THE FIRST ABO-INCOMPATIBLE KIDNEY TRANSPLANT IN HONG KONG

Dr Maggie Ma
Queen Mary Hospital
Ms So SM

- **PMH:**
  - HT: no secondary cause found
  - Obese

- **Known to have Chronic kidney disease**
  - Present with impaired kidney function (Cr 200+) and proteinuria 0.72g/D at age 32
  - Urinalysis: RBC +ve protein +ve
  - Immune marker (ANA, anti-dsDNA, C3,C4, ANCA, anti-GBM –ve)
  - USG kidney: normal size kidney, renal parenchymal disease
  - Patient refused kidney biopsy

  - Delivered baby boy in June 2013. Cx with increased Cr up to 400 after delivery

  - Admitted 5/2014 for AoCRF
  - Cr 384 (9/2013) → 898 (4/2014)
  - No use of nephrotoxic drug, no reversible cause found
Progress of Ms So

- Tenckhoff Catheter insertion performed 16 May 2014
- CCPD since 30 June 2014
  - Recurrent fluid overload
  - Tertiary hyperparathyroidism

- Put on transplant waiting list
  - no deceased donor kidney available yet
IN THE CONSULTATION ROOM......

My Sister would like to donate her kidney to me
In the consultation room......

My Sister would like to donate her kidney to me.

I am Blood Group O+.
My younger sister is Blood Group B+, is it ok?

Is blood group incompatibility an immunological barrier that cannot be overcome??
ABO incompatible kidney
-Tx protocol
**ABO blood group**

- Based on expression of A, B and H blood group antigens
  - RBC
  - Endothelial cells
  - Kidney parenchyma cells

- The presence of the preformed isohaemagglutinins (anti-A, anti-B) is the critical immunological barrier to ABOi organ Tx
KEY ELEMENTS OF ABOi DESENSITISATION PROTOCOL
**Rituximab**

- Replace splenectomy
- B cell depletion
  - To avoid prompt reappearance of blood group antibodies after transplantation and the associated risk of AMR
  - Does NOT deplete plasma cell

- Time to administer: 3-30 days prior Tx
- Dose: 200mg – 1g, 375mg/m² is most frequently adopted
- May increase infection risk
KEY ELEMENTS OF ABOi DESENSITISATION PROTOCOL
ANTIBODY REMOVAL

- Plasmapheresis
- Double filtration plasmapheresis
- Immunoadsorption
Our ABOi Tx protocol
ABO INCOMPATIBLE

-14 [day]  -7  -1

Rit

PP

Basi

Tx

FK

MMF

steroid

Bx  30

↑
ABO INCOMPATIBLE

-14 [day]  -7  -1  Tx

FK

MMF

steroid

Rit

PP

Basi

↑ Bx  30
ABO INCOMPATIBLE

-14 [day]  -7  -1

Rx

FK

MMF

steroid

Rit

PP

Basi

↑ Bx  30
ABO INCOMPATIBLE

-14 [day]   -7  -1

Rit

FK
MMF
Steroid

Tx

PP

Basi

Bx

30
- Anti-ABO titre monitoring in early post-operative period (~1-2 weeks)
- Post-op Plasmapheresis prn
- Protocol biopsy within 1st month post-Tx
- Universal PCP, CMV prophylaxis
Our first Case - Ms So
In 2017

- Ms So (blood group O+) agreed to have ABOi KTx
- Her younger sister, Ms So YY (blood group B+) would be the donor
DONOR – MS SO YY, 37/F

- Good past health, blood group B+
- Relationship with recipient: younger sister

- Cr 70umol/L
- CrCl (By DTPA scan): 118ml/min
- UP 0.06g/D
- Urine R/M: no active sediment
- Serology: Hep B/C –ve, anti-HIV –ve, CMV ab +ve

- CTA: bilateral single artery and vein
- Clin Psy assessment: psychologically fit for kidney donation
RECIPIENTS - Ms So SM, 39/F

- ESRD due to unknown cause
- CCPD since 30 June 2014
- PMH: HT, obese
- Blood Group O+

Serology:
- HBsAg –ve, anti-HBs +ve after vaccine
- Anti-HCV –ve
- Anti-HIV –ve
- CMV ab +ve, VZV Ig +ve, EBV VCA IgG +ve
Recipient Ms So

- Immunological risk assessment:
  - HLA 1 haplotype match
  - PRA 0%
  - CDC and flow XM: -ve
  - No Ig antibodies against HLA Class I and II Ag

- Baseline Anti-B titer: 1:64
Progress of Ms So

Creatinine (umol/L)

Anti-B

Creatinine
anti-B
Progress of Ms So

Target FK level: 8-12
Protocol Biopsy – 3 weeks
C4d
Protocol Bx:
- C4d staining without evidence of rejection

Latest Progress:
- ~18 months post-Tx
- Cr 103

ABO incompatible kidney transplant is technically feasible
ABO incompatible kidney Tx
-Long Term Outcome
ABO- INCOMPATIBLE LIVING KIDNEY TRANSPLANTS: EVOLUTION OF OUTCOMES AND IMMUNOSUPPRESSIVE MANAGEMENT


- ABOi KTx Vs ABOc KTx
- 1195 patients over the last 25 years
  - 1st Era - 1989-2004:

**Figure (A)**
Graft survival (non-censored for death) for transplantation in 1989 to 2004

**Figure (C)**
Patient survival for transplantation in 1989 to 2004

**Log-rank test: p=0.026**
Adjusted HR: 1.56 (95% CI: 1.04 to 2.34) p=0.030

**Log-rank test: p=0.919**
Adjusted HR: 0.84 (95% CI: 0.28 to 2.52) p=0.753
### Table 2: Cause of graft failure and death during 9 years follow-up duration

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</thead>
<tbody>
<tr>
<td></td>
<td>ABO-CLKT</td>
<td>ABO-ILKT</td>
<td>p-value</td>
<td>ABO-CLKT</td>
<td>ABO-ILKT</td>
<td>p-value</td>
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<tr>
<td><strong>Graft failure</strong></td>
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<td>Component graft failure</td>
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<tr>
<td>Death with functioning graft</td>
<td>17 (3.8%)</td>
<td>4 (3.9%)</td>
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<td>8 (2.4%)</td>
<td>2 (1.4%)</td>
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<tr>
<td>AAMR</td>
<td>8 (1.8%)</td>
<td>9 (8.7%)</td>
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<td>1 (0.3%)</td>
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<tr>
<td>CAMR</td>
<td>51 (11.3%)</td>
<td>14 (13.6%)</td>
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<td>2 (0.6%)</td>
<td>6 (4.2%)</td>
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<tr>
<td>Noncompliance</td>
<td>2 (0.4%)</td>
<td>2 (1.9%)</td>
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<tr>
<td>Nonfunctioning kidney</td>
<td>1 (0.2%)</td>
<td>–</td>
<td>0.179</td>
<td>–</td>
<td>–</td>
<td>0.160</td>
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<tr>
<td>FSGS</td>
<td>4 (0.9%)</td>
<td>1 (1.0%)</td>
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<td>2 (0.6%)</td>
<td>1 (0.7%)</td>
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<tr>
<td>IgA nephropathy</td>
<td>12 (2.7%)</td>
<td>1 (1.0%)</td>
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<td>1 (0.3%)</td>
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<tr>
<td>MPGN</td>
<td>1 (0.2%)</td>
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<tr>
<td>Other</td>
<td>3 (0.6%)</td>
<td>1 (1.0%)</td>
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<td>1 (0.3%)</td>
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<td><strong>Deceased patients</strong></td>
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<td>Component death</td>
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<tr>
<td>Infection</td>
<td>1 (0.2%)</td>
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<tr>
<td>Malignancy</td>
<td>1 (0.2%)</td>
<td>1 (1.0%)</td>
<td></td>
<td>1 (0.3%)</td>
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<tr>
<td>Cerebrovascular</td>
<td>2 (0.4%)</td>
<td>1 (1.0%)</td>
<td></td>
<td>1 (0.3%)</td>
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<tr>
<td>Cardiovascular</td>
<td>7 (1.5%)</td>
<td>1 (1.0%)</td>
<td></td>
<td>3 (0.9%)</td>
<td>2 (1.4%)</td>
<td>0.212</td>
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<tr>
<td>Digestive</td>
<td>4 (0.9%)</td>
<td>1 (1.0%)</td>
<td></td>
<td>1 (0.3%)</td>
<td>–</td>
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<tr>
<td>Other</td>
<td>2 (0.4%)</td>
<td>–</td>
<td></td>
<td>2 (0.6%)</td>
<td>–</td>
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<tr>
<td><strong>Follow-up period, months</strong></td>
<td><strong>108 [108–108]</strong></td>
<td><strong>108 [108–108]</strong></td>
<td>0.146</td>
<td><strong>56 [31–83]</strong></td>
<td><strong>48 [31–72]</strong></td>
<td>0.131</td>
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</tbody>
</table>

AAMR, acute antibody-mediated rejection; ABO-CLKT, ABO-compatible living kidney transplantation; ABO-ILKT, ABO-incompatible living kidney transplantsations; CAMR, chronic antibody-mediated rejection; FSGS, focal segmental glomerulosclerosis; MPGN, membranous proliferative glomerulonephritis.

1 Follow-up periods are expressed as the medians with the interquartile ranges because of skewed distribution.
ABO-Incompatible Living Kidney Transplants: Evolution of Outcomes and Immunosuppressive Management


- ABOi KTx Vs ABOc KTx
- 1195 patients over the last 25 years
  - 2nd Era – 2005-2013

(B) Graft survival (non-censored for death) for transplantation in 2005 to 2013

(D) Patient survival for transplantation in 2005 to 2013

Log-rank test: p=0.279
Adjusted HR: 1.38 (95% CI: 0.59 to 3.22) p=0.455

Log-rank test: p=0.532
Adjusted HR: 0.52 (95% CI: 0.11 to 2.49) p=0.414
IMMUNOSUPPRESSIVE RX AND DESENSITIZATION PROTOCOL BY TRANSPLANT YEAR
Three-Year Outcomes Following 1420 ABO-Incompatible Living-Donor Kidney Transplants Performed After ABO Antibody Reduction: Results From 101 Centers

Gerhard Opelz,¹ Christian Morath,² Caner Süsal,¹ Thuong Hien Tran,¹ Martin Zeier,² and Bernd Döhler¹

Transplantation 2015;99: 400-404

ABOi KTx performed between 2005-2012 that was reported to CTS were analyzed
The UK National Registry of ABO and HLA Antibody Incompatible Renal Transplantation: Pretransplant Factors Associated With Outcome in 879 Transplants

Laura Pankhurst, MSc,1 Alex Hudson, MSc,1 Lisa Mumford, MSc,1 Michelle Willcombe, MD,2 Jack Galliford, MD,2 Olivia Shaw, PhD,3 Raj Thuraisingham, FRCP,4 Carmelo Pulvetti, MD,4 David Talbot, PhD,6 Sian Griffin, PhD,6 Nicholas Torpey, PhD,7 Simon Ball, PhD,8 Brendan Clark, PhD,9 David Briggs, PhD,10 Susan V. Fuggle, PhD,1,11 and Robert M. Higgins, MD12

Transplantation Direct 2017
器官移植修訂條例刊憲 擬准配對捐贈 釐清「引誘」切除器官定義 (14:22)
Options of our Dialysis Patients

- If they do not have blood group compatible donors

- Stay in the waitlist for deceased kidney—long waiting time

- Living transplant from blood group incompatible donor
  - Desensitization protocol to overcome the blood group barrier

- Paired exchange program

Doctor, ABOi KTx Vs Paired Exchange

Which one should I choose?
ABOi Kidney Transplant & Paired Exchange Program
THE CHANCE OF GETTING A KPD MATCH IS NOT THE SAME......

Difficult match:
- Increasing age
- Sensitized patients
- Candidate blood group O

Easy match
- Donor blood group B and O

AJT 2018
Minireview

Renal Transplantation Across HLA and ABO Antibody Barriers: Integrating Paired Donation into Desensitization Protocols
**Should we perform ABO-incompatible kidney transplantation in Hong Kong?**

- **ABO incompatible kidney transplantation (ABO-I KTx)**
  - An established treatment option worldwide
  - Comparable patient and graft outcomes to conventional ABO-compatible KTx.

- **Organ donation rate is low in Hong Kong**
  - Over 2,000 patients with end-stage kidney failure (ESKD) are waiting for kidney transplantation.
  - Long-term dialysis is associated with inferior survival outcome and quality of life than transplantation.

- **Potential benefit of ABO-I KTx**
  - To increase kidney transplantation rate and improve outcomes of ESKD patients
  - To reduce healthcare cost incurred from long-term dialysis and its associated morbidity.
  - Complementary to paired kidney exchange program – allow desensitization of ‘difficult-to-match’ patients
**ACKNOWLEDGEMENT**

- QMH Renal team
- QMH Urology team
- QMH Haematology team
- QMH pathology team (*Haemato-pathology, Histopathology, T&I*)

- Tokyo Women Medical University – Profs Tanabe & Ishida
- Westmead Hospital, Sydney – Prof Chapman
Would standard dose Rituximab associate with increased infective risks?

- NDT (2016) 31: 1013

- Retrospective analysis of 213 KTx recipients
  - 118 ABOc KTx
  - 76 ABOi Std Rit (375mg/m²)
  - 19 ABOi reduced Rit (200mg)
The effect of rituximab dose on infectious complications in ABO-incompatible kidney transplantation

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Recipient age</td>
<td>0.996 (0.97, 1.02)</td>
<td>0.753</td>
</tr>
<tr>
<td>Rejection</td>
<td>1.579 (0.68, 3.69)</td>
<td>0.291</td>
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<tr>
<td>Preoperative plasmapheresis (≥ 5 sessions)</td>
<td>0.869 (0.3, 2.52)</td>
<td>0.796</td>
</tr>
<tr>
<td>Postoperative plasmapheresis</td>
<td>1.357 (0.42, 4.35)</td>
<td>0.607</td>
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<tr>
<td>ATG use</td>
<td>3.152 (0.87, 11.41)</td>
<td>0.080</td>
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<tr>
<td>RIT (375 mg/m²)</td>
<td>2.905 (1.39, 6.09)</td>
<td>0.005</td>
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</tbody>
</table>

ATG, anti-thymocyte globulin; RIT, rituximab; HR, hazard ratio; CI, confidence interval
The low dose of rituximab in ABO-incompatible kidney transplantation without a splenectomy: a single-center experience

Table 3. Peripheral CD19 level at baseline and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (500 mg)</th>
<th>Group 2 (200 mg)</th>
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<tbody>
<tr>
<td></td>
<td>Median: %, (range)</td>
<td>Median: %, (range)</td>
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<tr>
<td></td>
<td>n</td>
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<tr>
<td>CD19 (%)</td>
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<tr>
<td>Baseline</td>
<td>10.8 (2–31)</td>
<td>11.5 (2–27)</td>
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<tr>
<td>At operation</td>
<td>2.2 (0–5)</td>
<td>3.0 (0–7)</td>
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<tr>
<td>1 month</td>
<td>0.8 (0–3)</td>
<td>0.5 (0–3)</td>
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<tr>
<td>3 month</td>
<td>0.6 (0–2)</td>
<td>0.6 (0–2)</td>
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<tr>
<td>6 month</td>
<td>1.1 (0–3)</td>
<td>0.3 (0–1)</td>
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<tr>
<td>1 yr</td>
<td>3.0 (0–9)</td>
<td>0.6 (0–1)</td>
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<td>2 yr</td>
<td>3.5 (0–10)</td>
<td>0.6 (0–7)</td>
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<td>3 yr</td>
<td>4.3 (0–9)</td>
<td>0.6 (0–4)</td>
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<td>4 yr</td>
<td>6.4 (0–15)</td>
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<td>5 yr</td>
<td>7.0 (1–12)</td>
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At days 3–5 after rituximab treatment there was already a reduction in the levels of CD19. The effect of rituximab was long term. After 18 months, the peripheral CD19 levels were led to normal range in the long follow-up cases.

- The peripheral CD 19 level remains low 24 months after treatment in both group
Table 4. Clinical outcomes

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<tr>
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<th>Group I (500mg)</th>
<th>Group II (250mg)</th>
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<tr>
<td><strong>Current Cr level</strong></td>
<td>1.25 ± 0.47</td>
<td>1.32 ± 0.47 NS</td>
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<tr>
<td>(mg/dL; mean ± SD)</td>
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<td><strong>Current eGFR</strong></td>
<td>52.9 ± 18.1</td>
<td>48.8 ± 14.9 NS</td>
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<td>(mL/min/1.73 m²)</td>
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<tr>
<td><strong>Graft loss</strong></td>
<td>1/24</td>
<td>1/50 NS</td>
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<td><strong>Pathological finding within 1 month</strong></td>
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<tr>
<td>BC</td>
<td>1</td>
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<tr>
<td>Acute-TMR</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Acute-AMR</td>
<td>1 ⇒ graft loss</td>
<td>1</td>
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<td>FSGS recurrence</td>
<td>1</td>
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<tr>
<td>No evidence of rejection</td>
<td>17</td>
<td>35</td>
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<tr>
<td><strong>Pathological finding after 1 month</strong></td>
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<tr>
<td>BC</td>
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<td>3</td>
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<tr>
<td>Acute-TMR</td>
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<td>Chronic-AMR</td>
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<td>2</td>
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<td>IF/TA</td>
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<td>3</td>
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<tr>
<td>IgA N recurrence</td>
<td>3</td>
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<tr>
<td>No evidence of rejection</td>
<td>13</td>
<td>23</td>
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<tr>
<td><strong>Adverse effect</strong></td>
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<tr>
<td>CMV infection</td>
<td>9/24 (37.5%)</td>
<td>12/50 (24.0%) NS</td>
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<tr>
<td>CMV viremia</td>
<td>4</td>
<td>12</td>
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<td>CMV disease</td>
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<td><strong>Late onset neutropenia</strong></td>
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<td>Grade 1</td>
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<td>Grade 2</td>
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<td>Grade 3</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Grade 4</td>
<td>1</td>
<td>5</td>
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PLASMAPHERESIS

- Not selective
- Single circuit
- Replacement fluid needed
- Coagulopathy, infection, plasma sensitivity
DOUBLE FILTRATION PLASMAFHERESIS

- Not selective
- Dual circuit
  - Separate plasma from whole blood
  - Separate IgG and IgM
- Replacement fluid needed
- Coagulopathy, infection, plasma sensitivity
**Immunoabsorption**

- Selective
- Dual circuit
  - Separate plasma from whole blood
  - Plasma is processed through an immunoadsorbent column
- No replacement fluid needed
- Hypersensitivity
- Costly