# HLA and ABO: What is an incompatible transplant?

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# Overview

- Development of Transplants
- ABO
- HLA
- Passenger Lymphocyte Syndrome
- Hyperacute Rejection
- Graft vs Host Disease (and Host vs Graft)
- ABO conversion
- AMR

# Transplant Medicine

- Life saving/altering procedures for:
  - Leukemia
  - Lymphoma
  - Myeloma
  - Congenital Heart Defects
  - Cardiomyopathy
  - Liver Cancer
  - Cirrhotic Liver Disease
  - End-Stage Medical Kidney Disease

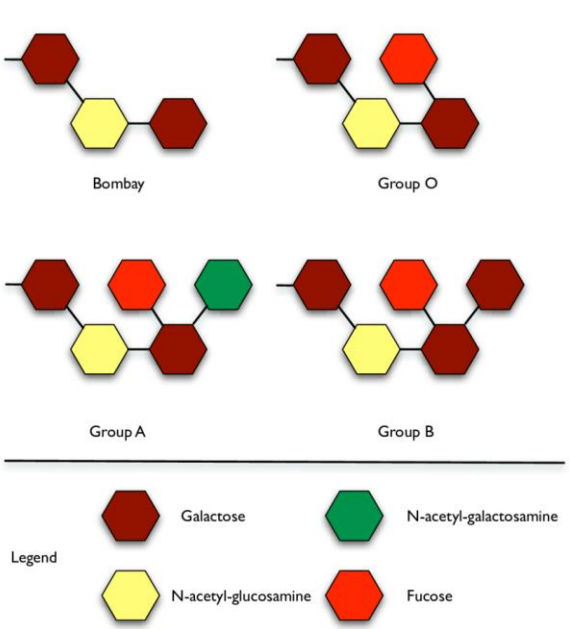
# Transplant Medicine

- Solid Organ Transplant
  - Finding an acceptable donor with quality organ
  - Rapid assessment to preserve organ
  - Refrigerate, but no freeze

- Hematopoietic Precursor Cell (HPC) Transplant
  - 'Bone Marrow' Transplant with peripheral venous access
  - Finding acceptable donor with quality HPC potential
  - Apheresis
  - Occasionally frozen (esp. during COVID-19)

# ABO

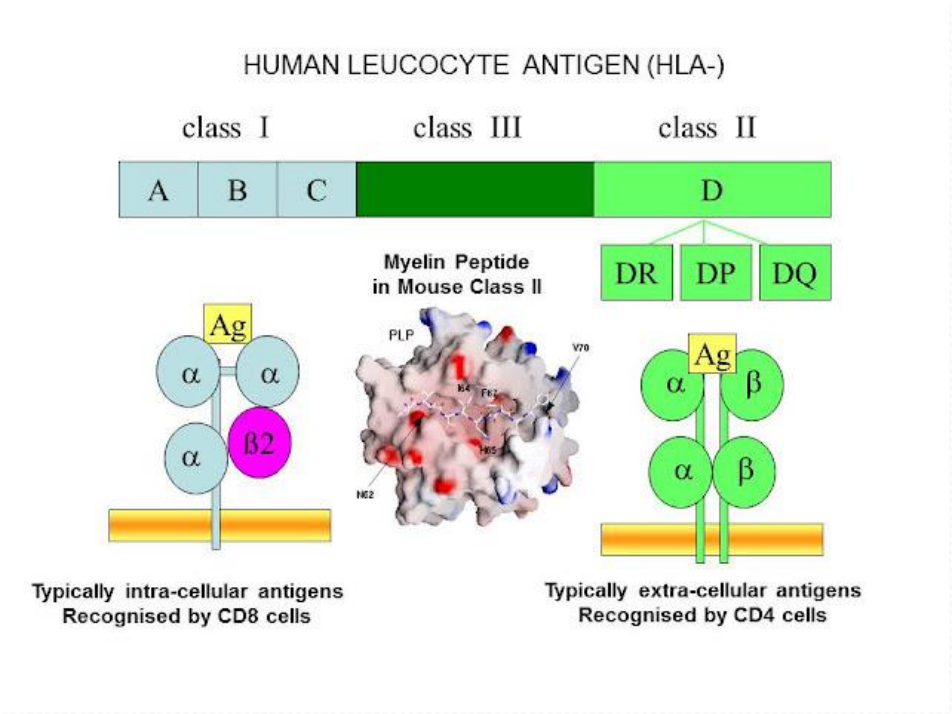
- Simple carbohydrate antigens with repetitive epitope potential
- Naturally occurring antibodies against non-self (due to environmental exposures)
- Non-erythroid specific
  - Endothelial Cells (Vessels)
  - Kidney Parenchymal Cells




https://www.researchgate.net/figure/Biochemical-basis-of-ABO-groups_fig1_233799814

# Human Leukocyte Antigen (HLA)

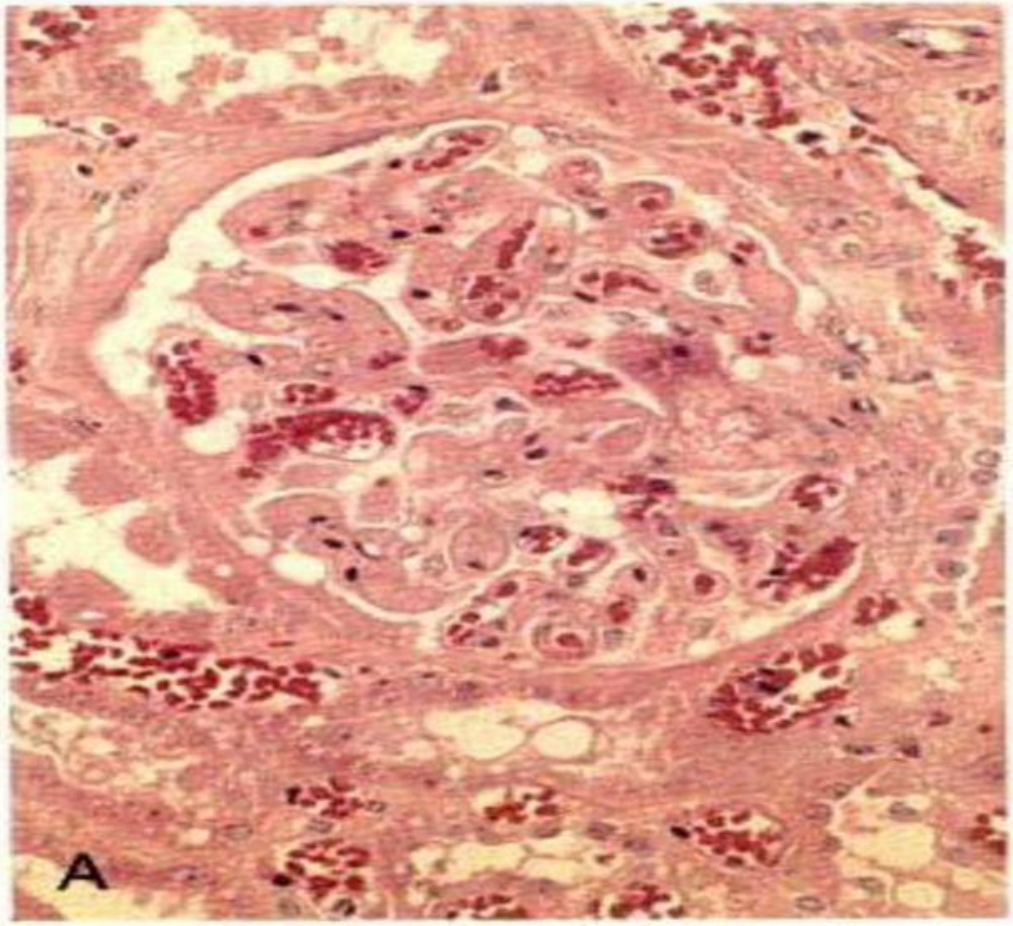
- Protein markers of self/non-self to the immune system
  - Works through cell mediated immunity with secondary stimulation of humoral immunity



# ABO causes hyperacute rejection

- Pre-formed antibodies attach to ABO antigens on vascular endothelium
- Complement proteins bind and are activated
- A ‘membrane attack complex’ is formed puncturing the cellular membrane and leading, in aggregate, to cell death
- Endothelial damage leads to thrombosis of the vessels
- Ischemic damage to the remaining tissue

Hyper acute rejection of a kidney allograft showing endothelial vascular damage (by preformed antibodies) with formation of fibrin-platelet thrombi in the glomerular capillaries.




Diseases of Immunity (Immunopathology) - ppt download

# ABO

- RBCs in the transplanted organ vessels
  - Rapid hemolysis of limited cells, but homostasis can quickly be obtained
- Lymphocytes in the transplant organ vessels (including lymph vessels)

- If can get through any hyperacute rejection, then a kidney/liver transplant tends to go the same as ABO matched (accommodation)

# ABO

- Apheresis to remove anti-ABO antibodies
  - Plasma exchange (most available)
  - Filtration to remove most immunoglobulin
  - Immunoadsorption
    - A and B antigens in gel to selectively remove antibodies
- Splenectomy vs Rituximab
  - Recent article said that these may be removed in kidney
  - Another article describes pre-transplant interventions in liver

# Passenger Lymphocyte Syndrome

- Lymphocytes find foreign antigens in the host
  - Activate and proliferate
  - B-cells produce antibodies (most rejection drugs are primarily targeted at other T-cell population)
- Antibody mediated rejection
  - Rituxumab
- Hemolysis and jaundice
  - Many are subclinical
  - Reports of donor-recipient passage of alloantibodies? (anti-M)

# ABO rules

- Only infants <1 year can get ABO incompatible hearts
  - ABO tolerance can be induced in the very young
    - ABO chimerism in the endothelial cells
  - Extremely limited supply of these hearts
  - Fatality rate of congenital heart disease
- Liver/Pancreas try for ABO matched
- Kidney – ABO incompatible with intervention

- United Network for Organ Sharing (UNOS) requires at least two separate tests for ABO type prior to transplant

# HLA I

- HLA I – all nucleated cells
  - Present representative peptides (~9 amino acids) that are made in that cell
  - HLA I mismatch targets the non-specific cytotoxic pathways

# HLA II

- HLA II – specialized cells that present antigens
  - Dendritic cells
    - Migrate to lymph nodes to “instruct” naïve T cells
  - Macrophages
    - Spleen and Liver
  - HLA II mismatch targets the specific inflammatory pathways

# Human Leukocyte Antigen (HLA)

- Inherited from each parent
  - No variability due to genetic recombination (antibodies)

## HUMAN LEUCOCYTE ANTIGEN IS HIGHLY POLYMORPHIC

| | MHC Class I Antigens | | | MHC Class II Antigens | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Locus | A | B | C | DR | | DP | | DQ | |
| | | | | α | β | α | β | α | β |
| No. Alleles | 893 | 1431 | 569 | 3 | 827 | 28 | 136 | 35 | 106 |
| No. Proteins | 681 | 1165 | 431 | 3 | 644 | 16 | 118 | 26 | 77 |

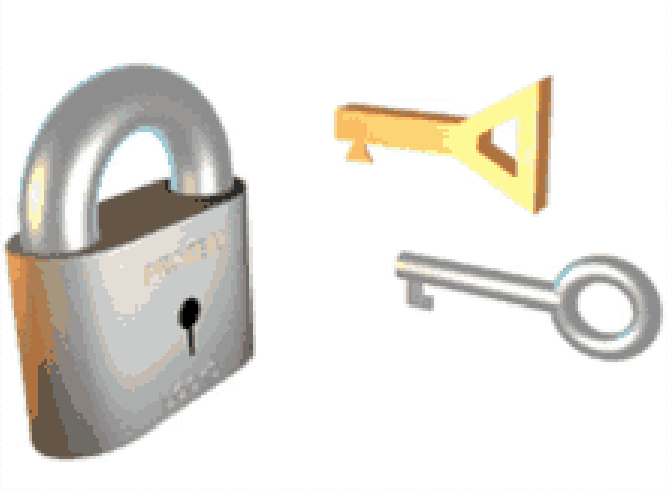
**$2.9 \times 10^{17}$ combinations**

# HLA matching

- Bone marrow elements responsible for immune system

BUT

- Transplanted HPCs (also referred to as hematopoietic stem cells – HSCs) will ultimately provide all immune cells with the exception of a few tissue plasma cells



# HLA

- Major mismatch
  - Recipient attacks donor cells
  - Problem with solid organ transplant
  - Manageable for HPC transplant
- Minor mismatch
  - Donor cells attack recipient
  - 'Graft vs host syndrome'
    - Graft vs leukemia effect

# HLA priorities (HPC)

- HLA I – must match
- HLA II
  - Permissive vs non-permissive
    - Minor vs major
- Ideally twelve of twelve (A,B,C,Dr,Dp,Dq x 2 alleles)

# ABO incompatible transplantation

- Better to match HLA antigens than ABO
- Major incompatibility (host vs graft)
  - Rapid clearance of RBC's with risk of hemoglobinemia
  - Delayed engraftment or, less common, engraftment failure
  - Red cell reduction of the product
- Minor incompatibility (graft vs host)
  - Transient (occult) hemolysis from passenger lymphocytes
  - Irradiated product
- Monitor for conversion in blood bank
  - Mixed field reactions

# ABO mismatch in HPC

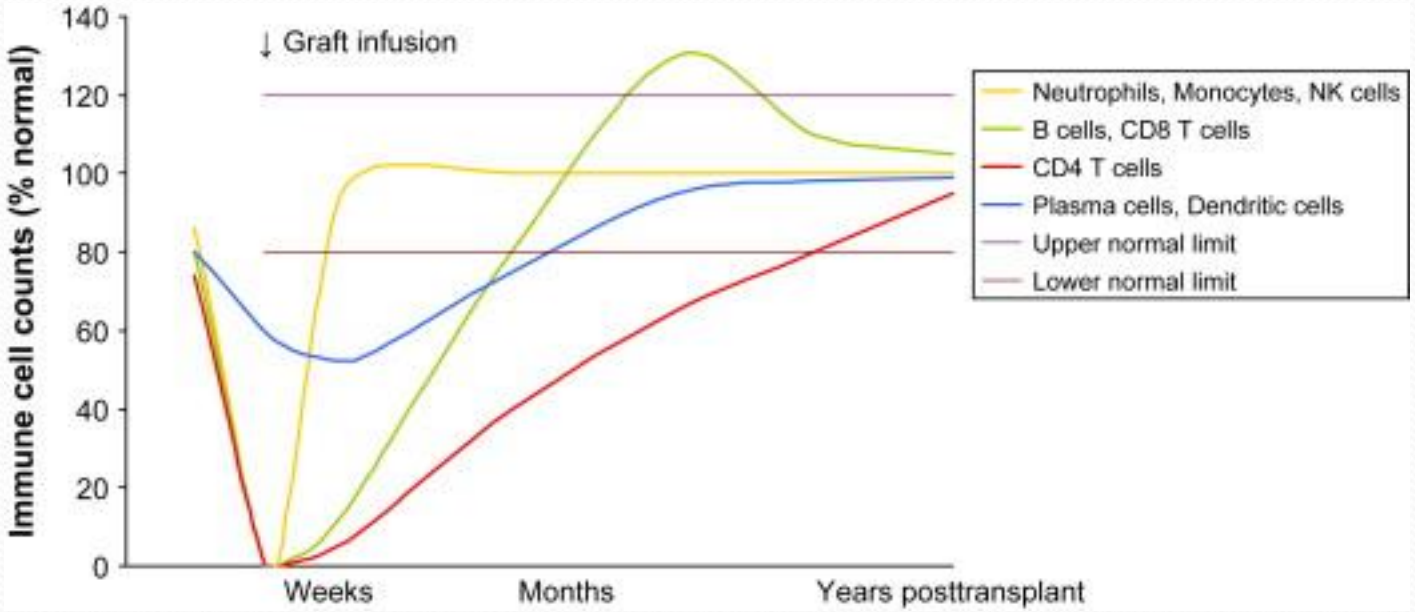
**TABLE 27-1.** ABO Compatibility during HSCT*

| Category | ABO Group | | Preferred ABO to Transfuse | | Clinical Challenges | Possible Interventions |
|---|---|---|---|---|---|---|
| | Recipient ABO | Donor ABO | RBCs | Platelets/Plasma | | |
| ABO compatibility | O | O | O | O, A, B, AB | None due to ABO | None |
| | A | A | A, O | A, AB | | |
| | B | B | B, O | B, AB | | |
| | AB | AB | AB, A, B, O | AB | | |
| Major ABO incompatibility | O | A | O | A, AB | Acute hemolysis<br>Delayed engraftment<br>PRCA | Red cell depletion of HPC product |
| | O | B | O | B, AB | | |
| | O | AB | O | AB | | |
| | A | AB | A, O | AB | | |
| | B | AB | B, O | AB | | |
| Minor ABO incompatibility | A | O | O | A, AB | Acute hemolysis<br>Passenger lymphocyte syndrome | Plasma reduction of HPC product<br>Monitoring HSCT patient for hemolysis |
| | B | O | O | B, AB | | |
| | AB | O | O | AB | | |
| | AB | A | A, O | AB | | |
| | AB | B | B, O | AB | | |
| Bidirectional ABO incompatibility | A | B | O | AB | Combination of major and minor ABO incompatibilities | |
| | B | A | O | AB | | |

*This table suggests possible guidelines for selecting blood components for each category and ABO group combination of recipient and donor. Challenges related to preparing the HPC and during engraftment are listed. Appropriate component selection should be determined by each center and is often more liberal than listed here, particularly for platelet components.
HPC = hematopoietic progenitor cell, HSCT = hematopoietic stem cell transplantation; PRCA = pure red cell aplasia; RBCs = Red Blood Cells.

Technical Manual, 21st ed

# Recovery after transplant



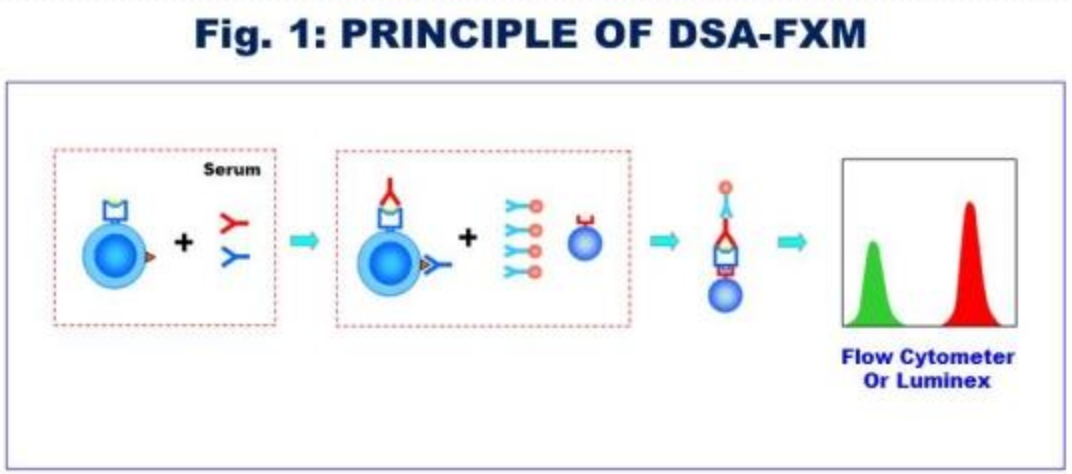

https://doi.org/10.1016/j.bbmt.2009.06.019

# Back to Solid Organs

- Antibody mediated rejection (AMR)
  - ABO – quite little (due to matching or immunosuppression??)
  - HLA
    - Pre-transplant
    - Post-transplant

# AMR

- Pre-transplant
  - Donor(?) specific antibodies (DSA)
    - Beads coated with HLA Ag with patient plasma and a fluorescent marker for binding




Detection of Donor Specific HLA-Ab (DSA) Against Native HLA Molecules Expressed On Donor Cell Surface to Eliminate False Positive DSA in Luminex Single Antigen Beads (LMX-SAB) - ATC Abstracts

# AMR

- High MFI – reject the organ
- Low MFI – transplant and monitor

- Apheresis is very poor at getting this Abs gone
- Rituxan did not show benefit (RITUX ERAH)

# AMR

- Development of post-transplant antibodies
  - Although non-HLA antibodies have been shown to contribute to rejection, still test only for HLA
- DSA to monitor
- Plasma exchanges and IVIg treatment can provide short term benefits
- Complement mediated toxicity means eculizumab may have benefit

# Review

- ABO
- HLA
- Hyperacute Rejection
- Graft vs Host Disease (and Host vs Graft)
- ABO conversion
- AMR

Questions?

# References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