NHS
Portsmouth Hospitals University
NHS Trust

Clinical Delivery

Blood Groups.

Working together To drive excellence in care for our patients and communities

Jennifer Mills

17/03/2024

Introduction

- More than just ABO/RhD!
- Initial overview:
  - Terminology
  - History
  - Clinical Significance
- Key blood groups: 3 parts.
  - Part 1: **Essential** Blood Groups
  - Part 2: **Important** Blood Groups
  - Part 3: Blood Groups that Confuse the Lab!

Key Terminology

Antigen
A cell **structure** the immune system responds to.

Antibody
A protein which removes **antigens**, from the body. **Antibodies are specific to an antigen.**

Alloimmunisation
The response of the immune system to a **non-self-antigen.**

Allele
Variants of a gene.

Sensitisation
The coating of cells with antibody.

Codominant.
Genes where **all inherited** alleles are **expressed.**

Antithetical.
Paired antigens coded for by the same gene e.g. E/e and Fya/Fyb

Recessive.
Two copies of the allele are required for expression.

Blood Groups: What?

- **Blood Group Systems** are determined by the **expression** of red cell membrane **structures**.
- **Variants** in these structures result in the different **Blood Group Antigens**.
  - Blood Group Antigens are **inherited**.
- There are **36** Blood Group Systems identified by the International Society of Blood Transfusion (ISBT).
  - There are >300 Blood Group Antigens!!
  - There are **6 Clinically Significant** Blood Group Systems.
    - These are systems are associated with **alloimmunisation** and **haemolytic reactions.**

Blood Groups: History

- All known blood groups were discovered in the past 120 years!
  - Often discovered when a patient gave birth to a baby with Haemolytic Disease of the Foetus/New-born (HDFN).
  - Often named after the discover, or “Patient Zero!”
- (Some) Key Discoveries:
  - 1901: Karl Landsteiner discovers ABO
  - 1940/9141: Rh Group discovered (Landsteiner and Weiner)
  - 1946: Kell Group discovered (Coombes, Mourant and Race)
  - 1951: Kidd Group discovered (Race)

Blood Groups: Why?

Blood Groups don't just exist to make transfusion difficult!

- Blood groups are cell structures, and so perform functions essential to activity and survival.
- Not all functions are understood, but include:
  - Ion transfer (Rh group)
  - Maintaining the red cell membrane (Rh, ABO)
  - Chemokine Receptor (Duffy)
  - Enzymatic Functions (Kell)

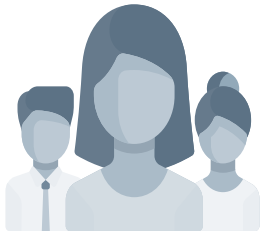
This is one of the reasons why we can can't just "manufacture" safe blood!

Why are blood groups clinically significant?

- The immune system protects the body by targeting non-self/foreign cells.
  - Foreign cells express different **antigens.**
  - Many Blood Group Antigens trigger the immune system.
  - This process is known as **alloimmunisation**.

- Repeated exposure results in a stronger response and more rapid destruction.
- Associated with clinical morbidity and mortality.

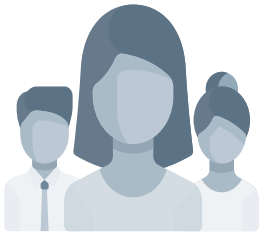
Haemolytic Transfusion Reactions (HTR)

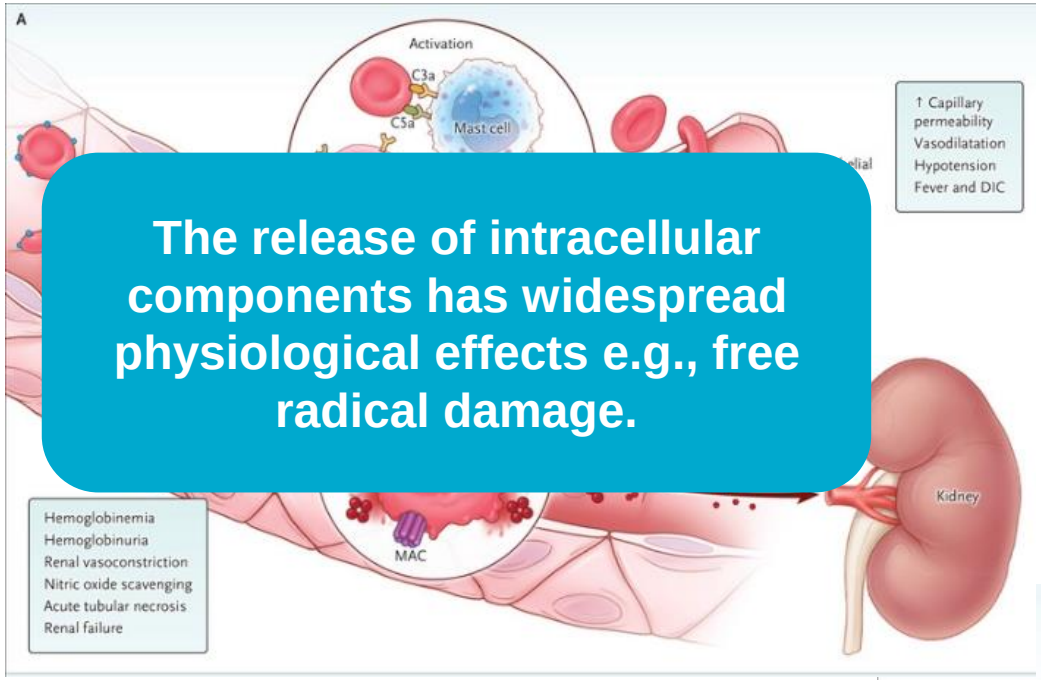


- HTRs occur when recipient allo-antibodies interact with the donor red cells.
- There are two types of HTR, delayed and acute.
  - Both result in destruction of transfused cells.

Feature	Acute	Delayed
Time of Onset	<24 hours.	>24 hours
Haemolysis Type	Intravascular	Extravascular
Implicated Groups	**ABO**, Duffy, Kell	All other groups e.g., Rh
Clinical Features	AKI, pain, fever, severe anxiety	Refractory anaemia, jaundice
Severity	High risk of mortality.	**Typically,** non-fatal.

Haemolytic Transfusion Reactions (HTR)

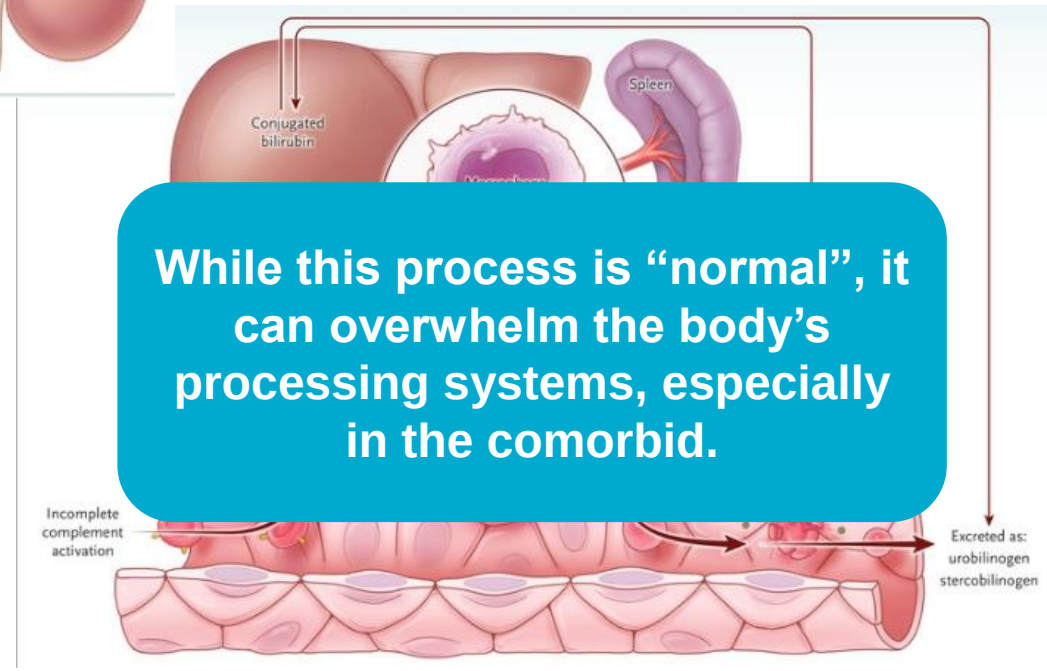




The release of intracellular components has widespread physiological effects e.g., free radical damage.

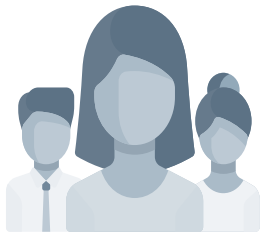
Intravascular Haemolysis: Red cells break down in blood vessels. This is not part of the body's normal red cell processing.

Extravascular Haemolysis: Red cells break down in the liver/spleen using the body's normal systems.

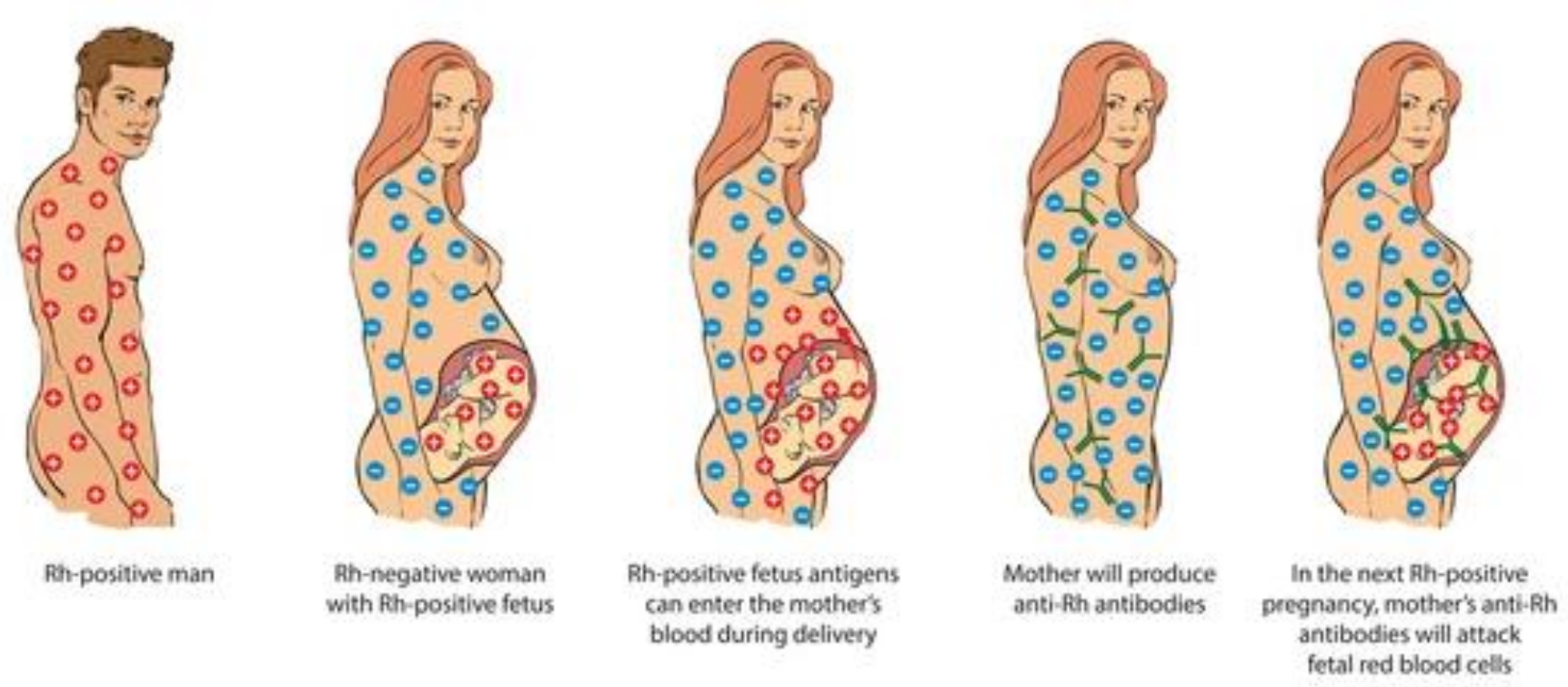


While this process is "normal", it can overwhelm the body's processing systems, especially in the comorbid.

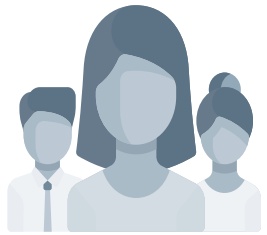
Haemolytic Disease of the Foetus and New-born (HDFN)



- HDFN is a significant complication of pregnancy.
  - It can result in foetal anaemia, abnormal development and pregnancy loss.



Haemolytic Disease of the Foetus and New-born (HDFN)



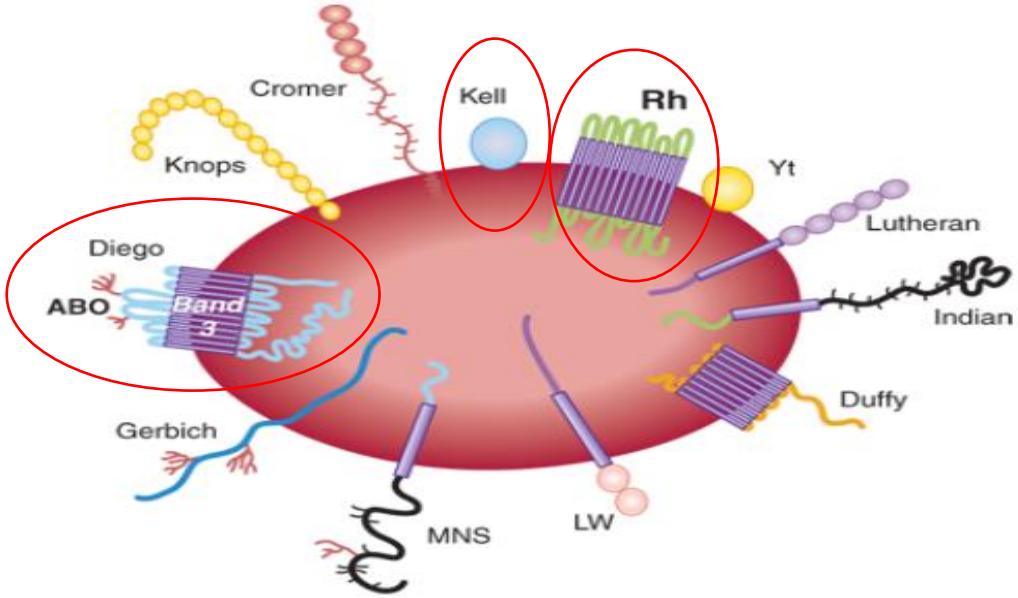
- Not ALL antibodies result in HDFN.
  - The antibody must be able to cross the placenta.
- HDFN can occur because of historical transfusions!
- “High Risk” Antibodies:
  - Anti-D
  - Anti-c
  - Anti-K
- Management includes:
  - Monitoring antibody levels
  - Intrauterine transfusions
  - Neonatal Exchange Transfusions

Prophylactic Anti-D protects patients from this.

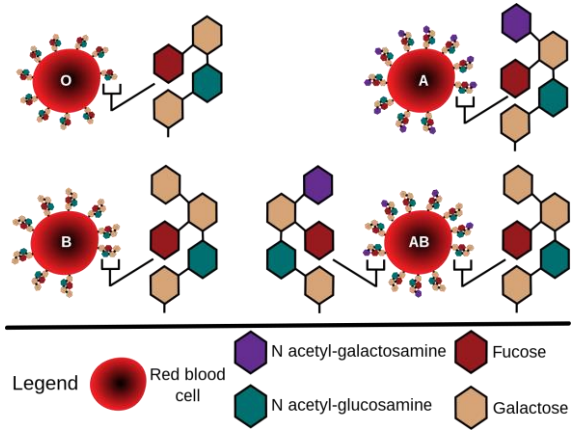
We don’t have any prophylaxis for these- but they can be as severe as Anti-D.

Part 1: Essential Blood Groups.

- These are the group you MUST understand.
  - These will cause severe, clinically significant reactions.
  - You're probably already familiar!
- This section will cover:
  - ABO (A, B, O)
  - Rh (D, C/c, E/e)
  - Kell (K, k)



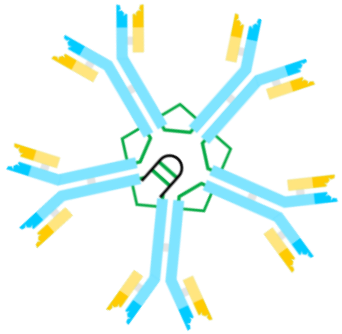
ABO



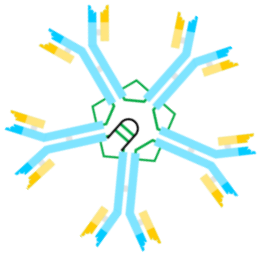
- ABO is the most well-known blood group system.
  - It's also the most important!
- ABO is a carbohydrate structure.
  - Group is determined by the "terminal carbohydrate."
- The gene is found on chromosome 9 (9q34).
  - Patients inherit 1 allele from each parent.

		Maternal Allele		
		A	B	O
Paternal Allele	A	AA: **Group A**	AB: **Group AB**	AO: **Group A**
	B	AB: **Group AB**	BB: **Group B**	BO: **Group B**
	O	OA: **Group A**	OB: **Group B**	OO: **Group O**

ABO: Why is it special?



Innate Immunity!



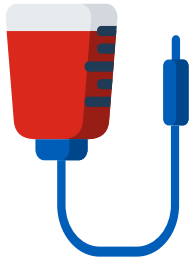
From 4 months of age patients have detectable ABO antibodies.

ABO antigens are **carbohydrates** so the immune system is exposed to them in the environment.

IgM antibodies can activate primary immune processes e.g., complement, to destroy cells intravascularly.

Portsmouth Hospitals University NHS Trust

ABO: Who gets what?



	Patient Group			
	A	B	AB	O
Antigen	A	B	AB	O
Antibody	Anti-B	Anti-A	None	Anti-A and Anti-B

		RECIPIENT GROUP			
DONOR GROUP		A	B	AB	O
Red Cells	A			AB is the universal Red Cell **Receiver**	
	B				
	AB				
	O	O is the universal red cell **Donor**			
Plasma	A				O is the universal Plasma **Receiver**
	B				
	AB	AB is the universal plasma **Donor**			
	O				

ABO: Clinical Significance

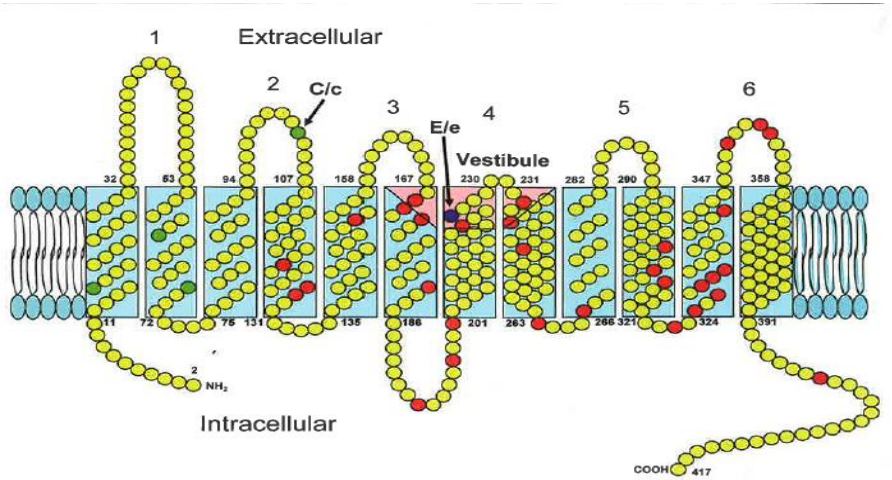
- ABO Incompatible Red Cell Transfusions can be FATAL.
  - The UK Department of Health classifies it as a **never-**
- T
  l
- L
  haemolysis.
  - DONATION IgM attaches to the RECIPIENT red cells and destroys them intravascularly.

ells

Transfusion with >50ml of blood (units are typically ~250-300ml) results in an HTR in >50% of patients, and death in 17% of cases. (*Namikawa et al. 2018*)

Rh Group

- The Rh Blood System group contains 49 antigens!
  - D, C, c, E and e are the most important.
  - Others: f, C^w, C^x etc.
  - Antigens are extracellular parts of a large transmembrane protein.
- Rh-associated glycoprotein (RhAg) protein is the base.
  - Rh-null patients have no RhAg and lack all Rh antigens.
    - Golden Blood!



Rh: Inheritance

- The Rh group is determined by multiple genes, including: ***RHD, RHCE***, *RHAG, RHCG* and *RHBG*.
  - **RHCE** codes for: C, c, E, e
    - RhC/c and RhE/e are two antigens but they're coded by the same gene.
  - **RHD** codes for: D.
    - There is NO antithetical for D.
  - Others genes are associated with the base protein.
- RHCE and RHD are inherited together (haplotype).
  - To keep track, labs use nomenclature.

Rh: Inheritance

Weiner	Fisher-Race	Antigens
R0	Dce	D, c, e
R1	DCe	D, C, e
R2	DcE	D, c, E
RZ	DCE	D, C, E
r	dce	c, e
r’	dCe	C, e
r”	dcE	c, E
ry	dCE	C, E

Historically, population frequencies, could be used to predict the risk of a foetus being incompatible with the pregnant person. **Now we use genetic analysis.**

Example: Parent Phenotypes		**Maternal: D- C+ c+ E- e+**	
		r dce	r’ dCe
Paternal: D+ C- c+ E+ e+	R2 DcE	DcE/dce	DcE/dCe
	r dce	dce/dce	dce/dCe

These foetuses would be RhD+

These foetuses would be RhD-

The other option is R0 (Dce), but this is uncommon in Caucasians.

RhD

- RhD is the second most important antigen after A and B
  - It's highly antigenic.
    - Because it's a **unique protein**.
  - **Exposure = alloimmunisation**
- RhD varies across populations
  - Caucasian population 85% Rh D Positive.
  - Asians/Native American 99% Rh D Positive.
  - Important when considering HDFN risks.

Rh Antibodies

- Rh Antibodies occur **only** after exposure to cells expressing antigens the recipient is lacking.
  - No innate antibodies here!
  - Rh is a protein so antibodies are IgG and can cross
- Variable antigenicity:
  - **Most antigenic c > E > C > e Least Antigenic**
- Antibodies to the Rh antigens can result in delayed HTRs.
- The main Rh antigens are all implicated in HDFN.

Patients of childbearing age and those requiring chronic transfusions should be matched for their Rh group where possible to reduce later complications.

Kell System

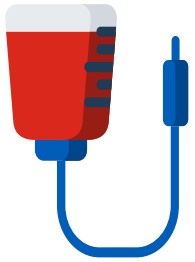
- 39 antigens.
- Only a couple are clinically significant.
  - **K/k**
  - Kpa/Kpb
  - Jsa/Jsb

	K/k	Kp^a / Kp^b	Js^a /Js^b
Phenotypes	**K-k+** • 91% Caucasians • 98% Black	**Kp (a-b+)** • 97.7% Caucasians • 100% Black	**Js (a-b+)** • 100% Caucasians • 80% Black
	K+k- • 0.2% Caucasians • Rare in Blacks		**Js (a+ b-)** • <1% Caucasians • 20% Blacks
	K+k+ • 8.8% Caucasians • 2% Blacks		

Kell: Clinical Significance.

- Anti-K
  - **IgG antibody**: Delayed HTRs.
  - Anti-K is associated with **severe** HDFN.
    - Anti-K can supress the production of foetal red cells.
    - Destroys erythroblasts in the foetal liver.
    - **There is no current prophylaxis.**
- Anti-k very rare!
  - But very hard to manage – as >99% of humans are k+.
- Other antibodies can cause delayed HTRs and mild HDFN.

Part 1: How can we protect patients?

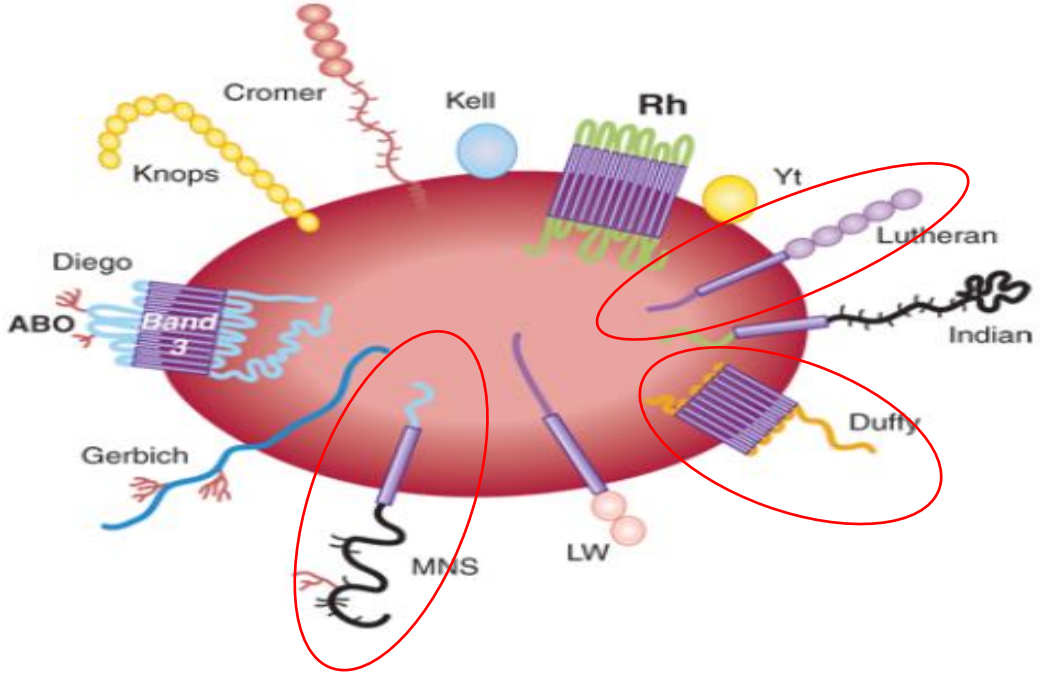


	Blood Group System			
	ABO	RhD	RhCE	Kell
Sampling	2 separate samples are required for fully matched units (WBIT protection)		N/A	
Testing	ABO/RhD results must agree across both samples. All anomalies resolved.		High risk patients are phenotyped for Rh/K.	
Component Selection	ABO compatible or HT- plasma products.	RhD matched.	Blood selected for high-risk patients should match their phenotype.	
Emergency Situations.	Group O **ONLY.**	**ONEG** if childbearing potential. **OPOS** if not.	**OPOS**: C+/c- E-/e+ **ONEG**: C-/c+ E-/e+	K-

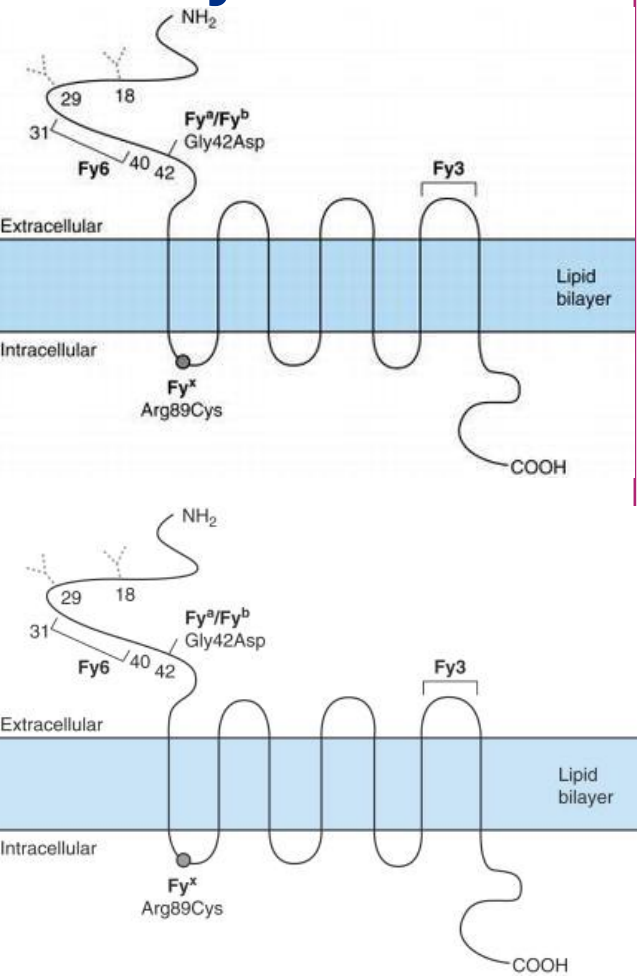
Emergency Units aren't always safe- If in doubt, ask the Lab!

Part 2: Important Blood Groups.

- These blood groups:
  - Often result in antibodies.
  - Can be clinically significant.
- This section includes:
  - Duffy
  - Kidd
  - Lutheran
  - MNS

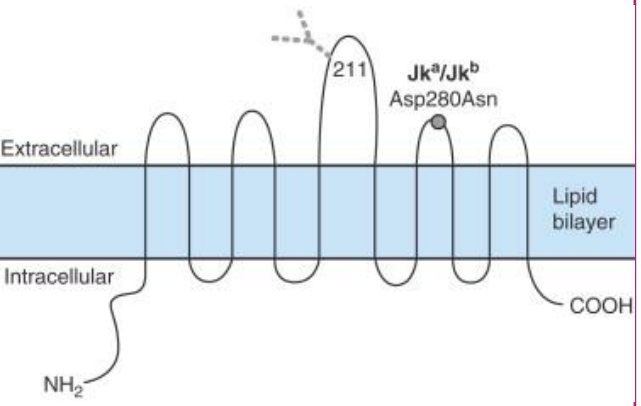


Duffy and MNS



	Duffy	MNS
Antigens	• 6 Antigens Known • Fya and Fyb are the most important. • Codominant Expression	• 50 glycoprotein antigens! • M, N, S, s, are the most important. • M/N are antithetical • S/s are antithetical.
Antibodies	IgG	IgM and IgG
Significance	• Moderately severe delayed HTRs. • Mild HDFN. • Black patients are at high risk of antibody development as many are Fya and Fyb negative.	• Anti-M and N are often cold IgM, and not significant. • Anti-M and N can cause HDFN, but it's very rare! • Anti-S and s are IgG and cause HDFN and HTRs.

Kidd and Lutheran

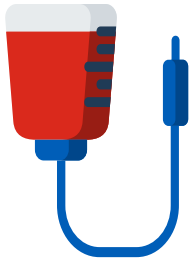


	Kidd	Lutheran

Antigens	• 3 antigens.
	  • Jka, Jkb and Jk3
	  • Jka/Jkb are codominant
		• 19 antigens with 4 pairs of antithetical antigens.
		• Lu(a)/Lu(b) are the pair of interest and are codominant.

Antibodies	IgG	IgG
Significance	• Severe and fatal delayed HTRs. • Antibodies can fall to low or undetectable levels. • Typically, mild HDFN.	• Mild HTRs. • Mild HDFN treated with phototherapy.

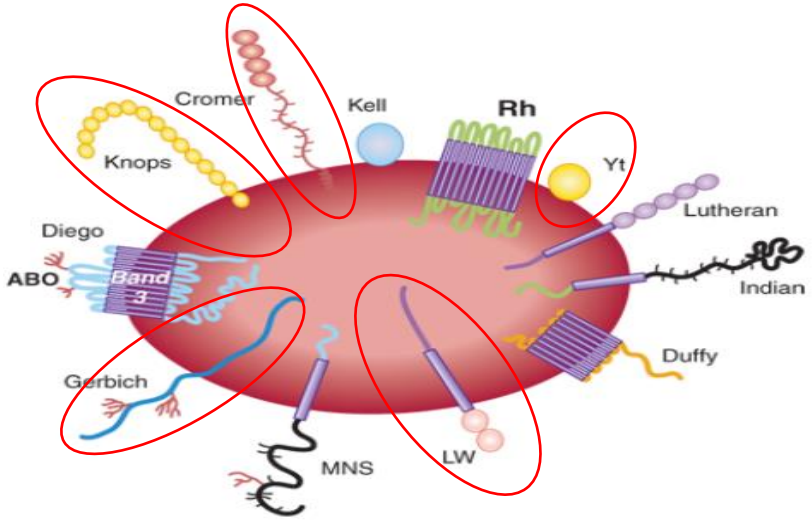
Part 2: How do we protect patients?



- If a patient is identified with a significant antibody, they MUST receive antigen negative units.
  - Even if the antibody is no longer detected.
  - Exceptions are made in emergencies.
- Patients with antibodies are at risk of developing more.
  - Future transfusions are Rh/K phenotyped where possible.
  - More antibodies = Harder to Match for!
- Pregnant patients need close monitoring.
  - Antibody titre monitoring.
  - Antenatal testing e.g., Middle Cerebral Artery Doppler.

Part 3: The Groups that Confuse the Lab!

- There are 300 blood group antigens!
  - Not all are clinically significant or result in antibodies .
- But they can complicate transfusions.
  - They can be non-specific or pan-reactive.
- The Lab may not know what the antibody is.
- The Lab may not be able to crossmatch in house!



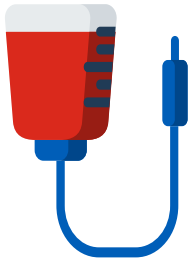
High Frequency Antigens

- Antigens which appear on 99% of the population.
  - Your patient is the 1%!
- Antigens include:
  - Vel
  - k
  - Yt^a
  - Ch^a
  - Rg^a
- Antibodies are often described as “pan-reactive.”
- Clinical significance varies.
  - Some can cause mild HDFN (k and Vel) and mild HTRs.
  - Most will make crossmatching difficult.

Low Frequency Antigens

- Antigens which appear on only 1% of the population.
  - Your patient was (unluckily) transfused with a unit from one of these donors.
- Antigens include
  - C^w
  - Wr^a
  - Kp^a
  - Js^a
- Antibodies are often described as “non-specific.”
- Antibodies typically aren’t clinically significant.
  - Low frequency Rh e.g., C^w have been associated with significant HDFN.

Part 3: How do we protect patients?

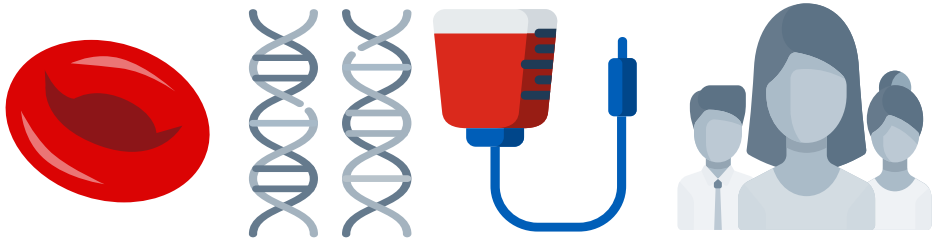


- Depends on the pattern of reactions.
- Any antibody positive patients are manually crossmatched.
  - Units will NOT be issued if patient plasma reacts with cells.
    - Exceptions made in emergencies.
- Non-specific Reactions (low frequency antigens)
  - Empirical crossmatch (selecting “best match” units)
- Pan-reactive Reactions (high frequency antigens)
  - Send to referral laboratory.
    - This will delay access of “safe” blood for at least 12 hours, usually 24-hour TAT.

The End!

Thank you for listening.

Any Questions?



Working together To drive excellence in care for our patients and communities