Review

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Clinical significance of antibodies to antigens in the Scianna, Dombrock, Colton, Landsteiner-Weiner, Chido/Rodgers, H, Kx, Cromer, Gerbich, Knops, Indian, and Ok blood group systems

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This article reviews information regarding the clinical significance of antibodies to antigens in the Scianna, Dombrock, Colton, Landsteiner-Wiener, Chido/Rodgers, H, Kx, Cromer, Gerbich, Knops, Indian, and Ok blood group systems. Like most blood group systems, antibodies to many of the antigens in these groups are rarely encountered because of the high prevalence of the associated antigens in most populations. For many, the clinical significance—that is, the potential to cause reduced survival of transfused antigen-positive red blood cells or a transfusion reaction (e.g., anti-Ge2, anti-H) and/or hemolytic disease of the fetus and newborn (e.g., anti-Co^a, anti-Ge3)—has been documented. Some of these antibodies are not always clinically significant, and because of the high prevalence of the antigen, antigen-negative blood may be extremely difficult to find (e.g., anti-LW, anti-In^b). The use of a monocyte monolayer assay may be helpful when making transfusion decisions for patients with these antibodies. For others, their prevalence is so rare that information on the clinical significance of their antibodies is not available (e.g., anti-Co4, anti-Ok). ***Immunohematology* 2018;34:103–108.**

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Scianna Blood Group System

The Scianna (SC) blood group system, named in 1974, contains seven antigens: five high-prevalence antigens (Sc1, Sc3, Sc5, Sc6, and Sc7) and two low-prevalence antigens (Sc2 and Sc4) (Table 1).[1] These antigens result from variants in the erythroid membrane-associated protein (ERMAP).[2] The Sc protein is expressed weakly on leukocytes and other tissues such as fetal liver, thymus, lymph nodes, spleen, and bone marrow in adults.[1]

Table 1. Antigen and antibody characteristics of the Scianna blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
SC1	Sc1	High	No report	No report (DAT+)
SC2	Sc2	Low	No	No to Mild (1 case) (DAT+)
SC3	Sc3	High	No to mild/ delayed	Mild
SC4	Rd	Low	No	Mild to severe
SC5	STAR	High	No report	No report
SC6	SCER	High	No report	No report
SC7	SCAN	High	Yes, delayed (1 case)	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; DAT = direct antiglobulin test.

Clinical Significance

SC antibodies are usually IgG and are detected by the indirect antiglobulin test (IAT). There are rare cases of hemolytic disease with enough information to convincingly attribute clinical relevance to SC antibodies (Table 1).[3] If possible, antigen-negative blood should be selected. SC:–1,2,3 blood may be available but is extremely rare. Donors being SC:–1,–2,–3 are not available.[4]

Antibodies to the two low-prevalence antigens, Sc2 and Sc4, have not been reported to cause hemolytic transfusion reactions (HTRs). However, they have been implicated in hemolytic disease of the fetus and newborn (HDFN). In the case of transfusion, IAT-compatible blood (most donors) should be selected.[2]

Dombrock Blood Group System

Besides the two antithetical antigens, Do^a and Do^b, the Dombrock blood group system (DO) contains eight antigens of high prevalence: Gy^a, Hy, Jo^a, DOYA, DOMR, DOLG, DOLC, and DODE (Table 2).[1,5,6] Do^a and Do^b are polymorphic with a prevalence of 67 and 82 percent, respectively, in Caucasian individuals. DO is a glycoprotein attached to the red blood cell (RBC) membrane by a glycosylphosphatidylinositol anchor.[5]

Clinical Significance

Anti-Do^a and -Do^b have caused immediate and delayed HTRs, but no clinical HDFN (Table 2).[1] They are mostly found in sera containing multiple RBC antibodies and often disappear in vivo. Anti-Do^a and -Do^b are usually IgG-reacting, optimally by the IAT using papain-treated RBCs.

For blood transfusion, antigen-negative blood should be selected.[4] Because of the lack of reliable anti-Do antisera, it used to be difficult to find compatible blood. With today's approach of molecular testing of donors, compatible donors are more easily found. Note, though, that the presence of other antibody specificities may complicate the finding of compatible blood.

Anti-Gy^a, -Hy, -Jo^a, and other DO antibodies are rare but have been reported to cause HTRs. Because of the rarity of these antibodies, evidence of clinical significance is limited (Table 2).[5] Serologically least-incompatible RBC units are recommended for patients with weak examples of the antibody, but antigen-negative RBCs should be provided for patients who demonstrate strong examples of the antibody.[4]

Table 2. Antigen and antibody characteristics of the Dombrock blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
DO1	Do^a	Polymorphic	Yes; I/D	No report (DAT+)
DO2	Do^b	Polymorphic	Yes; I/D	No report (DAT+)
DO3	Gy^a	High	No to moderate; D	No report (DAT+)
DO4	Hy	High	No to moderate; D	No report (DAT+)
DO5	Jo^a	High	No to moderate; D	No report
DO6	DOYA	High	No report (one case, pretransfusion medication)	No report
DO7	DOMR	High	No report	No report
DO8	DOLG	High	No report	No report
DO9	DOLC	High	No report	No report
DO10	DODE	High	No report	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; I = immediate; D = delayed; DAT = direct antiglobulin test.

Colton Blood Group System

The Colton blood group system (CO) consists of three high-prevalence antigens (Co^a, Co3, and Co4) and one polymorphic antigen (Co^b) (Table 3). The water channel-forming protein, aquaporin-1, is the carrier of the CO blood group antigens.[1]

Table 3. Antigen and antibody characteristics of the Colton blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
CO1	Co^a	High	No to moderate/ D or I/H	Mild to severe
CO2	Co^b	Polymorphic	No to moderate/ D/H	Mild
CO3	Co3	High	Mild; H	Severe
CO4	Co4	High	No report	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; D = delayed; I = immediate; H = hemolytic.

Clinical Significance

Anti-Co^a has caused delayed HTRs and severe HDFN, and patients with anti-Co^a should be transfused with Co(a–) blood.[4]

Whereas anti-Co^a is often seen as a single specificity, anti-Co^b is not. This rare antibody, detecting an antigen with a prevalence of about 10 percent,[1] has been reported to cause both acute HTR and a mild delayed HTR (Table 3).[7] About 90 percent of the donors are IAT compatible; these donor RBC units should be selected in case of a transfusion. There are no reports of anti-Co^b being implicated in a serious HDFN, although mild HDFN has been reported.[1]

Anti-Co3 and anti-Co4 are rare antibodies detecting antigens of very high prevalence (Table 3). Anti-Co3 has caused a mild HTR and serious HDFN. Only four Co4– probands have been identified, and because of the rarity of anti-Co4, no data are available on its clinical significance.[1] Co(a–b–) blood should be selected for compatibility testing, but because it is extremely rare serologically, least incompatible blood may be given with extra caution.[4]

Landsteiner-Wiener Blood Group System

Currently, there are three antigens assigned to the Landsteiner-Wiener blood group system (LW): LW^a, LW^{ab}, and LW^b (Table 4).[1] The LW antigens are carried on an intracellular adhesion molecule, glycoprotein ICAM-4.[7] LW^a and LW^b are antithetical, with LW^a being of high prevalence (100%) and LW^b being of low prevalence (<1%) in most populations. The prevalence of LW^b is greatest in the Baltic region (e.g., 8% in Estonians, 6% in Finns), and thus the likelihood of finding LW(a–) donors is greatest in these areas.[1]

Autoantibodies developed after antigen suppression are not uncommon, which makes the differentiation between allo- and autoantibodies difficult.

Table 4. Antigen and antibody characteristics of the Landsteiner-Wiener blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
LW5	LW^a	High	No to mild; D	No to mild
LW6	LW^{ab}	High	No report	Mild
LW7	LW^b	Low	No to mild	No to mild

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; D = delayed.

Clinical Significance

LW antibodies are usually IgG and are detected by the IAT. Mild cases of HTR and HDFN with anti-LW^a, anti-LW^{ab}, and anti-LW^b have been reported (Table 4).[1] For transfusion, antigen-negative blood is not required, but D– blood should be selected if possible, since the antigen expression is lower than that of D+ blood. In the presence of anti-LW^b, IAT-compatible blood should be selected.[4]

Chido/Rodgers Blood Group System

The antigens of the Chido/Rodgers blood group system (CH/RG) are carried on the C4d fragment of complement component C4; Ch antigens are carried on the C4B allotype and Rg antigens are carried on the C4A allotype.[1] These antigens adsorb onto the RBC surface in vivo.[1,8] Currently, nine antigens have been identified in the CH/RG system: six of high prevalence and one that is polymorphic for CH and two of high prevalence for RG (Table 5).

Table 5. Antigen and antibody characteristics of the CH/RG blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
CH/RG1	Ch1	High	No hemolytic	No report
CH/RG2	Ch2	High	No report	No report
CH/RG11	Rg1	High	No hemolytic	No report
CH/RG12	Rg2	High	No report	No report

Five additional antigens within the CH/RG blood group system have been identified but with no information.[1]

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn.

Clinical Significance

Anti-Ch and anti-Rg have not been found to cause an HTR or HDFN (Table 5).[2] Antigen-negative blood is not required for transfusion. Severe anaphylactic reactions have been reported in a few patients with antibodies to Ch or Rg antigens after infusion of plasma products and platelet concentrates since these contain soluble Ch/Rg antigen; however; these events are exceptional.[8]

H Blood Group System

The H blood group system contains only one antigen, H. The H antigen is present in all individuals except those with the Bombay (O_h) phenotype. Individuals with the para-Bombay (A_h or B_h) phenotype have very low levels of H (Table 6).[1]

Table 6. Antigen and antibody characteristics of the H blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
H	H	High	No to severe; I/D/H	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; I = immediate; D = delayed; H = hemolytic.

Clinical Significance

Individuals with the O_h phenotype (RBC H-deficient, non-secretor) always have anti-H in their serum/plasma. Like anti-A and -B, anti-H is likely to cause a severe immediate HTR. HDFN may occur, but there are no reports (Table 6).[1] In case of transfusion, blood of the O_h phenotype must be selected.

Individuals with the non-secretor A_h or B_h phenotype usually have anti-H in their serum/plasma, although often of lower titer. There is little information on the clinical

significance of anti-H in A_h or B_h individuals. Preferably, blood of the O_h phenotype should be transfused, but if not available, then RBCs of the appropriate ABO group (A for A_h, B for B_h) may be transfused with extra caution.[4]

Individuals with the secretor A_h or B_h phenotype may have anti-HI present in their serum/plasma. Typically, anti-HI is not reactive at 37°C, and ABO-identical blood, compatible at 37°C, can be used for transfusion.[4]

Anti-HI may also be found in group A_1, A_1B, or B individuals. If the antibody is reactive at 37°C, blood of the ABO group of the patient should be used for transfusion; blood of group O and A_2 should not be used. If the antibody is reactive only at lower temperatures, blood compatible at 37°C can be used for transfusion, regardless of ABO group.[4]

Kx Blood Group System

Kx was assigned blood group system status in 1990 and contains one antigen of very high prevalence (100%), Kx (Table 7). The Kx antigen is covalently linked to the Kell molecule on RBCs and is controlled by a gene on the X chromosome. The presence of the Kx protein is critical to normal RBC morphology, and silencing mutations are associated with McLeod syndrome, neuroacanthocytosis, and neuromuscular disorders in later life.[9]

Clinical Significance

Anti-Kx is often found together with anti-Km (anti-KEL20) in men with the McLeod phenotype and X-linked chronic granulomatous disease. These two antibodies (also called anti-KL) can cause severe HTRs; thus, antigen-negative (McLeod phenotype) blood should be selected for transfusion (Table 7).[4]

Table 7. Antigen and antibody characteristics of the Kx blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
XK1	Kx	High	Mild; D	Not applicable*

*Anti-Kx only made by male individuals with McLeod phenotype

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; D = delayed.

Gerbich Blood Group System

The Gerbich blood group system is expressed on glycophorin C and D and contains 11 antigens: 6 of high prevalence and 5 of low prevalence (Table 8).[10]

Table 8. Antigen and antibody characteristics of the Gerbich blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
GE2	Ge2	High	No to moderate; I/D	No report (DAT+)
GE3	Ge3	High	No to moderate; I/D	Positive DAT to severe
GE4	Ge4	High	No report	No report
GE5	Wb	Low	No report	No report
GE6	Ls[a]	Low	No report	No report
GE7	An[a]	Low	No report	No report
GE8	Dh[a]	Low	No report	1 report, very severe
GE9	GEIS	Low	No report	No report
GE10	GEPL	High	No report	No report
GE11	GEAT	High	No report	No report
GE12	GETI	High	No report	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; I = immediate; D = delayed; DAT = direct antiglobulin test.

Clinical Significance

Anti-Ge2, made by Yus, Gerbich, or Leach phenotypes, and anti-Ge3, made by Gerbich or Leach phenotypes, are usually IgG antibodies and can cause moderate immediate or delayed HTRs. Anti-Ge4 (made by Leach phenotypes), -GEPL, -GEAT, and -GETI are very rare, and no data are available on their clinical significance (Table 8).[10] Antigen-negative blood is not usually required for transfusion but should be considered for strong examples of these antibodies.[4]

Although Anti-Ge2 has not been implicated in clinical HDFN, newborns have shown positive direct antiglobulin tests (DATs).[1] Anti-Ge3 has caused severe HDFN due to suppression of the erythroid progenitor cell growth in the infant. Initial treatment of the infant at birth with subsequent follow-up for several weeks after birth may be indicated.[1] There is no information on the clinical significance with regard to HDFN for anti-Ge4, -GEPL, -GEAT, and -GETI.[1]

The antibodies to the low-prevalence antigens of the Gerbich system can be naturally occurring and may be IgM

or IgG. There are no reports that these antibodies have caused HTRs or HDFN.[1]

Cromer Blood Group System

The antigens of the Cromer blood group system are carried on the decay accelerating factor (DAF), a protein belonging to the regulators of the complement activation family. The system contains 16 high-prevalence antigens and three low-prevalence antigens (Table 9).[11]

Table 9. Antigen and antibody characteristics of the Cromer blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN*
CROM1	Cr[a]	High	No to moderate	No
CROM2	Tc[a]	High	No to severe	No
CROM3	Tc[b]	Low	No report	No report
CROM4	Tc[c]	Low	No to mild	No
CROM5	Dr[a]	High	No to mild	No
CROM6	Es[a]	High	Mild	No
CROM7	IFC	High	No to mild	No
CROM8	WES[a]	Low	No to mild	No
CROM9	WES[b]	High	No report	No, DAT+
CROM10	UMC	High	No report	No
CROM11	GUTI	High	No report	No
CROM12	SERF	High	No data	No
CROM13	ZENA	High	No data	No
CROM14	CROV	High	No data	No
CROM15	CRAM	High	No data	No
CROM16	CROZ	High	No data	No

*Decay accelerating factor adsorbs maternal antibody

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; DAT = direct antiglobulin test.

Clinical Significance

Antibodies to Cromer antigens are rare (Table 9). There is evidence that the antibodies may cause accelerated destruction of transfused RBCs, although functional assays on clinical significance are ambiguous.[11] Because of the high concentration of maternal DAF on the apical surface of the trophoblasts in the placenta, which is thought to adsorb the maternal antibodies, there is no risk of HDFN associated with Cromer system antibodies. Antigen-negative blood is not usually required for transfusion, but should be considered for strong-reacting antibodies.[4]

Knops Blood Group System

The antigens of the Knops blood group system are carried on complement receptor 1 (CR1). The major functions of CR1 are the binding of C4b/C3b opsonized complexes as well as complement regulation. The Knops blood group system contains nine antigens that are polymorphic, of low prevalence or of high prevalence depending on the origin of the individual (Table 10).[1,12]

Table 10. Antigen and antibody characteristics of the Knops blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
KN1	Kn[a]	High	No	No
KN2	Kn[b]	Low	No report	No report
KN3	McC[a]	High	No	No
KN4	Sl[a]	High (non-black) Polymorphic (black)	No to mild	No
KN5	Yk[a]	High	No	No
KN6	McC[b]	Low (non-black) Polymorphic (black)	No report, unlikely	No report
KN7	Vil	Low (non-black) Polymorphic (black)	No report, unlikely	No report
KN8	Sl3	High	No report, unlikely	No report
KN9	KCAM	High (non-black) Polymorphic (black)	No report, unlikely	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn.

Clinical Significance

Most of the Knops antibodies are not considered clinically significant since they do not cause apparent HTRs or HDFN, thus antigen-negative units are not indicated in the case of transfusion (Table 10).[4]

Indian Blood Group System

The Indian blood group system contains four antigens that are carried by CD44. In[a] and In[b] are antithetical antigens of low prevalence and high prevalence, respectively. INFI and INJA are both antigens of high prevalence (Table 11).[2]

Table 11. Antigen and antibody characteristics of the Indian blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
IN1	In^a	Low	Decreased cell survival	No, DAT+
IN2	In^b	High	No to severe D	No, DAT+
IN3	INFI	High	No report	Mild
IN4	INJA	High	No report	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn; DAT = direct antiglobulin test; D = delayed.

Clinical Significance

Indian antibodies are mostly IgG, reacting preferably by the IAT (Table 11). These antibodies do not bind complement and do not cause in vitro hemolysis.[6] In^a is rare in populations of European origin, but has a prevalence of about 3 percent in Indian individuals and 10 percent in Arab individuals. Anti-In^a is not reported to be clinically significant, although limited data are available. Blood compatible by IAT can be selected for transfusion.[4]

Anti-In^b may cause none to severe/delayed HTRs.[1] In(b–) blood is not usually required for transfusion but should be considered for strong-reacting antibodies.

No clinical data are available on anti-INFI and anti-INJA; INFI– and INJA– blood types are extremely rare. For transfusion, serologically least-incompatible blood should be used with extra caution.[4]

Anti-In^a, -In^b, and -INJA have not been implicated in HDFN.[1] Anti-INFI was implicated in one case of mild HDFN.[13]

Ok Blood Group System

The Ok blood group system contains three antigens carried on CD147 (Table 12).[14] The Ok blood group system was established in 1999. To date, the null phenotype, Ok(a–) has been found in eight Japanese families only.

Table 12. Antigen and antibody characteristics of the Ok blood group system

Antigen			Antibody	
ISBT name	Trivial name	Prevalence	HTR	HDFN
OK1	Ok^a	High	^{51}Cr cell survival reduced	No
OK2	OKGV	High	No report	No report
OK3	OKVM	High	No report	No report

ISBT = International Society of Blood Transfusion; HTR = hemolytic transfusion reaction; HDFN = hemolytic disease of the fetus and newborn.

Clinical Significance

Ok antibodies have not been implicated in HDFN.[1] There is almost no information on the clinical significance of Ok antibodies, but in vivo survival tests and cellular functional assays suggest that anti-Ok^a is clinically significant (Table 12).[1] Because Ok(a–) blood is extremely rare, serologically least-incompatible blood may be given with extra caution.[4]

References

1. Reid ME, Lomas-Francis C, Olsson ML. Blood group antigen factsbook. 3rd ed. San Diego, CA: Academic Press, 2012.
2. Wagner FF, Poole J, Flegel WA. Scianna antigens including Rd are expressed by ERMAP. Blood 2003;101:752–7.
3. Bunker PAR, Flegel WA. Scianna: the lucky 13th blood group system. Immunohematology 2011;27:41–57.
4. Thornton N. The clinical significance of blood group alloantibodies and the supply of blood for transfusion, 2016. SPECIFICATION SPN214/4. Available from http://hospital.blood.co.uk/media/29271/spn2144-the-clinical-significance-of-blood-group-alloantibodies-and-the-supply-of-blood-for-transfusion.pdf.
5. Lomas-Francis C, Reid ME. The Dombrock blood group system: a review. Immunohematology 2010;26:71–8.
6. Storry JR, Castilho L, Chen Q, et al. International society of blood transfusion working party on red cell immunogenetics and terminology: report of the Seoul and London meetings. ISBT Sci Ser 2016;11:118–22.
7. Bryne KM, Bryne PC. Review: other blood group systems—Diego, Yt, Xg, Scianna, Dombrock, Colton, Landsteiner-Wiener, and Indian. Immunohematology 2004;20:50–8.
8. Daniels G. Human blood groups. 3rd ed. Oxford, U.K.: Blackwell Science, 2013.
9. Denomme GA. Kell and Kx blood group systems. Immunohematology 2015;31:14–9.
10. Walker PS, Reid ME. The Gerbich blood group system: a review. Immunohematology 2010;26:60–5.
11. Storry JR, Reid ME, Yaser MH. The Cromer blood group system: a review. Immunohematology 2010;26:109–18.
12. Moulds JM. The Knops blood group system: a review. Immunohematology 2010;26:2–7.
13. Poole J, Tilley L, Warke N, et al. Two missense mutations in the *CD44* gene encode two new antigens of the Indian blood group system. Transfusion 2007;47:1306–11.
14. Smart EA, Storry JR. The OK blood group system: a review. Immunohematology 2010;26:124–6.

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