Blood Group Antigens: principles and practice

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3-95
References

1. NATHAN AND OSKI’S HEMATOLOGY AND ONCOLOGY OF INFANCY AND CHILDHOOD, 8th ed., 2015

2. Christopher D. Hillyer, et al., Handbook of PEDIATRIC TRANSFUSION MEDICINE, 2004

3. Rossi’s Principles of Transfusion Medicine, 5th ed., 2015
• More than 250 Ags

• Erythrocyte antigens are polymorphic inherited structural characteristics located on proteins, glycoproteins, or glycolipids on the **outside surface of the RBC membrane**.

• Erythrocyte antigens are clinically important in the **immune destruction of RBCs** in allogeneic blood transfusions, maternal-fetal blood group incompatibility, autoimmune hemolytic anemia, and organ transplantation
<table>
<thead>
<tr>
<th>Blood Group System</th>
<th>Gene Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrate Antigens</strong></td>
<td></td>
</tr>
<tr>
<td>ABO</td>
<td>Glycosyltransferase</td>
</tr>
<tr>
<td>P</td>
<td>Glycosyltransferase</td>
</tr>
<tr>
<td>Lewis</td>
<td>Glycosyltransferase</td>
</tr>
<tr>
<td>Hh</td>
<td>Glycosyltransferase</td>
</tr>
<tr>
<td><strong>Protein Antigens</strong></td>
<td></td>
</tr>
<tr>
<td>MNS</td>
<td>Glycophorin A, glycophorin B</td>
</tr>
<tr>
<td>Rh</td>
<td>D polypeptide</td>
</tr>
<tr>
<td></td>
<td>RHCE polypeptide</td>
</tr>
<tr>
<td></td>
<td>CcEe polypeptide</td>
</tr>
<tr>
<td>Lutheran</td>
<td>Lutheran glycoprotein</td>
</tr>
<tr>
<td>Kell</td>
<td>Kell glycoprotein</td>
</tr>
<tr>
<td>Kx</td>
<td>Xk glycoprotein</td>
</tr>
<tr>
<td>Duffy</td>
<td>Fy glycoprotein</td>
</tr>
<tr>
<td>Kidd</td>
<td>Jk glycoprotein</td>
</tr>
<tr>
<td>Diego</td>
<td>Band 3 (AE1)</td>
</tr>
<tr>
<td>Yt</td>
<td>Acetylcholinesterase</td>
</tr>
<tr>
<td>Xg</td>
<td>Xg* glycoprotein</td>
</tr>
<tr>
<td>Scianna</td>
<td>Sc glycoprotein</td>
</tr>
<tr>
<td>Dombrock</td>
<td>Glycoprotein (possibly adenosine 5'-diphosphate[ADP]-ribosyltransferase)</td>
</tr>
<tr>
<td>Colton</td>
<td>Channel-forming integral protein</td>
</tr>
<tr>
<td>LW</td>
<td>Glycoprotein</td>
</tr>
<tr>
<td>Chido/Rodgers</td>
<td>C' component 4 (C4)</td>
</tr>
<tr>
<td>Gerbich</td>
<td>Glycophorin C, glycophorin D</td>
</tr>
<tr>
<td>Cromer</td>
<td>CD55 (DAF)</td>
</tr>
<tr>
<td>Knops</td>
<td>CD35 (CRI)</td>
</tr>
<tr>
<td>Indian</td>
<td>CD44</td>
</tr>
</tbody>
</table>
مرکز تحقیقات بیماری‌های فونی مادرزادی کودکان
Carbohydrate blood groups

- ABO
- LEWIS
- P
- Hh
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Structure</th>
<th>Minimal determinant structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td><img src="image" alt="Structure H" /></td>
<td>Fuc-α1→2-Gal-β1-R</td>
</tr>
<tr>
<td>h</td>
<td><img src="image" alt="Structure h" /></td>
<td>Gal-β1-R</td>
</tr>
</tbody>
</table>

- **Gal**: Glucose
- **GalNAc**: N-acetylglucosamine
- **Fuc**: Fucose
- **GlNAc**: N-acetylneuraminic acid

*: residue could be glucose in case of glycolipids; yellow shade: minimal determinant or core structure; blue arrow: residue added by blood group gene product; examples of type 1 and 2 core structures are illustrated above but they can vary widely, as they can be assembled on at least six possible types of carbohydrate chains; also they can reside on a variety of protein or lipid glycan structures containing branches, repeats, etc.

### ABO Antigens & Enzymes Table

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Structure</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;O&quot; - H</td>
<td><img src="image" alt="Structure O" /></td>
<td>α-mannosidase - 2, 6-L galactosyltransferase</td>
</tr>
<tr>
<td>A</td>
<td><img src="image" alt="Structure A" /></td>
<td>α-1, 3-fucosyltransferase</td>
</tr>
<tr>
<td>B</td>
<td><img src="image" alt="Structure B" /></td>
<td>α-1, 3-galactosyltransferase</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Structure H" /></td>
<td>α-mannosidase - 2, 6-L galactosyltransferase</td>
</tr>
</tbody>
</table>
Table 13.1  Group A structures in humans

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 A</td>
<td>GalNAcα1 → 3Galβ1 → 3GlcNAc → R</td>
</tr>
<tr>
<td>A-1</td>
<td>↑ 2</td>
</tr>
<tr>
<td>Type 1, ALe b</td>
<td>GalNAcα1 → 3Galβ1 → 3GlcNAc → R</td>
</tr>
<tr>
<td>ALe b</td>
<td>↑ 2</td>
</tr>
<tr>
<td>Type 2 A</td>
<td>GalNAcα1 → 3Galβ1 → 4GlcNAc → R</td>
</tr>
<tr>
<td>A-2</td>
<td>↑ 2</td>
</tr>
<tr>
<td>Type 3 A</td>
<td>GalNAcα1 → 3Galβ1 → 3GalNAcβ1 → 3Galβ1 → R</td>
</tr>
<tr>
<td>(mucinous A)</td>
<td>↑ 2</td>
</tr>
<tr>
<td>Type 4 A</td>
<td>GalNAcα1 → 3Galβ1 → 3GalNAcβ1 → 3Galβ1 → 4Galβ1 → 4Glc → Cer</td>
</tr>
<tr>
<td>(globe-A, A1)</td>
<td>↑ 2</td>
</tr>
</tbody>
</table>

Cer, ceramide; Fuca, fucose; Gal, galactose; GalNAc, N-acetylgalactosamine; Glc, glucose; GlcNAc, N-acetylgulosamine.
<table>
<thead>
<tr>
<th>ABO Type</th>
<th>FUT1</th>
<th>ABO</th>
<th>Anti-A</th>
<th>Anti-B</th>
<th>UEA-1</th>
<th>A₁ RBC</th>
<th>B RBC</th>
<th>O RBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>A₂</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>+/0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
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<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>O</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Oₙ (Bombay)</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Inheritance of at least one functional FUT1 or ABO gene.

†Testing for H-antigen with lectin Ulex europaeus (UEA-1). Not routinely performed except to resolve ABO typing discrepancies.
• The fucosyltransferase (and thus the H antigen) is present in all persons except those with the rare Bombay (Oh) phenotype.

• The genes for the A and B blood group antigens are codominant.

• Antigens A&B are not fully developed until 2 to 4 years of age: ABO hemolytic disease of the newborn (HDN) is usually a mild disease.

• Isohemagglutinins from group A and B individuals are predominantly immunoglobulin M (IgM) that do not usually cross the placenta and cause HDN.

• However, as group O serum contains IgG isohemagglutins, ABO HDN is most frequently seen in non–group O infants of group O mothers.
Molecular basis of ABH

• Three genes control the expression of the ABO antigens:
  • \textit{ABO}, \textit{Hh}, and \textit{Se}.

• The \textit{H} gene attaches \textit{L-fucose} to the RBC membrane-anchored polypeptide
  • On red cells, platelets, and endothelium, ABH is primarily expressed on \textbf{type 2 chain} or \textbf{lactosamine} based structures.

• The secretor gene (\textit{Se}) controls the individual’s ability to secrete soluble
  • Genitourinary and gastrointestinal tissues, are rich in \textbf{type 1 chain ABH antigens}:
    depends on secretor gen \textit{FUT2}

• \textbf{The classic Bombay phenotype}: is an \textit{H}-deficient nonsecretor(\textit{hh,se/se}), with an absence of both type1 and type2 chain ABH antigens. As nonsecretors, \textbf{will also type as \textit{Le(b)}}

• \textbf{para-Bombay}: \textit{H}-deficient secretors(\textit{hh,Se/Se, or Se/se}) and retain synthesis of type1 \textit{H} antigen on mucosa and in secretions
  • Unlike Bombay cells, \textbf{para-Bombay red cells may have trace amounts of ABH antigen on red cells due to adsorption of soluble type1 ABH from plasma}

• \textbf{Acquired B phenotype}: group A patients transiently type as group B due to infection by deacetylase producing bacteria
Clinical Significance

• The antibodies of the ABO system are “naturally occurring” in that they are formed as a result of exposure to ABH-like substances from the gastrointestinal tract,

• Intravascular hemolysis due to incorrect blood transfusion

• Mild HDN; most often found in nongroup O infants of group O mothers because anti-A and anti-B from group O individuals often have a significant IgG component.
<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Caucasiens</th>
<th>African-Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40%</td>
<td>27%</td>
</tr>
<tr>
<td>B</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>AB</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>O</td>
<td>45%</td>
<td>49%</td>
</tr>
</tbody>
</table>
Lewis Antigens

- *Soluble* antigens produced by tissues and found in body fluids (plasma)
- Adsorbed on the RBC
- Le\textsubscript{a}; Le\textsubscript{b}; Lex; Ley

Lewis substance adheres to RBC becoming an antigen
<table>
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<tbody>
<tr>
<td>H</td>
<td><img src="image" alt="H Structure" /></td>
<td>Fuc-α1→2-Gal-β1-R</td>
</tr>
<tr>
<td>Le^a</td>
<td><img src="image" alt="Le^a Structure" /></td>
<td>Gal-β1→3&lt;br&gt; Fuc-α1→4&lt;br&gt;GlcNAc-β1-R</td>
</tr>
<tr>
<td>Le^b</td>
<td><img src="image" alt="Le^b Structure" /></td>
<td>Fuc-α1→2-Gal-β1→3&lt;br&gt; Fuc-α1→4&lt;br&gt;GlcNAc-β1-R</td>
</tr>
<tr>
<td>Le^x</td>
<td><img src="image" alt="Le^x Structure" /></td>
<td>Gal-β1→4&lt;br&gt;Fuc-α1→3&lt;br&gt;GlcNAc-β1-R</td>
</tr>
<tr>
<td>Le^y</td>
<td><img src="image" alt="Le^y Structure" /></td>
<td>Fuc-α1→2-Gal-β1→4&lt;br&gt;GlcNAc-β1-R&lt;br&gt;Fuc-α1→3</td>
</tr>
</tbody>
</table>

*: residue could be glucose in case of glycolipids; yellow shade: minimal determinant or core structure; blue arrow: residue added by blood group gene product; examples of type 1 and 2 core structures are illustrated above but they can vary widely, as they can be assembled on at least six possible types of carbohydrate chains; also they can reside on a variety of protein or lipid glycan structures containing branches, repeats, etc.
The Lewis System

• Le\textsubscript{a} individuals rarely make anti-Le\textsubscript{b}. Hence in most cases Lewis antibodies are made only in individuals who are Le(a\textasciitilde b\textasciitilde)

• May be detected soon after pregnancy because pregnant women may temporarily become Le(a-b-)

• Le antibodies in a patient can be neutralized by the Lewis antigens in the donor’s plasma (cancel each other out):
  • do not cause hemolysis except rarely when the antibody reacts at 37° C.
  • No HDN (usually IgM)

• Expressed on H. Pylori
The Ii Collection

i epitope

\[
\begin{array}{c}
\text{Gal} \\
\text{GlcNAc}
\end{array}
\]

\[\beta_1,4 \quad \beta_1,4 \quad \beta_1,3 \quad \beta_1,4 \]

\(n\) is the number of repeating lactosamine units - average of 6 for i antigen, and from 8-25 for I antigen. The structure is attached to glucose-ceramide in case of glycolipids or to N-linked sugars of the band 3 glycoprotein on red blood cells. The blue arrow designates the linkage added by the product of \(IGnT\).

I epitope

\[
\begin{array}{c}
\text{Gal} \\
\text{GlcNAc}
\end{array}
\]

\[\beta_1,4 \quad \beta_1,4 \quad \beta_1,6 \quad \beta_1,4 \quad \beta_1,4 \quad \beta_1,3 \]

\(n\)
I antigens

- These antigens may be I or i.
- They form on the precursor chain of RBC.
- Newborns have i antigen.
- Adults have I antigen.
- i antigen (linear) converts to I (branched) as the child matures (precursor chain is more linear at birth) at about 18 months.
li antibodies

• Auto Ab:
  • Most people have Autoanti-I (RT or 4°C)
  • Pathologic autoantibodies often react at 30°C in albumin.
  • The titer and thermal range of anti-I is often increased after infection with *Mycoplasma pneumoniae*
  • anti-i antibodies are sometimes present in *Epstein-Barr virus infection* (neither a sensitive nor a specific)

• Alloanti-I:
  • Very rare
  • Cold-reacting (RT or below) IgM antibody
  • Clinically insignificant
  • Can attach complement (no hemolysis unless it reacts at 37°C)

• Anti-I often occurs as anti-IH: This means it will react at different strengths with reagent cells (depending on the amount of H antigen on the RBC)
  • O cells would have a strong reaction
  • A cells would have a weaker reaction
Clinical Significance

- Levels of the i antigen can aid in differentiating Diamond-Blackfan anemia from transient erythroblastopenia of childhood:
  - Is enhanced on RBCs from patients with Diamond-Blackfan anemia (reflects stress hematopoiesis)
  - Is absent or of reduced strength on RBCs from children with transient erythroblastopenia of childhood (selective suppression of erythropoiesis)
  /enhanced during recovery
P Antigen

• Similar to the ABO system
• The most common phenotypes are $P_1$ and $P_2$
  • $P_1$ – consists of $P_1$ and $P$ antigens
  • $P_2$ – consists of only $P$ antigens
• Like the $A_2$ subgroup, $P_2$ groups can produce anti-$P_1$
• The $P1$ antigen expression:
  • is more strongly expressed on fetal cells than on neonatal cells
  • Adult levels are not reached until 7 years of age.
  • 75% of adults have $P_1$
  • Strength of the antigen decreases upon storage
• Found in secretions like plasma and hydatid cyst fluid
P antibodies

• Anti-\( P_1 \)
  • Naturally occurring IgM
  • Not clinically significant: (cold reacting Ab) no hemolysis; no HDN
  • Can be neutralized by hydatid cyst fluid to reveal more clinically significant antibodies

• Anti-\( P \)
  • Produced in individuals with paroxysmal cold hemoglobinuria (PCH)
  • This PCH antibody is also called the Donath-Landsteiner antibody
  • most frequently seen in children
  • This IgG autoantibody is a biphasic hemolysin that binds to RBCs in the cold and then hemolyzes them when warmed: IgG auto-anti-P attaches complement when cold (fingers, toes). As the red cells circulate, they begin to lyse (releasing Hgb)
  • This antibody should be considered when the patient has hemoglobinuria or anemia (or both) and C3 alone is present on the RBCs.
Clinical Significance

• The P antigen serves as a receptor for parvovirus B19 and pyelonephritic Escherichia coli:

• People with the rare p phenotype:
  • may produce anti-P1+P+Pk, a potent hemolytic antibody that can cause immediate hemolytic transfusion reactions; HDN; fetal death; and miscarriages during early pregnancy in women whose RBCs have the p phenotype
  • p phenotype lack the antigens P1, P, and Pk and are not susceptible to infection by parvovirus B19
Protein blood groups

• Rh system
• MNS system
• Kell system
• Duffy system
• Kidd system
• Lutheran system
Rh system

- Includes D, C, c, E, e, and 40 other antigens
- Rh Associated Glycoprotein (RHAG) is required for cell surface expression of the Rh antigens. D, C, c, E, and e antigens, encoded by at least two genes on chromosome 1.
- Only approximately 22% of D-negative patients transfused with D-positive RBCs make an anti-D antibody.
- Weak D:
  - 0.2% to 1% of white individuals
  - Fewer D Ag on RBCs
  - Safely receive D+
  - Weak D donor RBCs are labeled as D+
  - All D-negative donor blood is tested for weak D by the antiglobulin test.
- Partial D:
  - Truncated D
  - Can make Anti-D, despite of their phenotype which may be interpreted as weak D or D+
- Rh deficient syndrome (Rh Null):
  - Lack of RHAG
  - Mild spherocytic hemolytic anemia
Rh Antibodies

• Rh(D) antigen has greater immunogenicity than virtually any other RBC antigen, followed by Rh(c) and Rh(E).

• Most Rh antibodies result from exposure to human RBCs through pregnancy or transfusion.

• Are almost always IgG and do not bind complement:
  • Extravascular RBC destruction; HDN; mild to severe delayed transfusion reactions
<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Prevalence</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caucasians</td>
<td>African-Americans</td>
<td>Asians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-negative</td>
<td>15%</td>
<td>8%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-negative</td>
<td>32%</td>
<td>73%</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E-negative</td>
<td>71%</td>
<td>78%</td>
<td>61%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-negative</td>
<td>20%</td>
<td>4%</td>
<td>53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e-negative</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
<td></td>
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</tbody>
</table>

**TABLE 4.4 Rh Blood Group Phenotypes and Prevalence**

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Phenotypes</th>
<th>Prevalence</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caucasians</td>
<td>African-Americans</td>
<td>Asians</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CcDe</td>
<td>$R_1^cD_e$</td>
<td>34.9%</td>
<td>21%</td>
<td>8.5%</td>
<td></td>
</tr>
<tr>
<td>CDe</td>
<td>$R_1D_e$</td>
<td>18.5%</td>
<td>2%</td>
<td>51.8%</td>
<td></td>
</tr>
<tr>
<td>CcDee</td>
<td>$R_1D_e$</td>
<td>13.3%</td>
<td>4%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>cDe</td>
<td>$R_1^c$</td>
<td>2.1%</td>
<td>45.8%</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>cDee</td>
<td>$R_r$</td>
<td>11.8%</td>
<td>18.6%</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>cDE</td>
<td>$R_2D_e$</td>
<td>2.3%</td>
<td>0.2%</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>CDEe</td>
<td>$R_2D_e$</td>
<td>0.2%</td>
<td>Rare</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>CcDe</td>
<td>$R_3D_e$</td>
<td>0.1%</td>
<td>Rare</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>CDE</td>
<td>$R_3$</td>
<td>0.01%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>cde</td>
<td>$r$</td>
<td>15.1%</td>
<td>6.8%</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>Cce</td>
<td>$r^c$</td>
<td>0.8%</td>
<td>Rare</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>cEe</td>
<td>$r^c$</td>
<td>0.9%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>CcEe</td>
<td>$r^{cE}$</td>
<td>0.05%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

R1 = CDe
R2 = cDE
R0 = cDe
Rz = CDE
r = ce
r' = Ce
r'' = cE
MNSs Blood System

• 4 important antigens (more exist):
  • M
  • N
  • S
  • s
  • U:
    • ALWAYS present when S & s are inherited
    • U-negative cells are only found in the Black population

• M & N located on Glycophorin A

• S & s and U located on Glycophorin B
  • Remember: Glycophorin is a protein that carries many RBC antigens

• RBCs lacking GPA, GPB, or GPC are resistant to invasion by *Plasmodium falciparum* to varying degrees
MNSs Antigens

- Glycophorin A
- Glycophorin B

RBC

M & N only differ in their amino acid sequence at positions 1 and 5

S & s only differ in their amino acid sequence at position 29

COOH end ..... ....5, 4, 3, 2, 1 (NH$_2$ end)
## Frequency of MNSs antigens

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Blacks (%)</th>
<th>Whites (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M+</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>N+</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>S+</td>
<td>30.5</td>
<td>55</td>
</tr>
<tr>
<td>s+</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>U+</td>
<td><strong>99</strong></td>
<td><strong>99.9</strong></td>
</tr>
</tbody>
</table>

*High-incidence antigen*
Antibodies

• Anti-M and anti-N
  • IgM (rarely IgG): often naturally occurred
  • Clinically insignificant
  • If IgG, that react at 37° C may cause hemolysis of transfused cells and could be implicated in HDN (RARE)

• Anti-S, Anti-s, and Anti-U:
  • Clinically significant
  • IgG; occur after stimulation
  • Can cause RBC destruction and HDN
  • Anti-U
    • will react with S+ or s+ red cells
    • Usually occurs in S-s- cells
    • Can only give U-negative blood units found in <1% of Black population
    • Contact rare donor registry
MNSs Antibody Characteristics

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Ig Class</th>
<th>Clinically significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-M</td>
<td>IgM (rare IgG)</td>
<td>No</td>
</tr>
<tr>
<td>Anti-N</td>
<td>IgM</td>
<td>No</td>
</tr>
<tr>
<td>Anti-S</td>
<td>IgG</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-s</td>
<td>IgG</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-U</td>
<td>IgG</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Kell System

- Similar to the Rh system
- Over 20 Ags exist
- 2 major antigens
  - K (Kell), <9% of population (K-Neg donors are easy to find)
  - k (cellano), >90% of population (k-Neg donors are not easy to find)
- The K and k genes are codominant alleles on chromosome 7 that code for the antigens
- Well developed at birth
- The K antigen is very immunogenic (2\textsuperscript{nd} to the D antigen) in stimulating antibody production: acute and delayed transfusion reactions; hemolysis; HDN
Other Kell antigens

• Other sets of alleles also exist in the Kell system: Analogous to the Rh system: $C/c$ and $E/e$

• **Kp antigens**
  • $Kp^a$ is a low frequency antigen (only 2%)
  • $Kp^b$ is a high frequency antigen (99.9%)

• **Js antigens**
  • $Js^a$ (20% in Blacks, 0.1% in Whites)
  • $Js^b$ is high frequency (80-100%)

• Antibodies to other antigens on the Kell protein, such as $Kp_a$, $Kp_b$, $Js_a$, and $Js_b$, are less common but are also clinically significant.
Kx antigen

- Not a part of the Kell system, but is related
  - The XK protein is encoded by a gene on the X chromosome
  - Kx antigens are present in small amounts in individuals with normal Kell antigens
  - Kx antigens are increased in those who have no expression of Kell antigens (K₀)
**Kell_{null} or K_0**

- No expression of Kell antigens except a related antigen called Kx
- As a result of transfusion, K_0 individuals can develop anti-Ku (Ku is on RBCs that have Kell antigens)
- Rare Kell negative units should be given
Kell antibodies

- IgG (react well at AHG)
- Produced as a result of immune stimulation (transfusion, pregnancy)
- Clinically significant

- **Anti-K is most common** because the K antigen is extremely immunogenic
- k, Kp\(^b\), and Js\(^b\) antibodies are rare (many individuals have these antigens and won’t develop an antibody) since few donors have the antigen and accordingly are not easy to find compatible blood for them.
McLeod Syndrome

• No XK Ag and diminished other K antigens:
  • do not make anti-Kx and can be transfused with McLeod (KX neg) or Ko type blood
• Almost exclusive in White males
• Causes abnormal red cell morphologies and decreased red cell survival:
  • Acanthocytes – spur cells (defected cell membrane)
  • teardrop erythrocytes, and bizarre poikilocytes
  • Reticulocytes – immature red cells
• Other systemic problems:
  • subclinical myopathy
  • Progressive neuropathy
  • Psychiatric symptoms, and cognitive changes.
  • Cardiac symptoms, such as dilated cardiomyopathy and arrhythmias.
• Associated McLeod Syndrome with chronic granulomatous disease (CGD):
  • usually make antibodies to the XK and Kell protein in case of stimulation: should receive McLeod RBC(K0 & KX neg)
Kidd Blood Group

- 2 antigens: Jk<sup>a</sup> and Jk<sup>b</sup> (codominant alleles)
- Well developed at birth

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Whites (%)</th>
<th>Blacks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;Jk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Jk(a+b-)</td>
<td>26.3</td>
<td>51.1</td>
</tr>
<tr>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;Jk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Jk(a+b+)</td>
<td>50.3</td>
<td>40.8</td>
</tr>
<tr>
<td>Jk&lt;sup&gt;b&lt;/sup&gt;Jk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Jk(a-b+)</td>
<td>23.4</td>
<td>8.1</td>
</tr>
<tr>
<td>JkJk</td>
<td>Jk(a-b-)</td>
<td>rare</td>
<td>rare</td>
</tr>
</tbody>
</table>
Kidd antibodies

- Anti-Jk\textsuperscript{a} and Anti-Jk\textsuperscript{b}
  - usually IgG, but may be a mixture of IgG and IgM. They often bind complement lead to severe Intravascular HTR
  - Common cause of delayed HTR
  - HDN
  - Anamnestic or “rebound” phenomenon:
    - Are often weak and may become undetectable over time,
    - they may escape detection
    - increase in the titer of the antibody and hemolysis of the transfused antigen-positive RBCs.
  - Usually appears with other antibodies when detected
- Anti-Jk\textsubscript{3}
  - Found in some individuals who are Jk(a-b-)
  - Far East and Pacific Islanders (RARE)
Duffy Blood Group

• Predominant genes (codominant alleles):
  • $Fy^a$ and $Fy^b$ code for antigens that are well developed at birth
  • Antigens are destroyed by enzymes

• **Most African-Americans are $Fy(a-b)$**
  • Interestingly, certain malarial parasites (*Plasmodium knowlesi* and *P. vivax*)
    will not invade $Fy^a$ and $Fy^b$ negative cells
Duffy antibodies

- IgG
- Do not bind complement
- Clinically significant: HTR
- Stimulated by transfusion or pregnancy
- Anti-Fya has caused mild HDN, but anti-Fyb has not been implicated
- Do not react with enzyme treated RBCs
Lutheran Blood Group System

• 2 codominant alleles: $Lu^a$ and $Lu^b$
• Weakly expressed on cord blood cells
• Most individuals (92%) have the $Lu^b$ antigen, Lu(a-b+)
• The Lu(a-b-) phenotype is RARE; associated with acanthocytosis but no hemolysis
• Lu glycoproteins may be involved in the pathogenesis of sickle cell vaso-occlusive crises and may also be involved in the metastasis of certain types of malignancy.
Lutheran antibodies

• Anti-Lu\textsuperscript{a}
  • IgM and IgG
  • Not clinically significant
  • Reacts at room temperature
  • Mild HDN
  • Naturally occurring or immune stimulated

• Anti-Lu\textsuperscript{b}
  • Rare because Lu\textsuperscript{b} is high incidence antigen
  • IgG
  • Associated with transfusion reactions (rare HDN)
Maturation of Blood Group Antigens

• Several blood group antigens are not expressed or are only weakly expressed on cord RBCs and usually reach adult levels by 2 years of age
  • Antibodies to these antigens are unlikely to cause HDN.

• **No cord blood express:** Le\(_a\), Sd\(_a\), Ch, Rg, or AnWj antigens.

• **Weak cord blood express:** A, B, H, I, Le\(_b\), P\(_1\), Lu\(_a\) (but not Lu\(_b\)), Yt\(_a\), Vel, Do\(_a\), Do\(_b\), Gy\(_a\), Hy, Jo\(_a\), Xg\(_a\), and Bg
<table>
<thead>
<tr>
<th>Usually Clinically Significant</th>
<th>Sometimes Clinically Significant</th>
<th>Clinically Insignificant If Not Reactive at 37°C</th>
<th>Generally Clinically Insignificant</th>
</tr>
</thead>
<tbody>
<tr>
<td>A and B</td>
<td>At</td>
<td>A₁</td>
<td>Bg</td>
</tr>
<tr>
<td>Diego</td>
<td>Colton</td>
<td>H</td>
<td>Chido/Rogers</td>
</tr>
<tr>
<td>Duffy</td>
<td>Cromer</td>
<td>Le&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cost</td>
</tr>
<tr>
<td>H in O&lt;sub&gt;h&lt;/sub&gt;</td>
<td>Dombrock</td>
<td>Lutheran</td>
<td>JMH</td>
</tr>
<tr>
<td>Kell</td>
<td>Gerbich</td>
<td>M and N</td>
<td>Knops</td>
</tr>
<tr>
<td>Kidd</td>
<td>Indian</td>
<td>P&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Le&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>P, PP1P&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Jr&lt;sup&gt;a&lt;/sup&gt;</td>
<td>S&lt;sub&gt;d&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Xg&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rh</td>
<td>Lan</td>
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</tr>
<tr>
<td>S, s, and U</td>
<td>LW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vel</td>
<td>Scianna</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yt</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Importance of the Abs

Clinically significant antibodies occur in the following order, from most commonly to least commonly encountered in transfusion practice:

1. anti-D,
2. anti-K,
3. anti-E,
4. anti-c,
5. anti-Fya,
6. anti-C,
7. anti-Jka,
8. anti-S,
9. anti-Jkb

Clinically insignificant unless the alloantibodies are reactive in tests performed at 37°C:

- Anti-P1,
- anti-M,
- anti-N,
- anti-Lua (Lutheran),
- anti-Lea,
- anti-Leb,
- anti-Sda