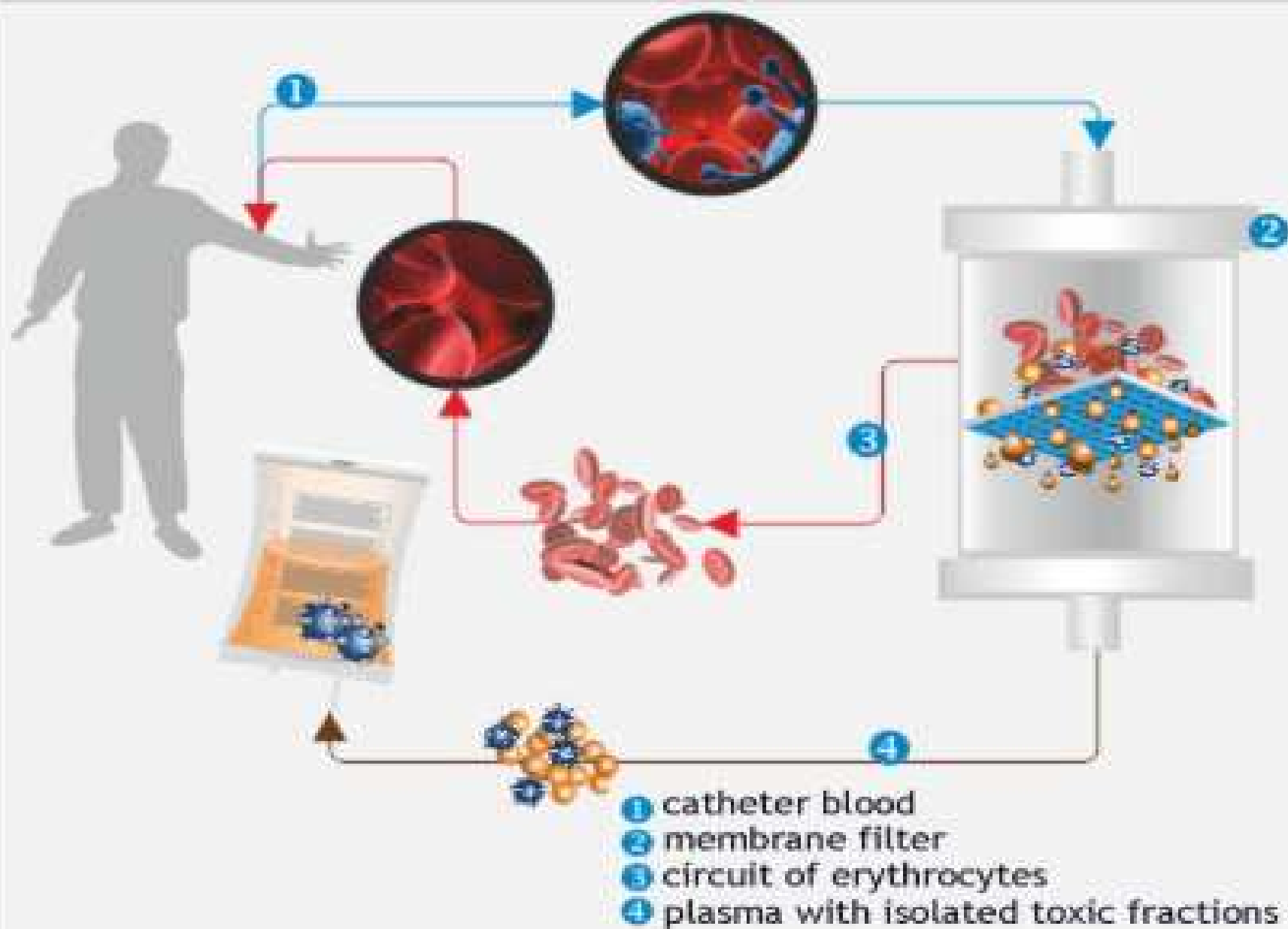
How does it work?

- Removal of toxic molecule e.g. anti-GBM, ULVWf multimers
- Possibly, removal of other inflammatory mediators e.g. complement
- Restoration of deficient factors e.g. ADAMTS13 in HUS / TTP

Blood / Plasma Constituents

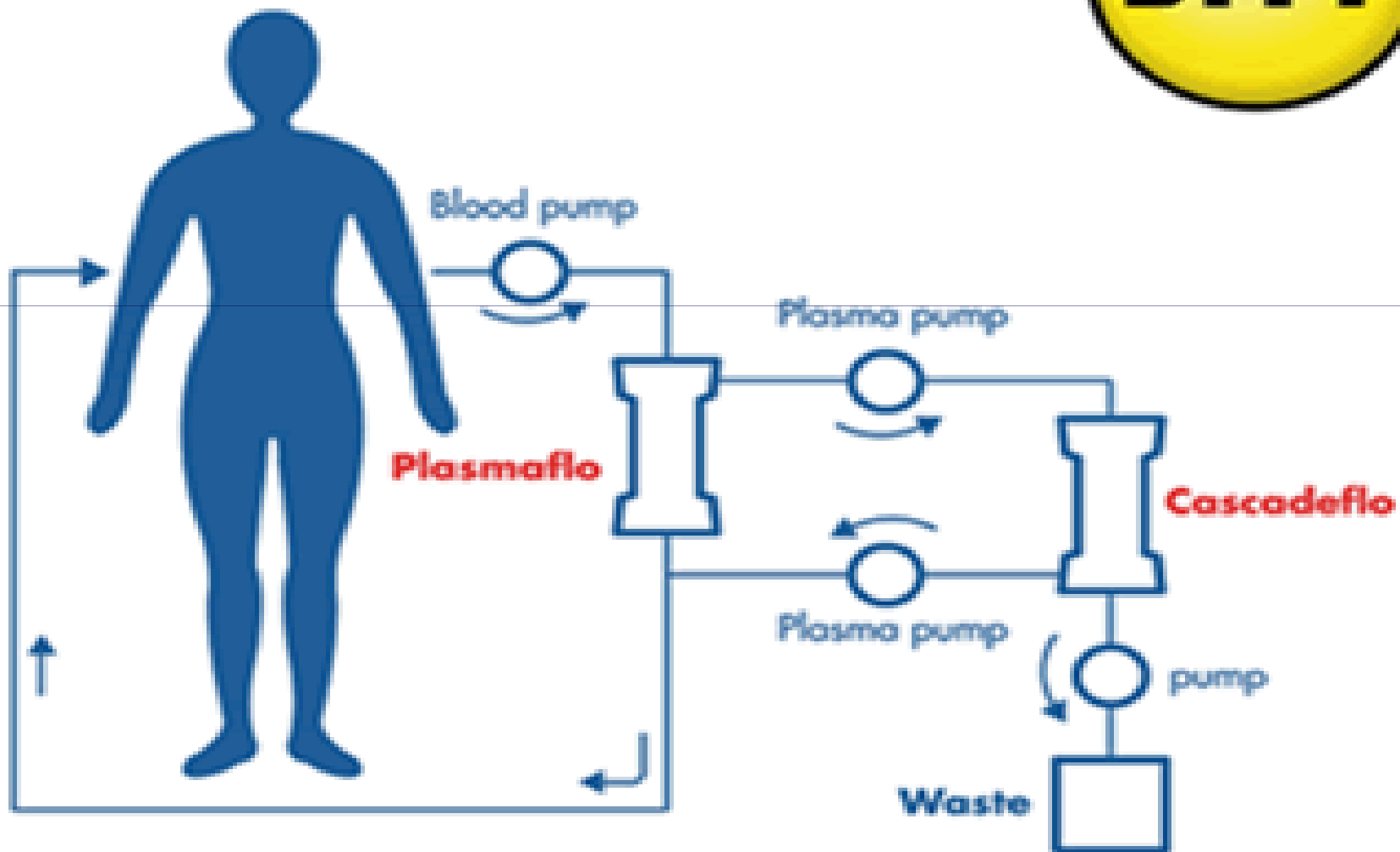


Standard Plasmapheresis



Double Filtration Plasmapheresis

DFPP



DFPP

Advantages	Disadvantages
More selective r/o plasma products	System more complex?
Minimal albumin replacement needed	Cost of extra filter
Minimal FFP replacement needed	Extra staff training?
Cost?	Cost?

Prescription

- Depends on urgency of removal of antibody
- 1.0 plasma volume = 60% removal
- 1.5 plasma volume = 75% removal
- Or: 50-60 ml / kg
- Approx 5 sessions over 8 days removes 90% of IgG (assuming minimal new synthesis)
- Often we do 5-7 sessions over 10 days then pause and reassess

Prescription

- Daily in severe anti-GBM disease or TTP
- 1.0 plasma volume = 60% removal
- 1.5 plasma volume = 75% removal
- Or: 50-60 ml / kg
- Approx 5 sessions over 8 days removes 90% of IgG (assuming minimal new synthesis)
- Often we do 5-7 sessions over 10 days then pause and reassess

Calculating Volumes

Estimated plasma volume (in litres) = $0.07 \times \text{wt}$
(kg) \times (1 - hematocrit)

So, 1 plasma volume in 80kg male with Hct of 30
(0.3) = $0.07 \times 80 \times 0.7 = 3.92\text{L}$

1.5 plasma volumes = $3.92 \times 1.5 = 5.88\text{L}$

Whereas... 1 plasma volume in 60kg female with
Hct of 35 (0.35) = $0.07 \times 60 \times 0.65 = 2.73\text{L}$

Replacement Fluids

- Depend on underlying disease
- Some combination of: albumin + NS + FFP
- Where FFP not indicated: 2/3 albumin + 1/3 NS
- Where FFP is indicated: % replaced as FFP varies
- Hyperviscosity: 100% replace with NS!

Indications for Replacement with FFP

- HUS / TTP (replace 100% with FFP)
- Kidney biopsy / surgery / other invasive procedure within last 48 hrs (partially replace with FFP)
- Active / recent bleeding inc pulmonary hemorrhage
- Multiple TPE sessions even if no bleeding: partially replace with FFP every 3rd-4th session

Complications

- Related to vascular access
- Hypotension
- Allergic reactions
- Hypocalcemia – especially if using FFP (citrate)
- Metabolic alkalosis if lots of FFP (citrate)
- Coagulopathy / bleeding
- Infection

When do you stop?

- Severe complications
- Markers of disease have normalised e.g. LDH, plts in HUS / TTP
- Levels of toxic molecule now normal e.g. anti-GBM but watch for rebound!
- Sometimes empiric
- Again, depends whether IgG or IgM

Other Practical Points

- Always prescribe some heparin, as otherwise, system will clot
- Ensure any antibody therapies are NOT given just before TPE
- In renal transplant, IVIg often given after the course of TPE

Indications: Renal

- Anti-GBM disease
- ANCA vasculitis (severe: with Cr >500 or pulmonary haemorrhage)
- Certain forms of HUS
- Hyperviscosity syndrome

Indications: Renal Transplant

- Desensitization across HLA incompatibility for kidney transplant
- Desensitization across ABO incompatibility for kidney transplant
- Acute antibody mediated rejection of transplant
- Recurrence of primary FSGS

What about Myeloma?

- Acute renal failure a/w myeloma: the evidence is now poor

Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial; Clark et al. 2005, 143:777-84

- Hyperviscosity syndrome a/w myeloma is still an indication for TPE

Indications: NonRenal

- Myasthenia gravis
- Acute and chronic demyelinating neuropathies
- Anti-NMDA receptor encephalitis
- TTP (emergency)
- Hyperviscosity syndrome
- Catastrophic anti-phospholipid syndrome

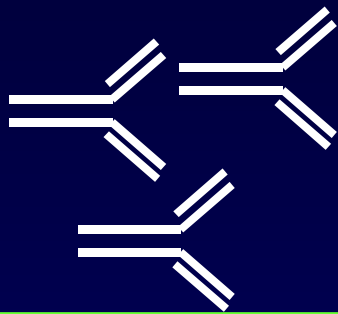
When do we use plasmapheresis in renal transplantation?

- Desensitization across HLA incompatibility for kidney transplant
- Desensitization across ABO incompatibility for kidney transplant
- Acute antibody mediated rejection of transplant
- Recurrence of primary FSGS

Anti-ABO and anti-HLA antibodies

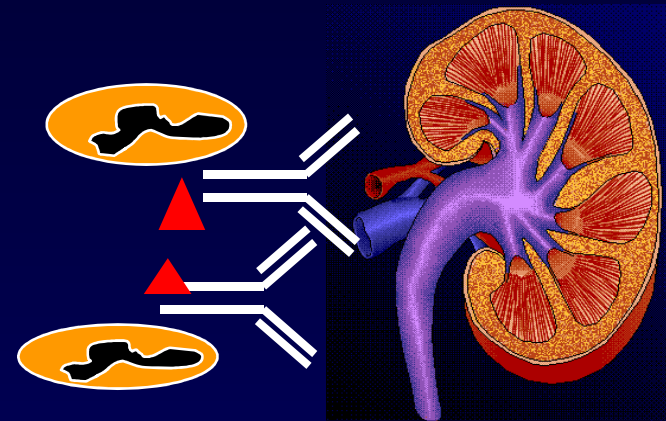
- Anti-A / B occur naturally, depending on pt's blood group
- Anti-HLA occur after blood transfusion or pregnancy or previous transplant
- Transplanting across these antibodies can cause severe antibody mediated rejection and kidney damage (loss)

Severe antibody-mediated rejection: hyperacute or acute

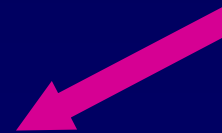


Preformed or rapidly
formed anti-donor
antibody*

*Directed against HLA
or ABO or other antigens



Binding of Ab to endothelium,
recruitment of complement
and neutrophil polymorphs



Massive inflammation,
thrombosis and graft loss

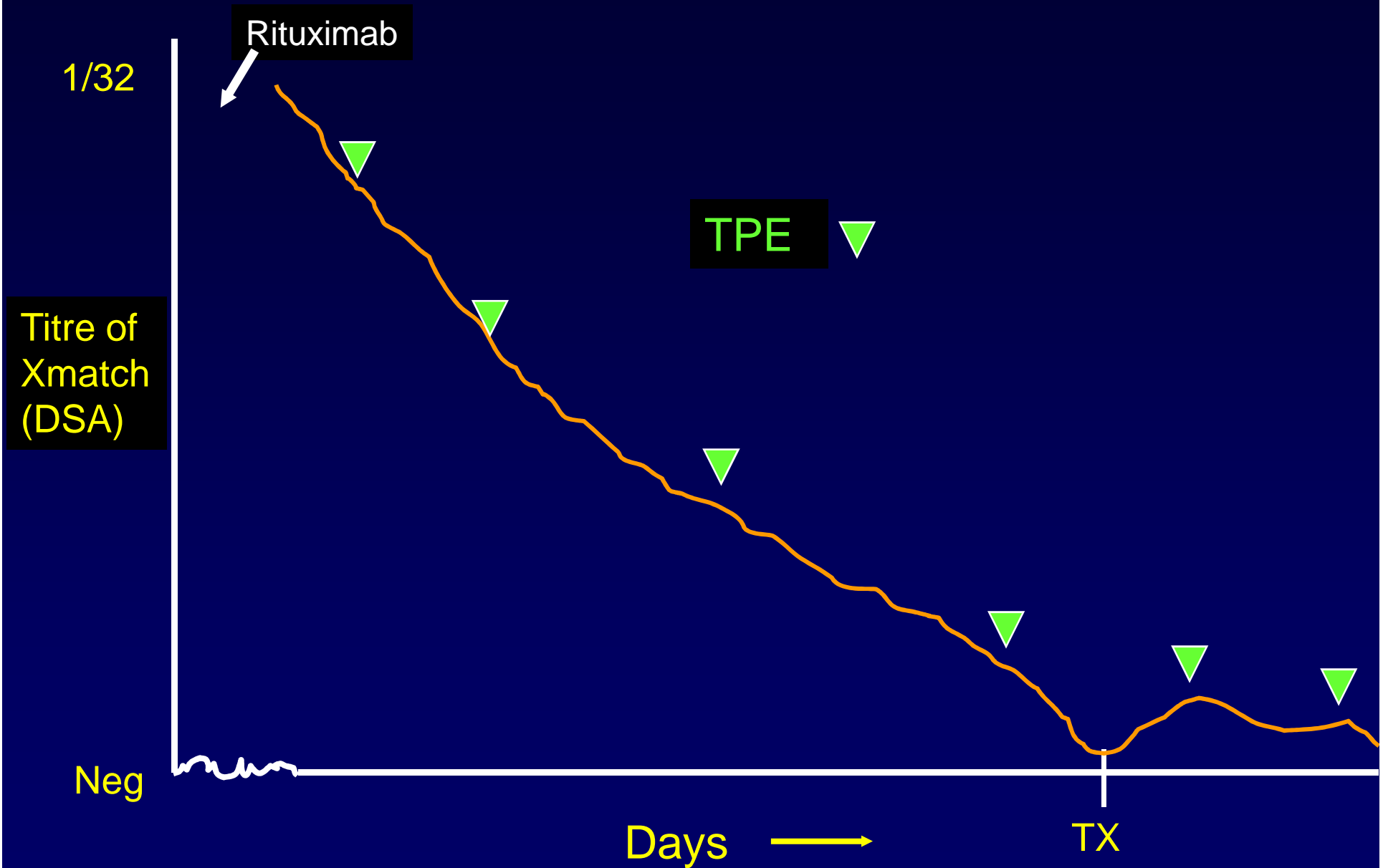
Desensitization across HLA incompatibility for kidney transplant

- Desensitization: rendering the crossmatch negative / near-negative, thus allowing transplantation to proceed
- In practice, more suitable for living – not deceased – donor transplantation
- Medium and long-term outcomes not optimal
- Still being used in pts with no other transplant options (preferably low level DSA)

Desensitization across HLA incompatibility for kidney transplant

- Plasmapheresis combined with standard immunosuppression +/- rituximab
- Transplant when crossmatch negative
- Often more pheresis posttransplant
- Risk of bleeding, rejection

Typical Protocol for Desensitization



Desensitization across ABO incompatibility for kidney transplant

- Goal is to reduce anti-A / B titres to low level, allowing safe transplantation
- Medium and long-term outcomes better than with HLA incompatible transplants
- Protocol broadly the same

Protocols for ABOi Transplantation

Hopkins Protocol (Pre and Post):

Starting Titer	Number TPE preTx	Number TPE postTx**
<16	2	2
16-32	3	2-3
64	4	3
128	5-6	4
256	7-8	4
512	8-9	5
>512	>10	6

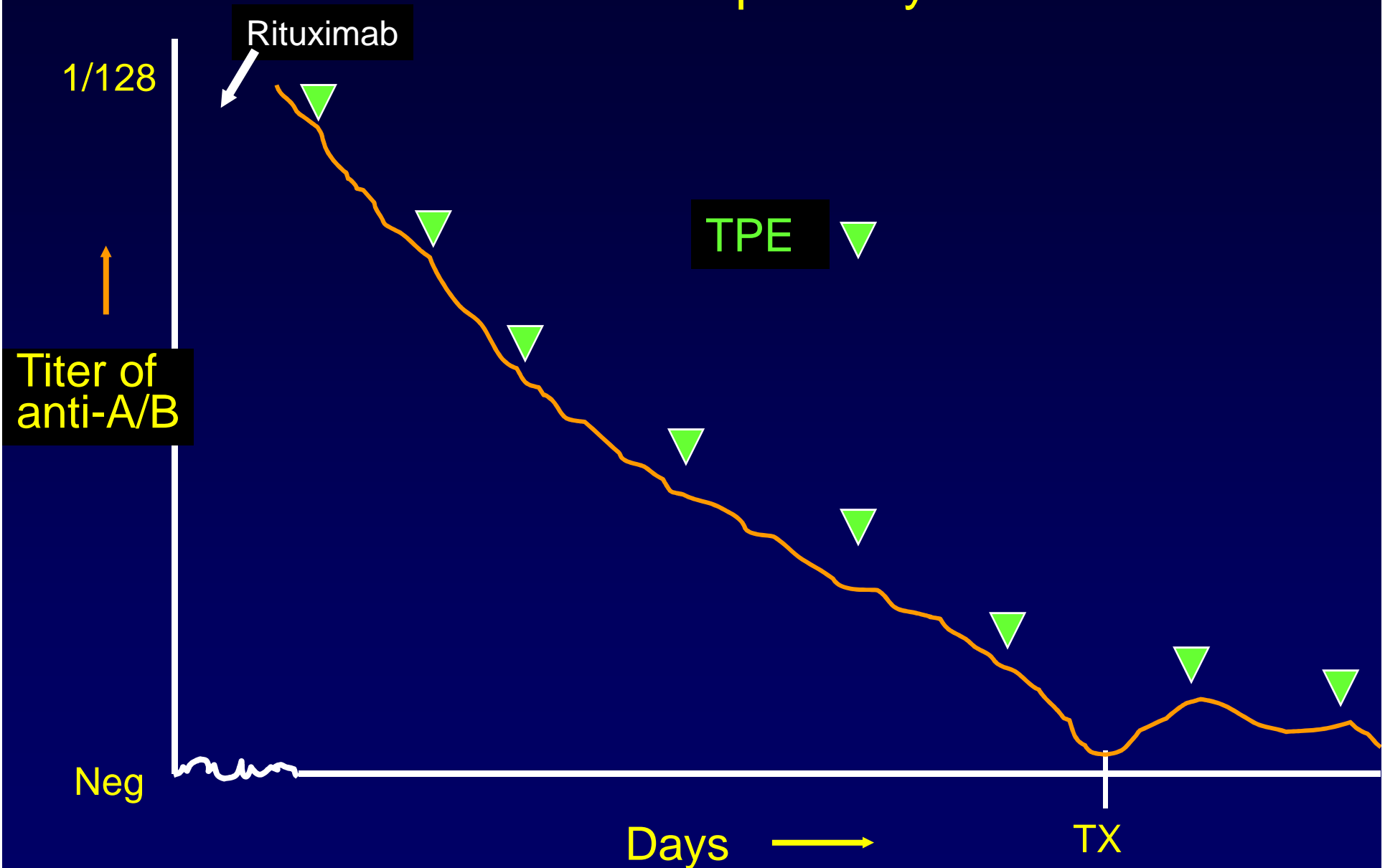
Immunoadsorption

- Specifically remove the anti-A/B antibody

Alternative PostTx Protocol [Geyer et al]:

- Daily anti-A/B in first 7 days. TPE if titer $\geq 1/8$
- Then anti-A/B every 2 days: postop day 8, 10, 12, 14. TPE if $\geq 1/16$

Typical protocol for transplantation across ABO incompatibility



Transplantation across ABOi: recent case

- 32 year old male, ESRD due to IgA nephritis
- One previous transplant – late severe rejection (nephrectomy)
- ABOi, PGEN 99%
- Brother ABO-A1 but 2-haplotype match
- Informed consent from both for ABOi transplant

Transplantation across ABOi: recent case

- Rituximab + MMF + tacrolimus
- DFPP
- Anti-A titres (IgG and IgM) down to 1/4
- Transplant surgery uneventful; minimal FFP etc. needed
- Only 1 DFPP post-op
- Now 20 days posttransplant, Cr 130

Minimising Complications

Complication	Prevention / Treatment
Hypotension	Slow removal of plasma; bolus with NS
Allergic reactions	Avoid ACE-I; minimise FFP; premedicate with paracetamol, anti-histamines
Hypocalcemia	Minimise FFP; slow infusion of FFP; IV or PO calcium
Alkalosis	Minimise FFP
Thrombocytopenia	Adequate heparin!
Coagulopathy / Bleeding	Adequate FFP; only do within 24hrs of bx / procedure if TPR urgently indicated

What Prescription?

1. 70kg male with severe TTP
2. 60kg female with hyperviscosity syndrome (IgM paraprotein)
3. 80kg male with acute anti-GBM disease (renal limited)
4. 60kg lady with acute pulmonary-renal syndrome, ANCA+