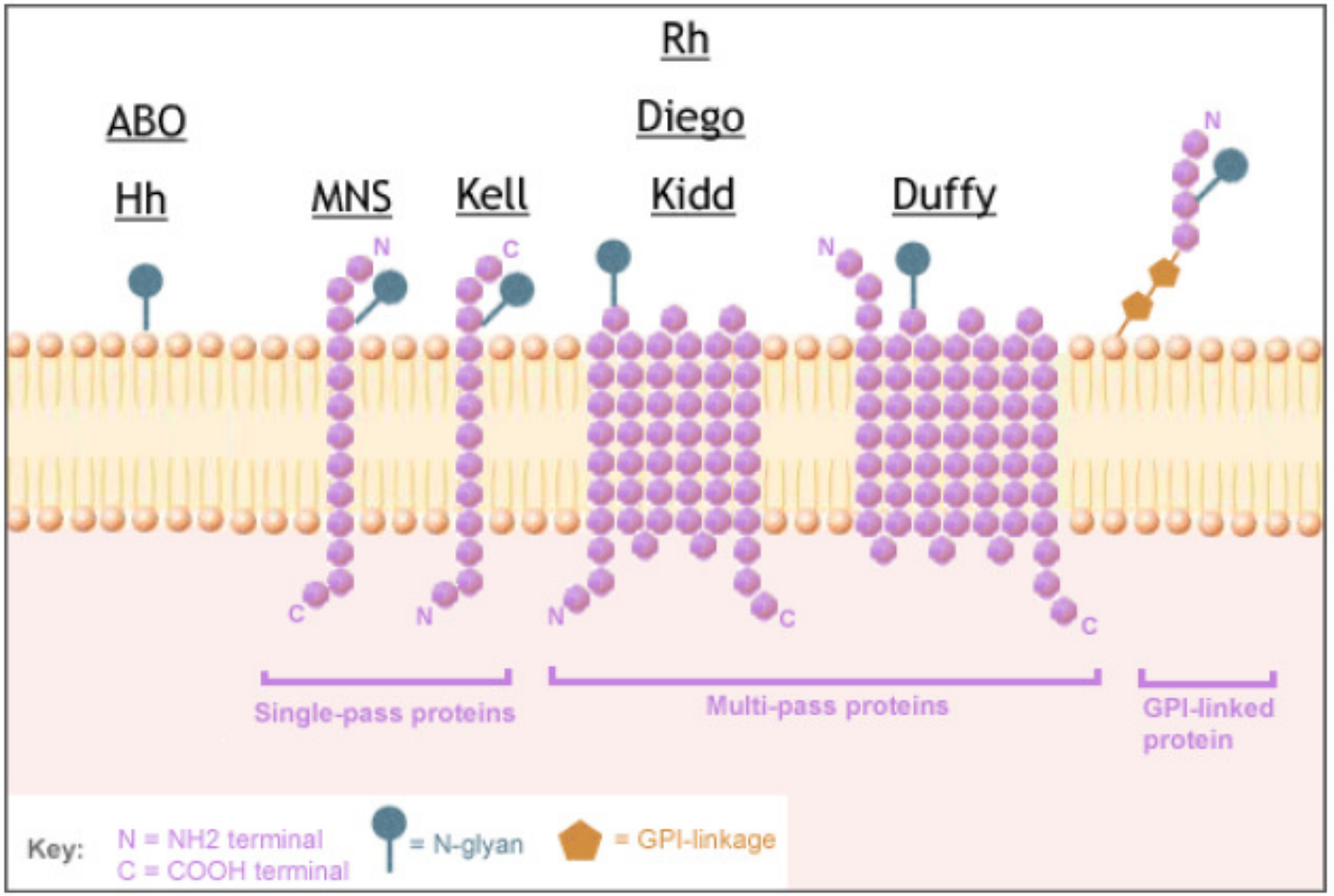
Other Blood group systems

Blood group systems



Dean, L (2005)

Blood Group systems

- Blood group systems can be divided into:

1- ***Carbohydrate based systems*** such as Lewis, P and Ii (ABO system also belong to this group of blood systems)

2- ***Protein based systems*** such as Kidd, Kell, Duffy, Lutheran and MNS (Rh system also belong to this group of blood systems)

- 29 different blood group systems are known (9 are major blood groups).

Major blood group systems

Table 6·1 Major blood group systems (9 of 29)

ISBT No	Blood group system name	Major antigens	Chromosome location no.
001	ABO	A, B, A_1B, A_1	9
002	MNS	M, N, S, s, U	4
003	P	P_1	22
004	Rh	D, C, E, c, e	1
005	Lutheran	Lu^a, Lu^b	19
006	Kell	K, k, Kp^a, Kp^b, Js^a, Js^b	7
007	Lewis	Le^a, Le^b	19
008	Duffy	Fy^a, Fy^b, Fy3	1
009	Kidd	Jk^a, Jk^b, Jk3	18

Carbohydrate antigens

- Lewis System
- P system
- Ii system

Common among all of these systems is that their genes encode for transferase enzymes that attach sugars to oligosaccharides precursor chains

Lewis system

- Two major antigens: Le^a and Le^b
- They are not true red cell antigens
- Lewis antigens are synthesized in secretary tissue, such as gut epithelium, and released into the plasma as soluble glycolipids
- They are then adsorbed onto the red cell surface from the plasma
- This binding is reversible (i.e. Lewis antigens may disappear from the red cell surface)
- These antigens may be lost from the red cell surface of stored red cells
- therefore, you always need to use fresh red cells when you want to detect Lewis antigens or anti-Lewis antibodies

Lewis antigens

- Lewis antigens show variable expression from individual to individual (pregnant women often type as Le(a-b-))
- They are also unstable on storage
- They develop only during the first 12-15 months after birth
- Presence of the Le^b antigen is associated with the development of peptic ulcers and stomach cancer
- This is thought to to be due to the fact that the Le^b antigen, expressed on the cells of the mucosal surface of the stomach act as receptor for *Helicobacter pylori*

Lewis antibodies

- anti-Le^a and anti-Le^b are often type IgM naturally occurring antibodies (developed by type Le(a-b-) individuals)
- They generally react best at temperatures below 37°C
- anti-Le^a and anti-Le^b are usually not clinically signficant and therefore it is not usually necessary to provide antigen negative blood to someone who does not express Lewis antigens
- Lewis antibodies do not cause HDFN as fetal and newborn red cells lack Le^a and Le^b antigens

P system

- The most important antigen in this system is P_1
- The frequency of $P_1$is 79% in white population and 93% in the black population
- It shows variable expression between individuals from weak to very strong
- This antigen is not fully expressed on fetal and new natal red cells
- P system antigens have been found on urinary tract epithelium where it may act as a receptor for microorganisms such as *Escherichia coli* and so play a role in the pathogenesis of urinary tract infections

P_1 antibody characteristics

- Usually a type IgM antibody. Commonly encountered as a cold agglutinin but occasionally reacts at 37°C
- Some rare examples may bind complement, and in this case it may cause transfusion reactions
- Anti-P_1 antibodies are generally not considered clinically significant and its not usually necessary to select antigen negative blood
- This antibody has not been reported to cause HDFN

I system

- Two antigens: I and i
- Both are high-frequency antigens (i.e. most people express them)
- Their expression is inversely proportional
- Fetal and neonatal red cells express the i antigen with little I antigen. However, during the first 18 months of life, the expression of i slowly decreases and the expression of I increase
- This is because at 18 months an enzyme is produced that converts i antigen into I antigen
- Therefore, most adult red cells express large amounts of I antigen and very little amounts of i antigen
- Thus normal adult red cells are positive for I antigen (I+) and neonatal red cells are positive for i antigen (i+)

I antibodies

- Anti-I antibodies are usually type IgM antibodies that occur frequently as cold reacting antibodies
- They are usually not clinically significant
- Sometimes they exist as autoantibodies and cause autoimmune disease
- Anti-I antibodies have not been implicated in HDFN disease

Protein antigens

- MNS system
- Lutheran system
- Kell system
- Duffy system
- Kidd system

MNS system

- There are 43 antigens in this system, the most important are M, N, S, and s
- The MN antigens are situated on glycophorin A (GPA) and the Ss antigens on glycophorin B (GPB)
- There are two amino acid differences between M and N on glycophorin A and a single amino acid difference between S and s on glycophorin B
- They are well developed on the red cells at birth

Antibody characteristics

- Anti-M and anti-N are usually cold agglutinins (react mainly at low temperatures, so not important physiologically). Those antibodies very rarely cause transfusion reactions
- Anti-S and anti-s, in contrast, are considered **clinically significant** and can cause transfusion reactions and therefore antigen **negative blood should be selected**
- Anti-S and anti-s may also cause severe HDFN

Antigens of the MNS blood group

Number of antigens	**42: including M, N, S, and s**
Antigen specificity	**Protein** Amino acid sequence determines the specificity of MNS antigens
Antigen-carrying molecules	**Glycophorins** Glycophorins are transmembrane, single-pass glycoproteins that contain carbohydrate, mostly in the form of sialic acid. Glycophorins A and B carry the MNS antigens, and they may also serve as receptors for cytokines and pathogens, including the malaria parasite, *Plasmodium falciparum*.
Molecular basis	**Two genes encode the MNS antigens, GYPA and GYPB.** Both genes are located on chromosome 4 (4q28.2-q13.1). A third gene, GYPE, may be involved in the creation of variant MNS antigens. GYPA has two codominant alleles, M and N, which result from three SNPs (59C→T, 71G→A, 72G→T), and the corresponding M and N antigens differ by two amino acids (S1L, G5E). The codominant alleles of GYPB, C and c, result from one SNP (143C→T), and the corresponding S and s antigens differ by a single amino acid (T29M).
Frequency of MNS antigens (%)	**M**: 78% Caucasians, 74% Blacks **N**: 72% Caucasians, 75% Blacks **S**: 55% Caucasians, 31% Blacks **s**: 89% Caucasians, 93% Blacks (1)
Frequency of MNS phenotypes (%)	**M+N+S-s+**: 22% Caucasians, **33% Blacks** **M+N+S+s+: 24% Caucasians,** 13% Blacks **M-N+S-s+**: 15% Caucasians, 19% Blacks **M+N-S+s+**: 14% Caucasians, 7% Blacks **M+N-S-s+**: 8% Caucasians, 16% Blacks **M-N+S+s+**: 6% Caucasians, 5% Blacks **M+N-S+s**: 6% Caucasians, 2% Blacks Less common phenotypes are M+N+S+s- (4% Caucasians, 2% Blacks) and M-N+S+s- (1% Caucasians, 2% Blacks). The phenotypes M+N-S-s-, M+N+S-s-, and M-N+S-s- are rare in Caucasians but are found in ~0.5% of Blacks (1).

Antibodies produced against MNS antigens

Antibody type	**IgG and IgM** The Ig class depends upon which antigen is targeted.
Transfusion reaction	**Uncommon but potentially severe** Anti-S and anti-s are among the MNS antibodies implicated in causing transfusion reactions.
Hemolytic disease of the newborn	**Uncommon but potentially severe** Anti-S is more common that anti-s, but both are capable of causing severe-to-fatal HDN (2).

Lutheran system

- Two major antigens: Lu^a and Lu^b
- They are poorly developed at birth and poorly immunogenic
- Lu^b is a *high* frequency antigen whereas Lu^a is a *low* frequency antigen
- Antibodies against both of these antigens have been reported to cause mild or delayed transfusion reactions, but have not been reported to cause HDFN because both antigens are not well developed at birth

Kell system

Antigens of the Kell blood group

Number of antigens	28 The K antigen is one of the most clinically significant Kell antigens.
Antigen specificity	**Protein** Amino acid sequence determines the specificity of Kell antigens
Antigen-carrying molecules	**Glycoprotein with enzymatic function** The Kell glycoprotein is a transmembrane, single-pass protein that carries the Kell antigens. It is an endothelin-3-converting enzyme; it cleaves "big" endothelin-3 to produce an active form that is a potent vasoconstrictor (1).
Molecular basis	**The KEL gene encodes the Kell antigens.** KEL is highly polymorphic. It has two major codominant alleles, k and K, which result from a SNP (698C→T), and the corresponding k and K antigens differ by a single amino acid change (T193M).
Frequency of Kell antigens	**~100%:** k, Kp^b, Ku, Js^b, K11, K12, K13, K14, K18, K19, Km, K22, K26, K27 **K antigen: 2%** in Blacks, **9%** in Caucasians, up to **25%** in Arabs **~2%:** Kp^a, $U1^a$ **~0.01%:** Js^a (0.01% in Caucasians, 20% in Blacks), Kp^c, K23 Others: K17 (~0.3%), K24 (rare), VLAN (rare), K16 (unknown) (2)
Frequency of Kell phenotypes	**K-k+** in 91% Caucasians and 98% Blacks **K+k-** in 0.2% Caucasians and is rare in Blacks **K+k+** in 8.8% Caucasians and 2% Blacks **Kp (a-b+)** in 97.7% Caucasians and 100% Blacks **Js (a-b+)** in 100% Caucasians and 80% Blacks (2)

Anti Kell antibodies

Antibodies produced against Kell antigens	
Antibody type	**IgG** IgM is uncommon
Antibody reactivity	**Does not bind complement** If hemolysis does occur, it is extravascular in nature.
Transfusion reaction	**Can cause a severe hemolytic transfusion reaction** Anti-K and anti-Ku are capable of causing a severe reaction. A milder reaction is caused by anti-k, anti-Kp^a, anti-Kp^b, anti-Js^a, and anti-Js^b.
Hemolytic disease of the newborn	**Can cause severe fetal anemia** Kell isoimmunization is the third most common cause of HDN after Rh and ABO. Anti-Kell causes severe fetal anemia by suppressing fetal RBC synthesis (3, 4).

Clinical significance of Kell system

Clinical significance of Kell antibodies

- The K antigen is the most immunogenic antigen after the antigens of the ABO and Rh blood group systems.

Transfusion reactions

- Anti-Kell antibodies are usually of the antibody class IgG (IgM is far less common). The antibodies that have been implicated in causing transfusion reactions, include, anti-K, anti-k, anti-Kpa, and anti-Jsb.

- The production of anti-Ku in patients with Ko has resulted in a fatal hemolytic transfusion reaction.

Hemolytic disease of the newborn

- Anti-Kell is an important cause of HDN.
- It tends to occur in mothers who have had several blood transfusions in the past, but it may also occur in mothers who have been sensitized to the Kell antigen during previous pregnancies.

Kell system

- There are 28 antigens in or associated with this system
- The most important are: K and k, Kp^a and Kp^b and Js^a and Js^b
- K antigen is the mot immunogenic antigen outside the ABO and Rh systems
- The K antigen is a low frequency antigen
- Kell system antigens are well developed at birth

Frequncy of K and k antigens

Phenotype	White	Black
K+k-	0·2	< 0·1
K+k+	8·8	3·5
K-k+	91·0	96·5

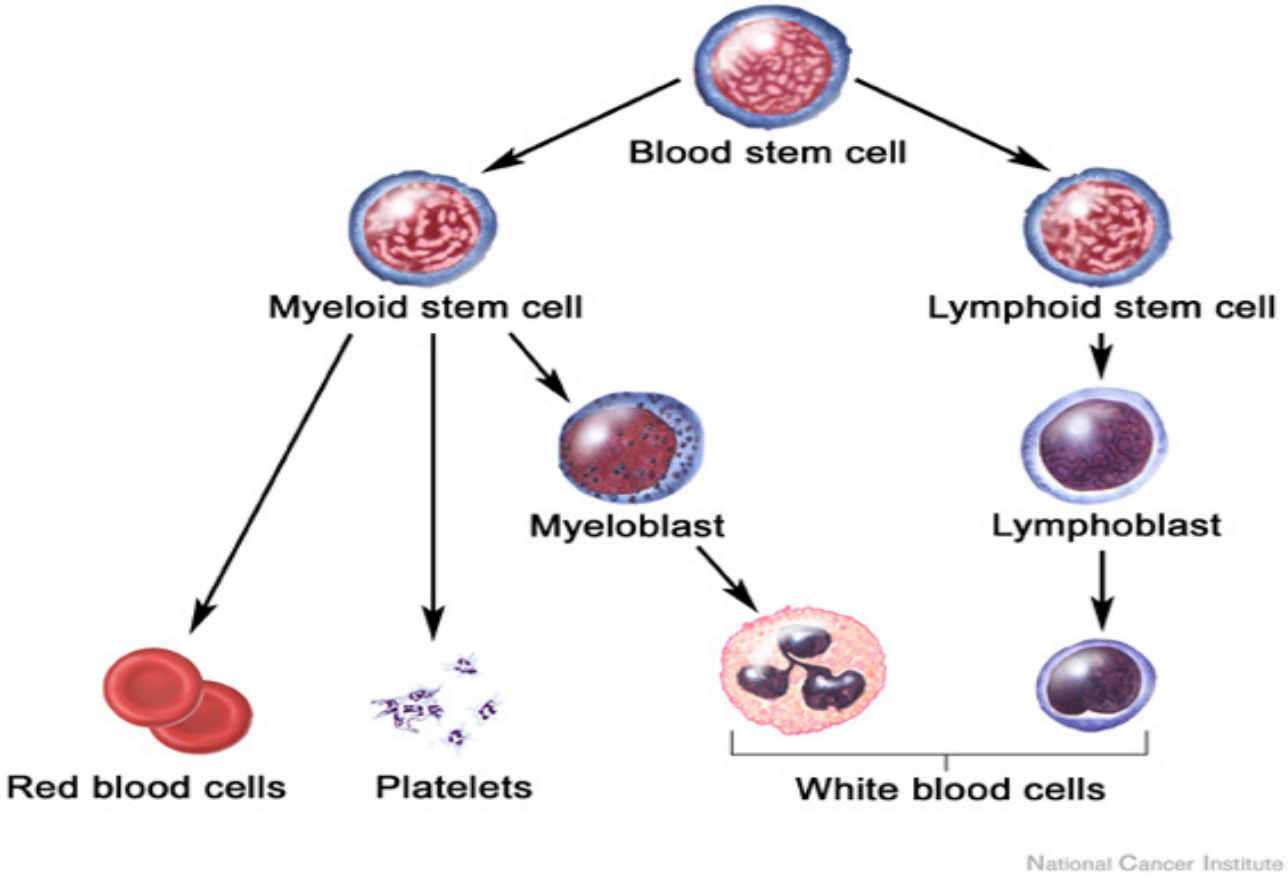
Antibody characteristics

- Anti-K and anti-k are usually type IgG antibodies
- Usually are immune antibodies (require previous exposure). But in rare conditions may exist as naturally occuring
- If a patient develops anti-k it will be difficult to provide compatible blood because of the low frequency of k- blood
- Anti-K and anti-k are clinically significant antibodies (can cause severe haemolytic transfusion reactions)
- K- or k- blood should be provided to patients with anti-K or anti-k antibodies, respectively.
- In patients requiring long term transfusion therapy, units matched for K should be provided
- Generally antibodies to the Kell system are usually of clinical significance and may cause severe or delayed transfusion reactions.
- If a patient has an antibody to a high frequency antigen in the Kell system it may be necessary to provide antigen negative blood from a rare donor registry

Anti-K antibodies and HDFN

- Anti-K antibodies differ from other blood group system antibodies that cause HDFN as the antibodies appear to destroy precursor red cells, causing severe anaemia

Kell antibodies and HDFN



Duffy system

- Contain six antigens, the most important are Fy^a and Fy^b
- Those two antigens are inherited by two co-dominat genes
- The minus/minus phenotype, Fy(a-b-), which lacks the Fy protein, occurs in individuals homozygous for the silent gene *Fy*
- Fy(a-b-) is very rare in white populations but occurs in 68% of black populations
- The Duffy antigens are interesting because they are the site of of attachment to the red cell for the malarial parasites *Plasmodium vivax* and *P. knowlesi*
- Those who are Fy(a-b-) have an advantage over those who have the antigens because they are resistant to invasion by these two parasites (important when living in malarial areas)

Duffy system

- The Duffy antigens are moderately immunogenic and are well developed at birth
- Anti-Fy^a and anti-Fy^b are type IgG (stimulated by transfusion or pregnancy)
- These antibodies are capable of causing severe transfusion reactions and HDFN

Kidd system

- The Kidd blood group antigens are expressed on a red cell transmembrane glycoprotein which transports urea across the red cells membrane
- The two important antigens are: Jk^a and Jk^b
- The frequency of the Kidd blood groups system antigens varies between different populations
- Kidd antigens are well developed in the newborn

Kidd antibodies

- Antibodies are type IgG that can activate complement (stimulated by transfusion or pregnancy)
- They can cause severe haemolytic transfusion reactions. When the antibodies are present, antigen negative should be provided
- However, they rarely cause HDFN

Notes

- It is important to be aware of the other blood group systems
- These antibodies detected in patients who were given ABO and Rh compatible blood is due to antigens that belong to those other blood system
- It is important to know what antibodies are clinically significant and what are not as this knowledge helps in issuing the right blood
- Also its important to know the frequency of antigens in the population

Reference for RBC groups