

ABO INCOMPATIBILITY AND TRANSPLANTATION

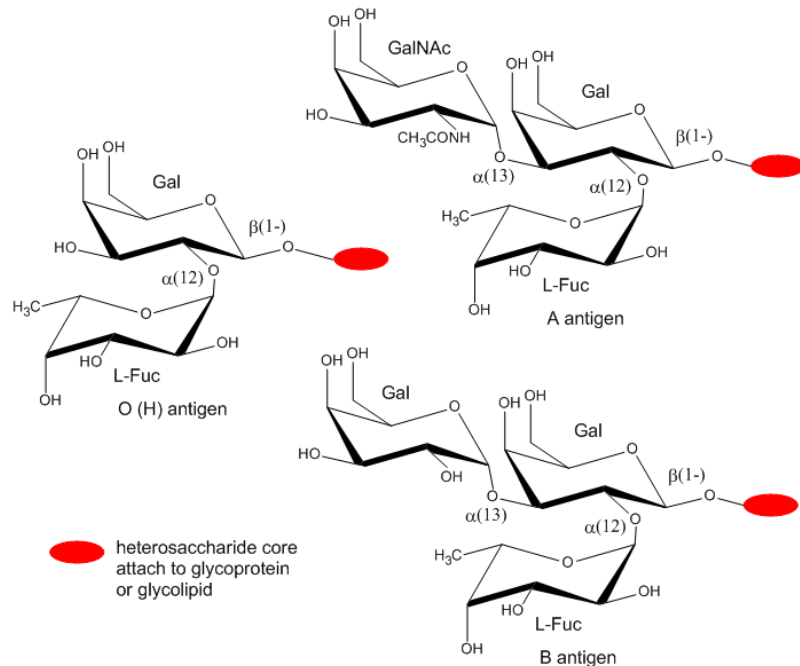
Aleksandar Mijovic

Consultant Haematologist/Senior Lecturer

King's College Hospital/NHS Blood and
Transplant

London, UK

ABO antigens



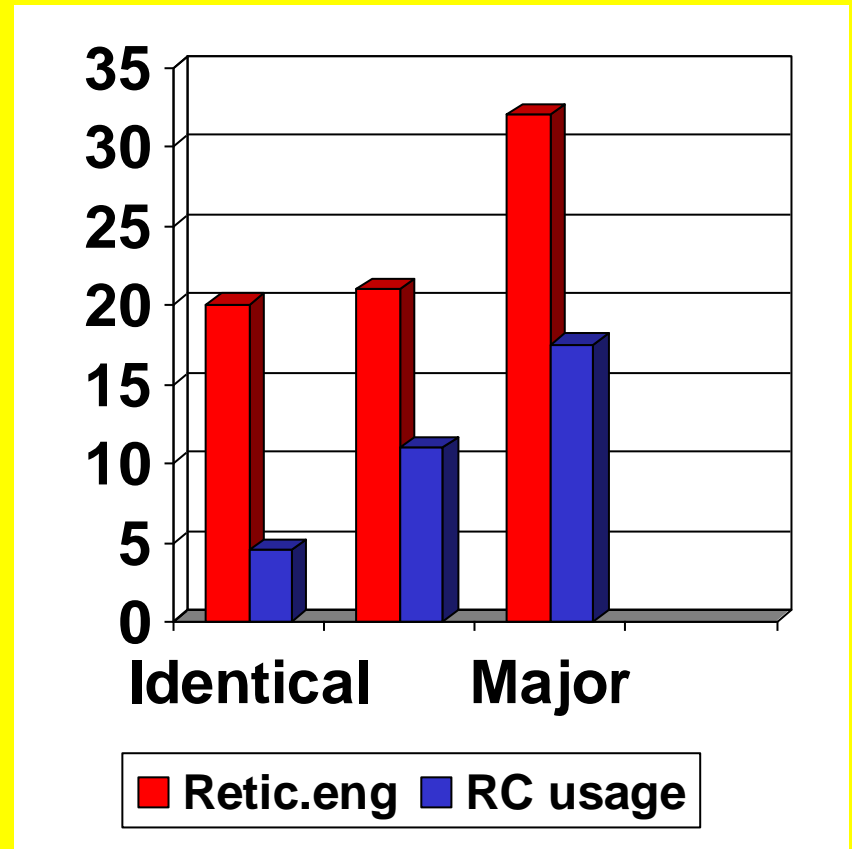
- Expressed on erythroid cells from early progenitor stage
- But also on most epithelial and endothelial cells, kidney tubuli and glomeruli
- Function not known

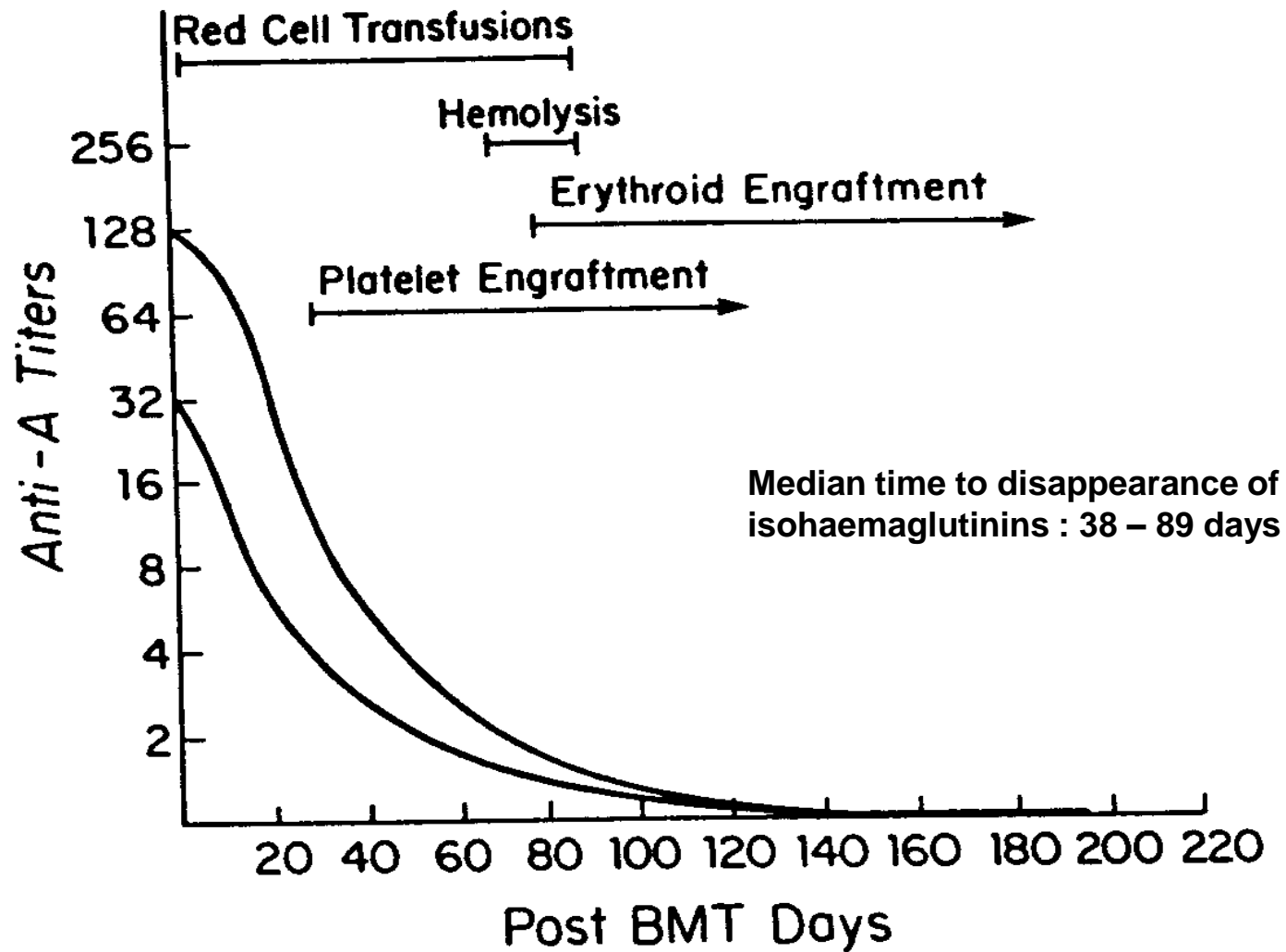
ABO system in Haemopoietic cell Transplantation

- ABO mismatch (major/minor/bidirectional):
 - 50-60% unrelated donor transplants
 - 25-40% sibling donor transplants

Impact of Major ABO mismatch on HSC transplantation

- Acute Haemolysis
- Delayed red cell engraftment
- Pure Red Cell Aplasia (5-20%)
- Loss of HSC due to processing





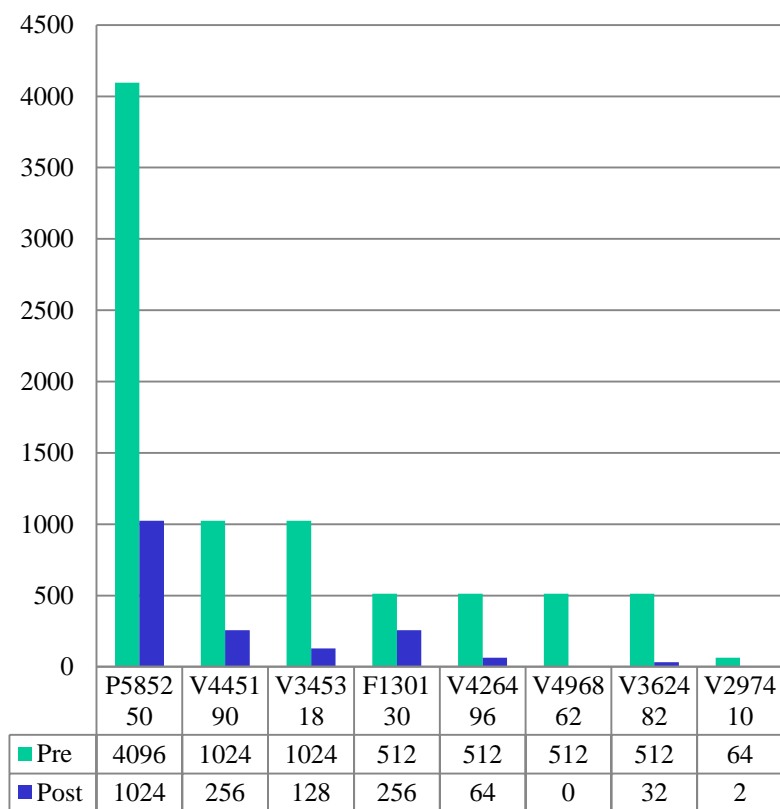
Sniecinski 1988

Management of ABO incompatibility in HSCT

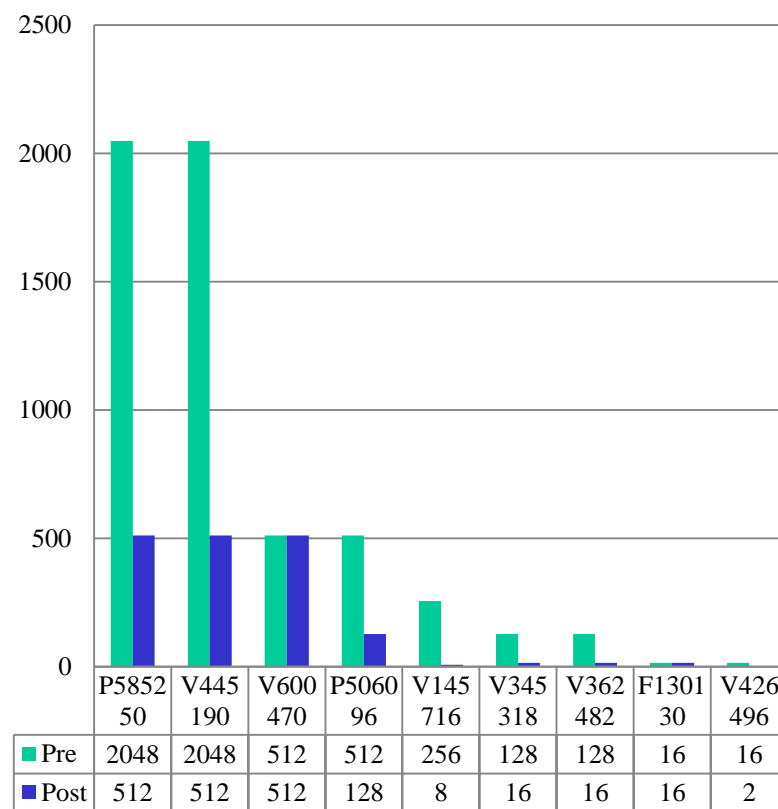
- **Prior to HSCT**
 - Bone marrow processing (red cell/plasma depletion)
 - Major ABO incompatibility
 - Minor incompatibility with high anti-A/B titres (≥ 128)
 - Plasma exchange/adsorption (days -2,-1,0)
 - Major ABOin , host anti-A/B ≥ 64
- **Post HSCT - Pure Red Cell Aplasia**
 - Plasma exchange/adsorption. Withdrawal of Cyclosporin
 - Steroids. Rituximab. Other immunosuppressive agents
 - Erythropoietin.
- **Post HSCT – Donor-derived ABO antibody**
 - Steroids. Red Cell exchange

Removal of Anti-A/B with PEX

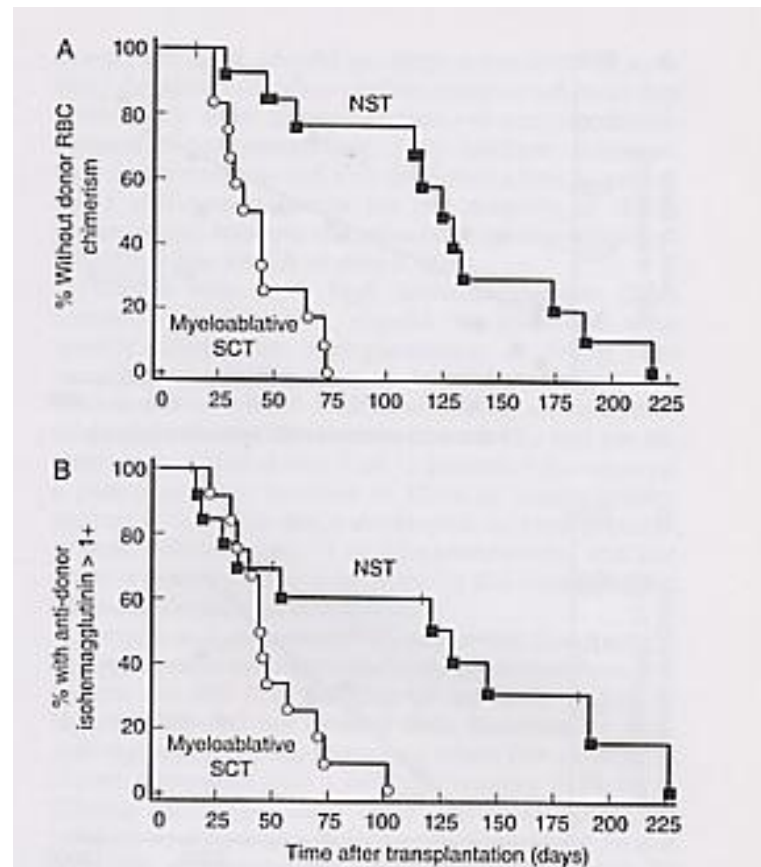
Anti-A



Anti-B

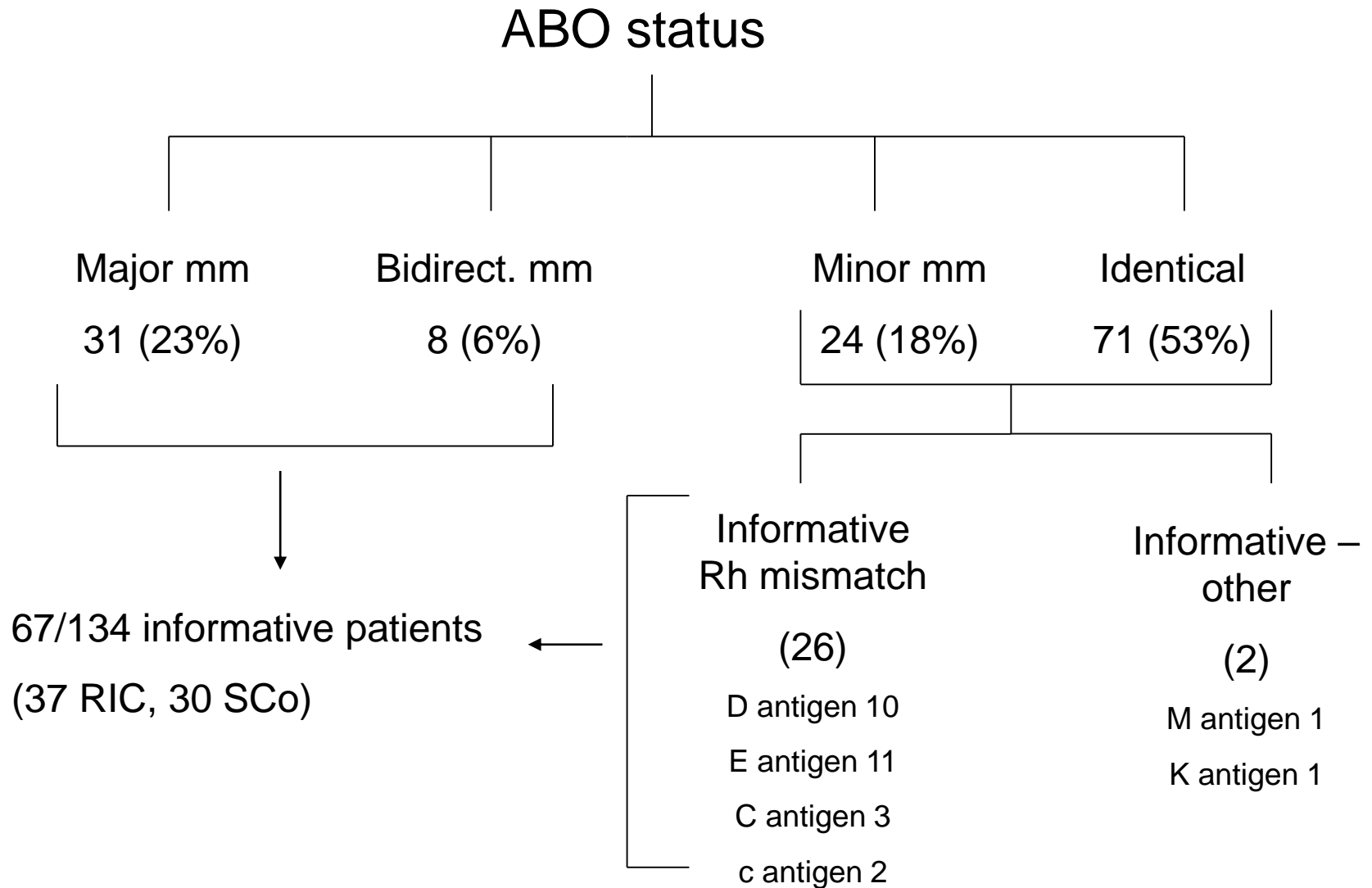


Delayed disappearance of host anti-A/B in RIC transplants

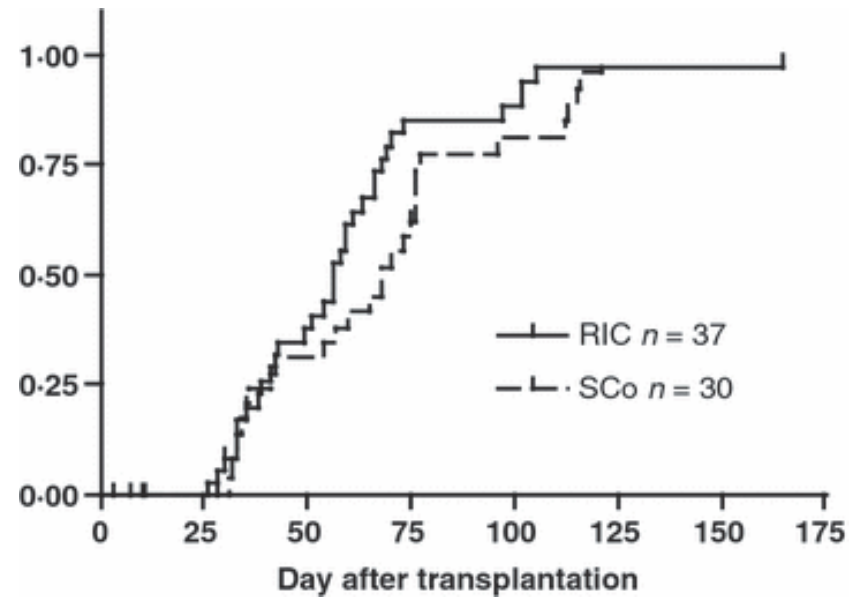


Serological Assessment of Donor Red Cell Engraftment

Mijovic A et al, B J Haem 2008



Emergence of donor red cells after reduced-intensity and standard conditioning allogeneic transplantation

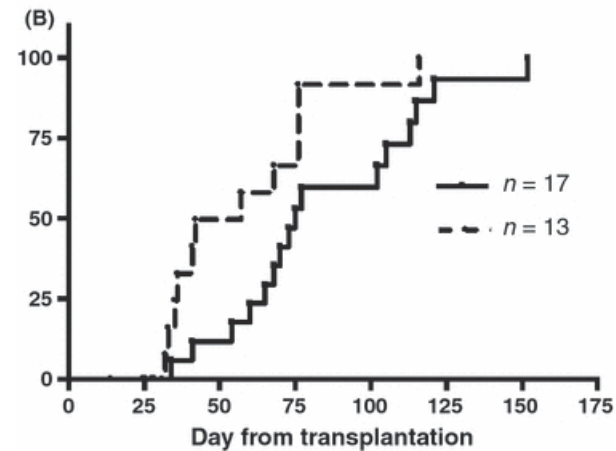
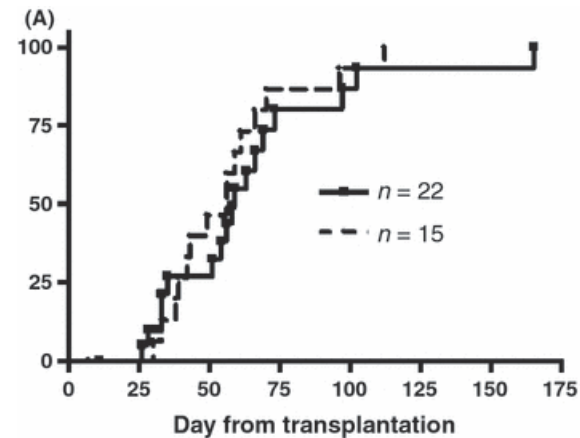


EFFECT OF ABO-MISMATCH ON EMERGENCE OF DONOR RED CELLS IN ALEMTUZUMAB-CONTAINING RIC (A) AND STANDARD CONDITIONING (B) REGIMENS

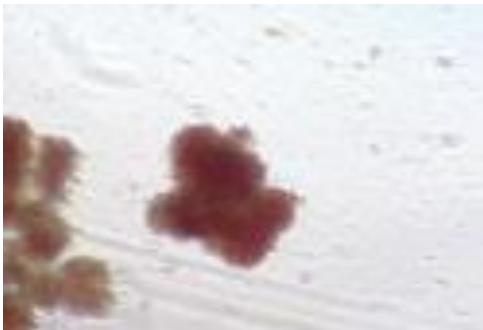
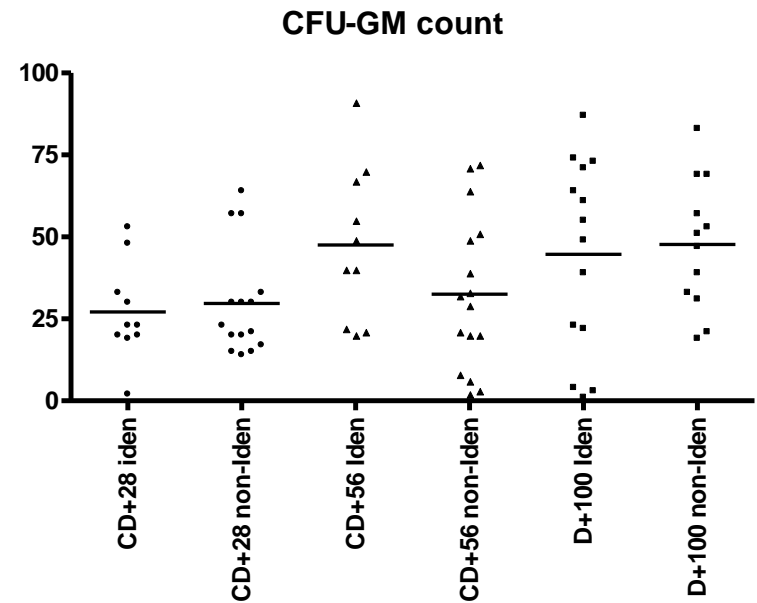
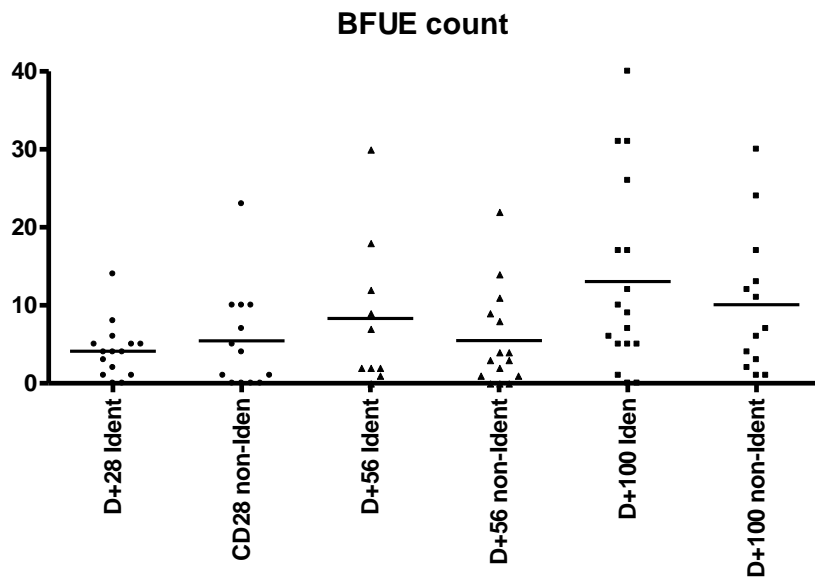
LEGEND:

Solid line: Major ABO mm

Dotted line: Minor ABO mm /
ABO identical



Does ABO incompatibility affect BFU regeneration after RIC HSCT?



What have we found?

- Our findings suggest neither delayed disappearance of host anti-A/B, nor delayed donor red cell chimerism, in RIC (mainly FBC/FMC) transplants.
- Appearance of donor-type anti-A/B was slow (18.75% at 1 year), reducing the risk of “passenger lymphocyte” haemolysis.
- These effects are likely due to the use of Alemtuzumab in our RIC regimes.

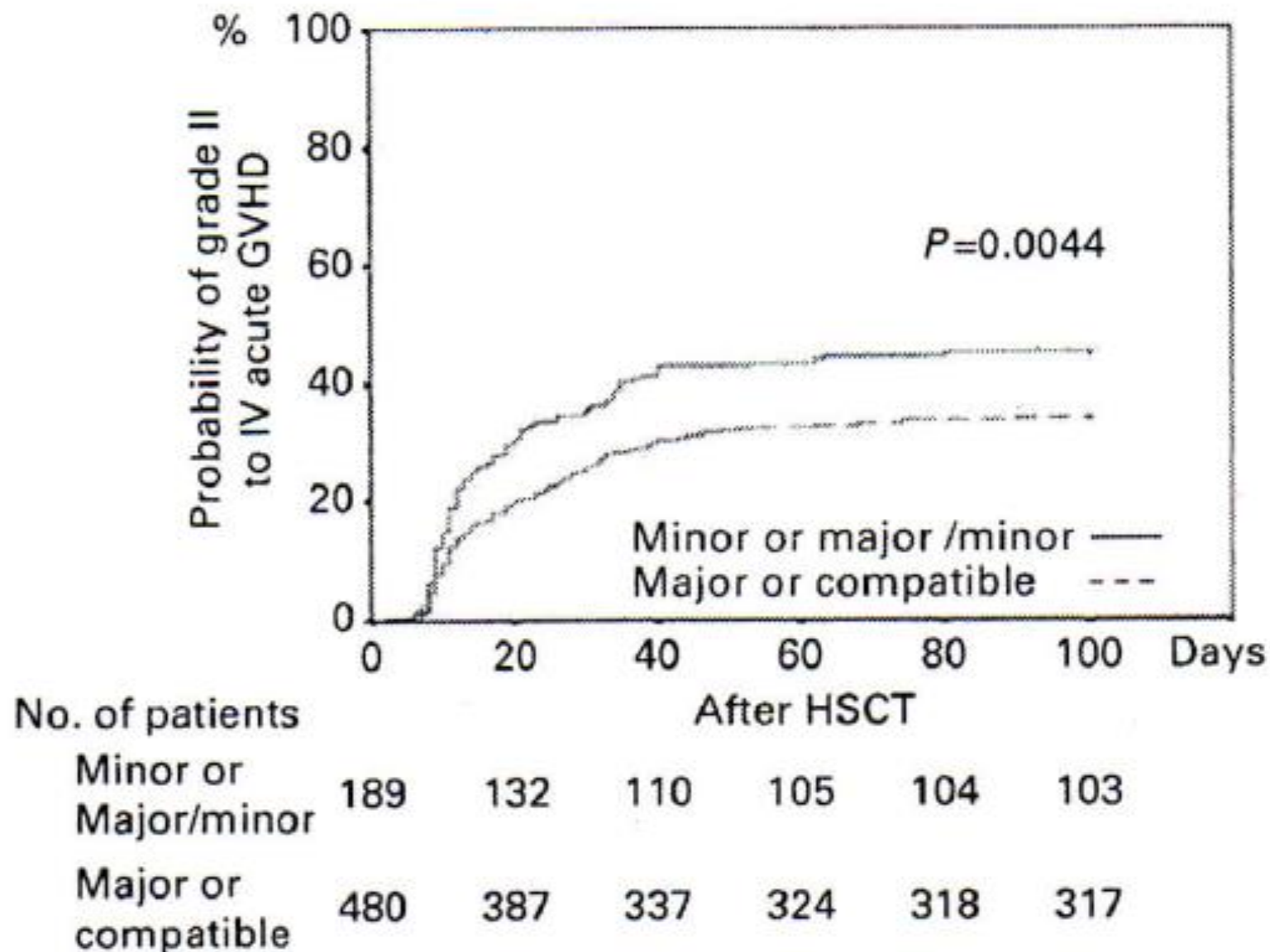
ABO mismatch in 594 transplants

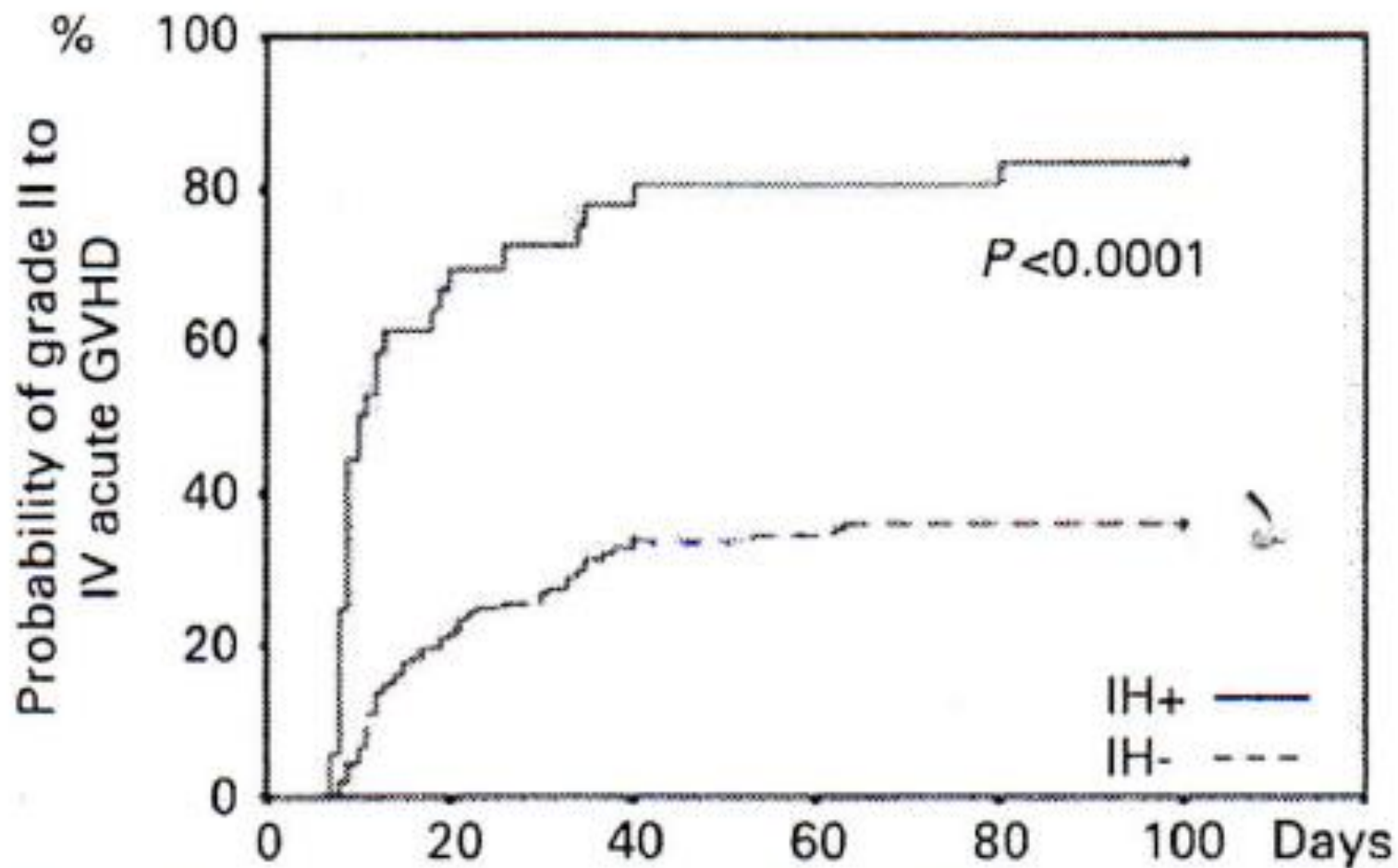
Brierley CK et al, Bone marrow transplant 2015

No significant effects of minor/major/bidirectional ABO mismatch on:

- Overall survival,
- Relapse-free survival
- Non-relapse mortality
- Acute GVHD
- Red cell and platelet transfusion requirements in the first 100 days post transplant

Incidence of extensive cGVHD was higher in patients with minor and major mismatch (HR 1.74, $P = 0.032$ for minor, HR 1.69 $P = 0.0036$ for major mismatch).





No. of patients

After HSCT

IH- 153 121 103 99 97 96

IH+ 36 12 8 8 7 6

Impact of ABO mismatch on outcomes of HSCT

- **Does it increase the incidence of acute GVHD?**
 - No consistent findings: YES in Japanese studies (effect of relative scarcity of A_2 ? weak *FUT2/FUT3* alleles?)
- **Does it increase the incidence of chronic GVHD?**
 - Only one study found the association
- **Does it prevent relapse?**
 - No evidence
- **Does it affect survival?**
 - No consistent result; effect probably small

ABO system in solid organ transplantation

- Major ABO incompatibility may lead to acute, antibody-mediated rejection of the transplanted organ
- Kidney transplants are ABO-matched - except when a compatible donor is not available (includes A2 organs into O/B recipients)
- Liver and heart/lung transplants – < 1% ABO incompatible (typing/clerical errors !)
- Small children tolerate ABO-incompatible transplants better (? Tolerance induction)

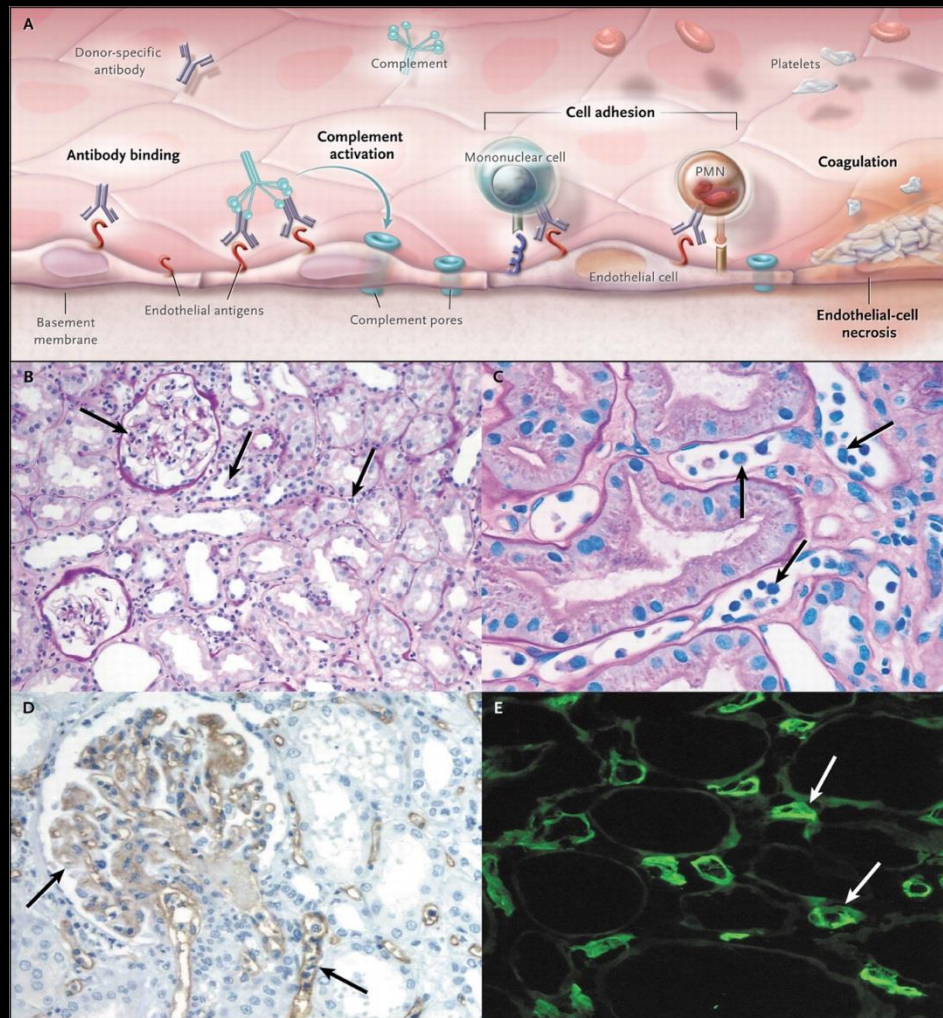
How common are ABOmm transplants?

ABO match	Kidney Tx 2013/14 [%]	Kidney Tx 2014/15	Liver – Elective [%]	Liver – Super Urgent
Identical	-	-	98.3	67
Compatible			1.5	32
Incompatible	2.88	2.33	0.15	0.5
Japan ^a	~ 30 ^a			

NHSBT, ODT report 2015

^aMuramatsu M et al 2014

Acute Antibody-Mediated Rejection.



“Accomodation”

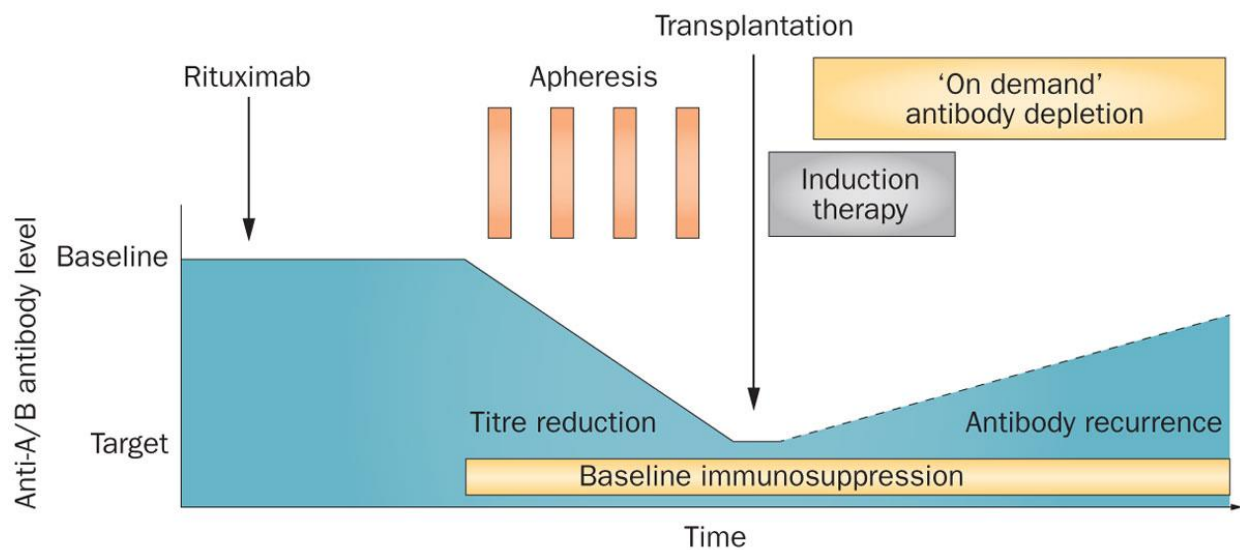
- Acquired resistance to humoral injury, clearly shown to exist in ABO-incompatible allografts.
- Following removal of antibodies from the recipient by means of plasmapheresis or immunoadsorption, isohaemagglutinins can rise to pretreatment levels after transplantation, adhere to the microvasculature, and activate complement, yet they generally do not injure the endothelium.
- This anomaly has been attributed to “accommodation” within the kidney, but the mechanism responsible for this benign response is unknown

Nankivell BJ & Alexander SI,
NEJM 2010; 363:1451-1462.

Immune modulation protocols in kidney Tx

- Belgium 1982-1989: ABOin, living donors.
PEX, CyA, Azathioprine, ALS, Splenectomy
78% allograft survival at 2 yr
- Japan 90's – largest experience with living donors. : PEX, CyA, ALS, Splenectomy; “triple maintenance” (Tacro,MMF,Pred)
 - > 4yr graft survival nearly equivalent mm vs match
- Mycophenilate mofetil further improved graft survival
- Rituximab (combined with plasma exchange/adsorption and IVIG) eliminated the need for splenectomy (Tyden et al 2005; Sonnenday et al 2004, Am J Transplant). Triple maintenance.

Figure 3 Key elements of recipient desensitization in ABO-incompatible transplantation



Nature Reviews | Nephrology

Pro & Contra ABOin Kidney Transplantation

Pro

- Reducing waiting list and time
- Expanding living donor pool
- Improvement of patient's prognosis
- Excellent graft survival (comparable with ABOc-KT)

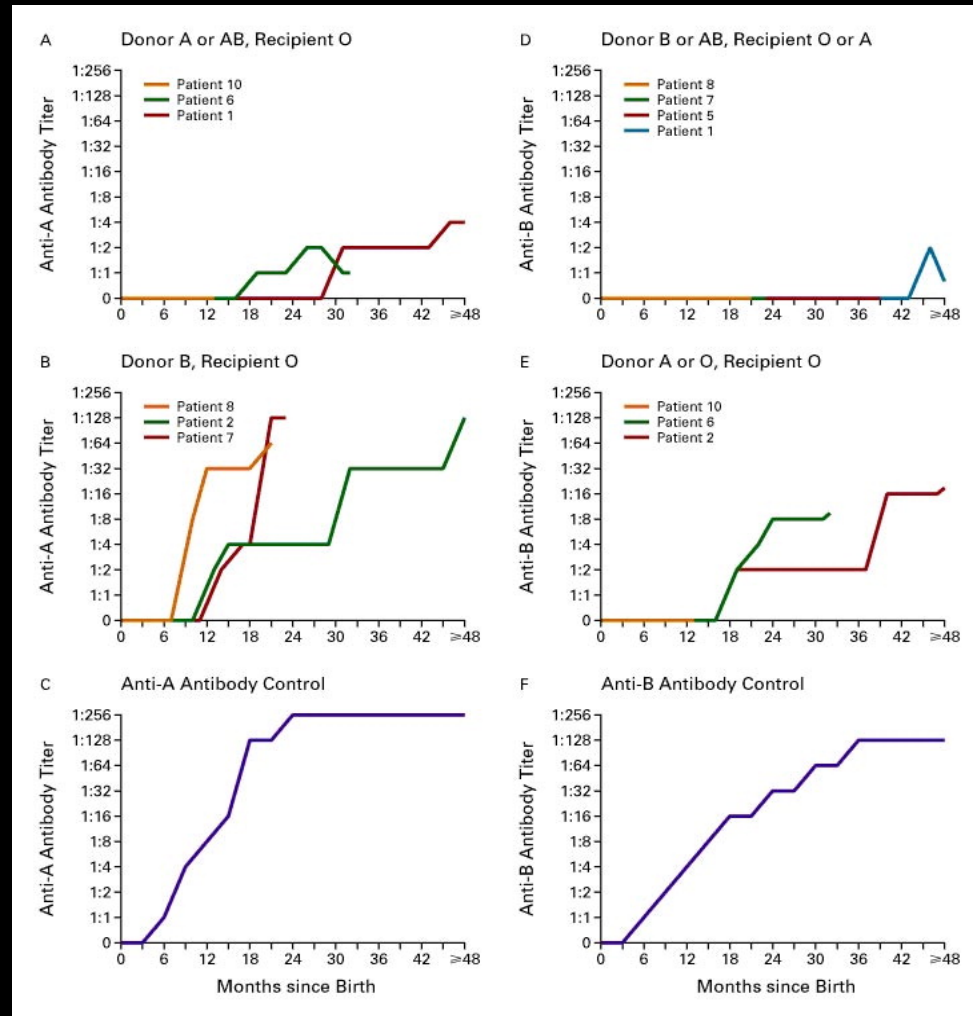
Contra

- Higher incidence of acute AMR
- Intensified immunosuppression
- Antibody depletion therapy
- Increasing cost
- Higher incidence of viral infection

Role of the Transfusion Laboratory/Service in ABO-incompatible organ transplantation

- Seek A₂ organ donors (A₁ lectin, ABH genotyping): 20% in USA vs 0.15% in Japan
 - If using an A2 kidney and anti-A titre is $\leq 1:8$, no antibody reduction is required
- Select blood products to avoid passive transfer of anti-A/B
- Titrate IgG/IgM ABO antibodies
- Plasma exchange to control anti-A/B levels pre- and peri-operatively

Serum Antibody Development in Infants with Grafts from ABO-Incompatible Donors Transplanted before the Onset of Isohemagglutinin Production.



Thank You !