NHS
Blood and Transplant

All you wanted to know about transfusion support for transplants

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Caring Expert Quality

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When / why / why not?
What ABO group?
Do ‘other’ groups matter?

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Transplantation

- Bone Marrow-Stem cell transplantation

- Solid organ transplantation

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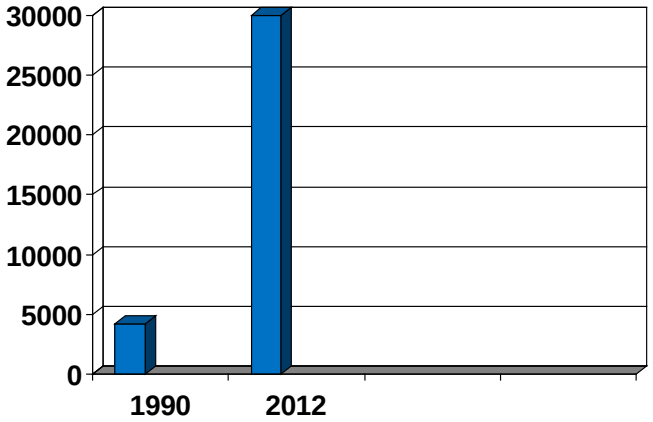
BMT-the numbers

- since 1990, haematopoietic stem cell transplants performed in Europe has risen
- from 4200 to over 30 000 annually

(*Passweg et al, 2012*)



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Transfusion Support for BMT
Why?

- Underlines disease
- Conditioning
- Transplant related complications
  - Delay engraftment
  - GVHD
  - ABO incompatibility
  - AIHA
  - PLS
  - Medications

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Blood components required

Red cells

– Thresholds?

Platelets

Bone marrow failure/Bleeding

Fresh Frozen Plasma (FFP)

Liver failure, DIC , Tr-TTP

Cryoprecipitate

DIC

- Granulocytes

Infection

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Issues to be addressed

- **Selection of ABO blood**
  - **ABO mismatched HSCT**
- **Alloimmunisation (red cell and HLA antibodies)**
- **Establishing thresholds**
- "Red Blood Cell Transfusion: 2016 Clinical Practice Guidelines from the AABB," (JAMA), October 12.
- **TA-GVHD**
- **Haemolysis**
  - **Underline mechanism**
- **Iron overload**
- **The role of CMV**

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ABO incompatible BMT

- Limitations in donor availability
- Prioritisation of HLA matching for optimal outcomes necessitates donor–recipient ABO incompatibility for significant number of BMT transplantation.
  - 30–50% of haematopoietic SCT
  - 15-25% sibling allografts

- Major:
  - Alloagglutinins anti-A,B,AB reactive to donor red cells (recipient group O, donor A)
- Minor
  - Alloaglutinins anti A, B,AB reactive to recipient red cells in donor plasma (recipient A, donor O)
- Bidirectional
  - Presence of reactive alloaglutinins in both recipient and donor plasma (e.g. recipient group B, donor group A).

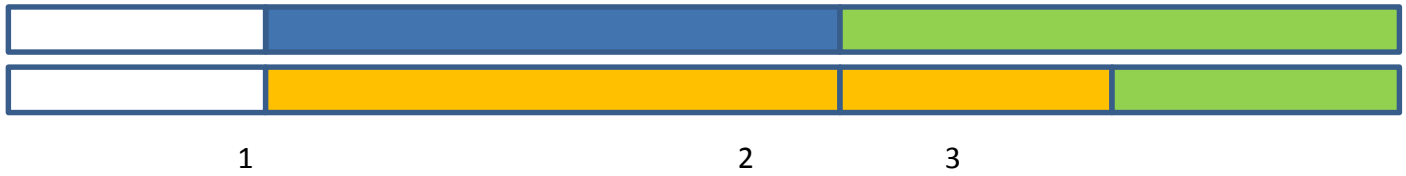
- Recipient group Group O Group AB Donor group
- **Major ABO incompatibility (recipient O/ donor A)**
  - Red cells
  - Plasma/PLT

Minor ABO incompatibility (recipient A, donor O)

  - Red cells
  - Plasma/PLT

Major and minor ABO incompatibility (Recipient A, donor B)

  - Red cells
  - Plasma/PLT



1. HSCT 2.ABO antibodies to donor RBC not detected. DAT negative
   3. RBC of recipient group no longer detected ★ recipient type red cells

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Blood group selection

- Pre-transplant: Patient's own blood group

- Post transplant
  - Rules until engraftment achieved
    - ABO antibodies against donor's cells are undetectable
    - and DAT negative
    - Chimerism studies

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ABO mismatch and transplant outcomes

- ABO mismatch on transplant outcomes is variable
- Small and heterogeneous studies in the literature.
- Of the larger studies, a French registry study of 1108 RIC HSCT patients reported that MN ABO incompatibility was associated with **reduced OS.**
- In the RIC subgroup of the largest registry study to date, Kimura *et al.* reported **increased transplant-related mortality** (TRM) for MN, MJ and BD ABO-mismatched patients.
- Recently, ABO mismatch was found to have no effect on OS, non-relapse mortality or GVHD in 2 studies of 310 patients and 503 patients undergoing RIC allograft, but both noted **increased transfusion requirements** in patients with MJ/BD mismatch.
- **In a large UK study, ABO mismatch in RIC HSCT has no clinically significant effect on survival outcomes but appears to modify susceptibility to extensive chronic GVHD.** C K Brierley et al*Bone Marrow Transplantation* (2015) **50,** 931–938; doi:10.1038/bmt.2015.51; published online 13 April 2015

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Reported effects of ABO incompatibility include

- Immunohaematological reactions(acute or delayed haemolysis in 15-30% patients)
- Acute haemolysis
  - Reduction of red cells < 20 ml (major)
  - Reduction of plasma if titre >1/256 (minor)
- Pure red cell aplasia, delayed erythropoietic recovery and increase transfusion requirements
- Passenger lymphocytes

- Pure red cell aplasia, delayed erythropoietic recovery and increase transfusion requirements
  - Elytroid precursor engraftment not reconstitution
  - Correlation of isohaemagglutinin titters (IgM, IgG) with red cell reconstitution
    - Low retics predict increased blood transfusion requirements

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“Passenger lymphocyte syndrome”

- **Unexpected antibodies of A and B specificity**
  - Minor mismatch
  - 7-10 days post transplant
  - Rarely seen in T-cell depleted grafts or CD34 positive selection

- **Antibodies to red cell antigens outside the AB system have been reported in association with transplanted**
  - **kidney, pancreas-kidney, pancreas, liver, and heart-lung**

- **1980 :kidney allografts from ABO minor mismatched donors**

- **1991:liver, kidney, pancreas, spleen, heart, lung, and heart-lung**

- Viable donor B lymphocytes passively transferred with the organ at the time of transplantation

- If they are stimulated shortly after transplant by recipient or transfused red cell antigens, they can start producing antibodies during their life.

- PLS with severe haemolytic anaemia was due to an anti-JKα on day 19 after allogeneic peripheral blood stem cell transplantation

  - DAT POSITIVE
  - The serum antibody is predominantly
    - IgG, but it may also be IgM.
- Passenger lymphocyte derived antibodies are short-lived
- Haemolysis is usually mild and self-limited
- Persisting for about 2–3 weeks in liver transplant recipients
  - and 5 weeks in kidney transplant recipients
- In some cases, substantial morbidity such as acute renal failure, DIC, hypotension, and multi organ failure, has been reported

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AIHA and bone marrow transplantation

- AIHA
  - Immunodeficiency
  - Antibody defects
- Transplantation incidence 4/5%
  - Unrelated donors
  - Chronic extensive GVHD

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Case presentation

- 45 year old Caucasian male
- Diagnosis: MM
- Underwent unrelated BMT
- Reduction/discontinuation of immunossupression
- Anaemia(15 months post transplantation)
  - Bone marrow examination
    - Absent erythroid precursors
    - Chimerism:95%

- Required blood transfusion
- Experience recurrent haemolytic transfusion reactions
- Developed anti-E antibody
- Reactions persisted despite provision of E negative blood

- DAT = C3d 3+ positive
  - Anti-E
  - Eluate negative

Investigations repeated at NHSBT- RCI

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- ***Pre-transplant***

- Fya POSITIVE
- Fyb POSITIVE
- Fy GATA mutation NEGATIVE
- Jka POSITIVE
- Jkb POSITIVE
- **K (KEL1) NEGATIVE**
- k (KEL2) POSITIVE
- M POSITIVE
- N POSITIVE
- **S NEGATIVE**
- s POSITIVE

- ***Donor's sample***

- Fya POSITIVE
- Fyb NEGATIVE
- Fy GATA mutation NEGATIVE
- Jka POSITIVE
- Jkb NEGATIVE
- **K (KEL1) POSITIVE**
- k (KEL2) POSITIVE
- M POSITIVE
- N POSITIVE
- **S POSITIVE**
- s POSITIVE

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Pre-transplant	***Post transplant***
Fya POSITIVE	Fya POSITIVE
Fyb POSITIVE	Fyb NEGATIVE
Fy GATA mutation NEGATIVE	Fy GATA mutation NEGATIVE
Jka POSITIVE	Jka POSITIVE
Jkb POSITIVE	Jkb NEGATIVE
K (KEL1) NEGATIVE	**K (KEL1) POSITIVE**
k (KEL2) POSITIVE	k (KEL2) POSITIVE
M POSITIVE	M Undetermined
N POSITIVE	N Undetermined
S NEGATIVE	S Undetermined
s POSITIVE	s Undetermined

- Transfused uneventfully S(-) and K(-) blood
- Re-start immunosuppression

- Currently transfusion independent
- Although no antibody was detected, it seems reduced chimerism allowed reaction from his own K neg cells

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Red cell phenotyping

- Recipient up front
- Donor Rh, Kell, and more specifically as required based on recipient's antibodies

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How to we cross match?

- Patients are not suitable for electronic cross match
  - If they had an ABO-incompatible marrow or haemopoietic stem cell transplant
  - If they had an ABO-incompatible solid organ transplant in the last 3 months
  - Antibodies

Selection of blood

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- Irradiated cellular blood components
- CMV negative issues
  - CMV testing: many more reasons to test/not only for selection of blood and blood components
- No thresholds and targets
- Conservative approach-patient's symptoms
- Consider single unit for stable hospitalised in patients

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Blood Transfusion issues for solid organ transplantation-Renal transplantation

- ABO incompatible renal transplantation
  - Titration
  - Selection of compatible plasma rich components

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Recipient Group	Donor Group	Group of FFP 1st choice / 2nd choice	Group of Cryo 1st choice / 2nd choice
A	O	A then B	A
A	B	AB then HTN B	B
A	AB	AB then HTN A	A
B	O	B then AB	B
B	A	AN then HTN A	A
B	AB	AB then HTN B	B
O	A	A then AB	A
O	B	B then AB	B
O	AB	AB then HTN A	A
AB	O	AB then HTN A	A
AB	A	AB then HTN A	A
AB	B	AB then HTN B	B

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HLA sensitisation

- Renal transplantation
- Possible link to red cell transfusions

- Transplantation 2012 Feb 27;93(4)
  - RR 4.1 (p=0,02)
- Transplantation 2012 Dec 15;94(1)
  - HLA selected red cells offers protection=0.002)

HLA sensitisation: can it be prevented?Pediatr Nephrol. 2015; 30(4): 577–587.

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Transfusion support for liver transplantation

- History of significant number of transfusions
  - Antibodies present (limitation to transplantation)
  - O RhD positive female patient
    - Anti-C, K, Jkb, Fya

- Often coagulopathic

- Time restrictions for optimisation
    - Cell savers
    - Near patient testing

Early Blood Transfusion contribution at Transplant MDTs

ABO incompatible liver transplants

In the past

- Error
- Emergencies
- Paediatric practice

- Now:
- Emergencies
- No previous preparation
- Possible some titration prior to transplant

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Example:

- 55 year's old female patient
- Blood group O RhD positive
  - Antibodies negative
- Urgent liver transplant
- Donor's blood group
  - A RhD positive

- **Risks**
- Viability of the organ
- Acute haemolytic transfusion reactions
- Passenger lymphocyte syndrome

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Optimisation

- Can we avoid possible reaction?
- Anti-A IgG :1/64
- Anti-A IgM :1/8
- Red cells and FFP compatible with donor and recipient
- Surgical preparation of the organ (flash)
- Further immunosuppressant
  - Ritoximab
  - IVIG?
  - **Eculizumab**

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Multi visceral transplantation

- Patients with co-morbidities
- Often coagulopathic
- Rapid changes during transplantation
  - Assessment
  - Protocols
- Some with very low body weight (BMI 15)

RhD positive organs to RhD negative recipients

- Women of child bearing potential

- Although sensitisation is described to be low a number of cases are reported

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Ex vivo normothermic perfusion

- Ex-vivo normothermic perfusion (EVNP) is a novel technique that may help to *recondition* ischaemically injured kidneys and livers prior to transplantation.

- The aim of EVNP is to restore metabolism and function to the organ prior to transplantation by circulating a warm oxygenated red cell based solution through the organ.

- EVNP has recently been introduced into clinical practice for kidneys and livers from marginal donors

- Experience suggests that the technique is feasible, safe and may improve early graft function.

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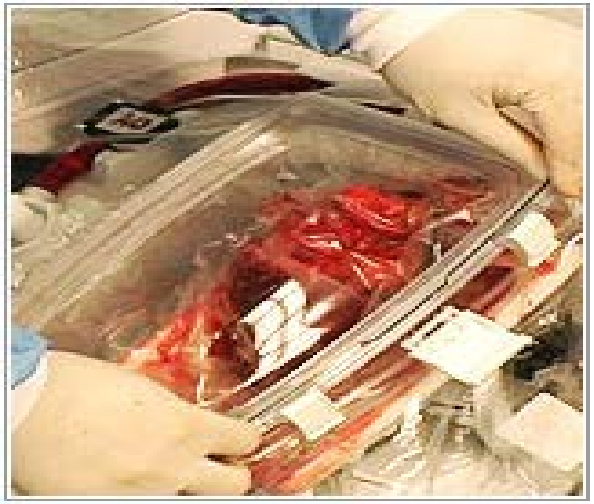

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Transfusion issues

- Selection of blood group and issuing blood to an organ
- Selection of RhD type and issues of RhD incompatibility
- Traceability
- SaBTO

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Section title

Thank you