Patient Safety

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Transfusion Medicine and Patient Safety

DE GRUYTER

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Introduction

Transfusion medicine has its roots in immunohematology – the science that studies erythrocyte antigens and the antibodies working against them.

Looking back in history, we can retrace the main achievements of this extraordinary science that deals with blood, an incredibly precious, irreplaceable resource received as a free, voluntary gift from many donors.

Milestones in transfusion medicine: from legends to molecules

- Egyptian princes bathed in blood.
- Romans drank it.
- Native Americans offered it to the gods.
- **1628**: William Harvey described how the heart and blood circulation function.
- 1795: Philip Syng Physick performed the first human blood transfusion.
- 1825–1830: James Blundell successfully treated a severe post-partum hemorrhage by transfusing the patient with her husband's blood.
- **1901**: Karl Landsteiner identified the first three blood groups as A, B and C, based on the substances found on the surface of the red blood cells.
- 1902: Alfred von Decastello and Adriano Sturli discovered the AB blood group.
- 1907: Reuben Ottenberg completed the first transfusion using typing and cross-matching.
- 1908: Carlo Moreschi described the principle of the antiglobulin test.
- **1926**: The world's first transfusion service was created by the British Red Cross.
- 1939: Karl Landsteiner, Alex Wiener and Philip Levine discovered the Rh system.
- **1945**: Robin Coombs, Arthur Mourant and Rob Race described the use of anti-globulin (the Coombs test) to identify incomplete antibodies.
- 1970: Monoclonal antibodies came into use.
- **1970**: Automated systems were introduced at the immunohematology laboratory.
- 1980: Molecular biology was applied to the study of blood groups.
- **1988**: Microcolumn technology was introduced.
- 1990: Microarray technology was introduced.

When Karl Landsteiner (1868–1943) discovered blood groups at the beginning of the last century, initially calling them A, B and C, he was possibly not entirely aware of the importance of his observations. Just before World War I, the description of the blood groups, and particularly of the corresponding antibodies determining their compatibility or incompatibility for transfusion purposes, contributed to saving many lives.

In merely a century, transfusion medicine covered a lot of ground: the other main blood group systems were identified, such as the Kell/Cellano, Duffy, Lutheran, and MNSs systems to name just the clinically most significant; as was the Rh system and its pathogenic mechanisms, responsible for one of the diseases typical of the period after

World War II, i.e. hemolytic disease of the newborn (HDN), which could be virtually wiped out within a few decades.

At least as important, particularly for patients' and the general public's perception of the safety of transfusion therapy, have been the advances made in recent years regarding transfusion-transmitted diseases. In the 1970s, alanine transferase assay was the only test performed on blood before its transfusion, and screening for HBsAg was added a little later on.

In the early 1980s, the first cases of AIDS (acquired immunodeficiency syndrome) in the San Francisco community brought the threat of HIV (human immunodeficiency virus) to the attention of the general public: this disease could be transmitted with the transfusion of blood and blood products, as sadly came to light when diagnostic tests subsequently became available on a wider scale.

Another dark moment in the history of transfusion medicine came in the late 1980s, when Qui-Lim Choo, together with Michael Houghton and George Kuo of the Chiron Corporation, described the hepatitis C virus (previously known as nonA-nonB), another disease transmissible in blood and blood products, and responsible for severe chronic liver conditions that often degenerate into hepatocarcinoma (1, 2).

While, for many years, scientists were constantly racing to keep pace with and find solutions for the problems that kept emerging in relation to blood transfusion, for at least a decade now transfusion policy has been focusing on risk prevention, investing heavily in technology, automation, computer technologies, the appropriate use of blood components, hemovigilance, and quality control.

Italian and European legislation has played an important part in transfusion risk prevention, establishing technological and safety standards, introducing innovation and implementing new screening methods.

The main landmarks in the course of Italian legislation on the topic are as follows:

- 1967: Italian Law No. 592 on the "Collection, storage and distribution of human blood" contained the first regulations for blood collection and particularly established the principle that blood and its components cannot be a source of profit.
- 1971: Italian Presidential Decree (DPR) No. 1256, implementing Law No. 592, contained the first minimum requirements for blood collection centers and transfusion centers, also establishing donor suitability criteria.
- 1978: Memorandum No. 68 from the Ministry of Public Health made an HBsAg assay compulsory as part of the screening process for transfusion purposes.
- 1988: Decree No. 14 from the Ministry of Public Health contained regulations that aimed to rule out the risk of HIV infections.
- 1990: Law No. 107 was the first framework law governing transfusion activities relating to human blood and blood components, and the production of plasma derivatives.
- 1990: the Ministerial Decree of 21 July contained regulations designed to rule out the risk of hepatic infections derived from blood transfusions, making it compulsory to search for anti-HCV (hepatitis C virus) antibodies as well as alanine aminotransferase (ALT) assays.

A major advance was subsequently made when molecular biology was used to search for the viral material of the three main viruses that affected transfusion safety, concentrating on the HCV first (in 1999) and in later years on HIV and HBV (hepatitis B virus).

In 2005, important changes were made to the legislation, starting with the Italian Ministerial Decree of 3 March, and later with Law No. 219 enacted by the Italian Parliament on 21 October 2005 on the topic of "New rules for transfusion activities and the national production of blood products". This law redesigned the Italian transfusion system, replacing the earlier Law No. 107.

The European Parliament's Directive 2002/98/EC was replaced by the Italian Legislative Decree of 20 December 2007, No. 261, revising the Decree No. 191 of 19 August 2005, and establishing quality and safety rules for the collection, control, processing, preservation and distribution of human blood and blood components. Directives 2005/61/EC and 2005/62/EC were replaced by the Legislative Decrees of 9 November 2007, Nos. 207 and 208, respectively; the latter defining the requirements for a transfusion service quality system.

The European Union is strongly involved in regulating blood transfusion activities by means of a series of regulations, directives and quality standards for blood components. These include Recommendation No. R(95)15, which is the definitive text on the quality requirements for the control of the whole transfusion process, from the first steps taken by the donor to the completion of the transfusion of whole blood, blood components and blood products.

Although there is no way to reduce the related risks to nil, in transfusion medicine just like any other medical discipline, it is safe to say that blood and the transfusion process have never been safer than they are today. They are safe, not only as regards transfusion-transmissible diseases, but also from the immunohematological standpoint. Operators nonetheless need to take the utmost care at all stages in the process, during which technological support has become the aspect in which the human mind and hand can best express their abilities.

References

1. Saito I., Miyamura T., Ohbyashi A., et al. (1990) Hepatitis C virus infection is associated with the development of hepatocellular carcinoma. Proc. Natl. Acad. Sci. USA 87:6547–49.
2. Resnick R.H., Koff R. (1993) Hepatitis C-related hepatocarcinoma. Prevalence and significance. Arch. Intern. Med. 153(14):1672–77.

1 Basics of transfusion medicine

1.1 The ABO and Rh blood group systems

When Landsteiner described the first blood groups in 1900 (those now called A, B and O), he referred to the fact that the people studied could be placed in one of three groups by testing the red blood cells, drawing serum samples from each patient and swapping the cells and serum in the tests. Although the blood groups are defined by the antigens on the surface of the red cells, they are not specific to red cells; they are also found on most of the cells and tissues in the body, as well as in the secretions in individuals revealing the specific gene, i.e. in 70% of the population.

The term "blood group" can only be used if this is established using the specific antiserum (1). From a biochemical standpoint, the blood group antigens may be proteins, glycoproteins or glycolipids, and they can be divided in functional terms into five groups:

1. Membrane carriers and channel proteins, which facilitate the passage of polar solutes through the phospholipid bilayer of the red cell membrane and are essential to cell metabolism and to preserving systemic homeostasis, and the acid-base balance in particular. The structure of these important molecules typically includes from six to 13 transmembrane domains, such as band 3, an anion exchanger found in more than a million copies per red cell, aquaporin 1 (AQP1), and a urea transporter (JK/hUT-B1).
2. Ligand receptors, which are integral membrane proteins that enable extracellular molecules to be inserted in the cell. They act as receptors of viruses, bacteria and parasites.
3. Adhesion molecules are used in the processes of cell growth, differentiation and repair.
4. Enzymes, such as glycosyltransferase and fucosyltransferase.
5. Structural *proteins* essential to the red cell's architecture and morphology, with a relevant role in red cell membrane stiffness.

The ABO system includes the A, B, AB and O blood groups, and is the main system used to ensure an essential level of transfusion safety; in other words it represents the minimum level of compatibility for transfusion therapy (2).

The ABO system antigens are hereditary traits transmitted according to Mendel's Law and governed by a gene located on chromosome 9, which can be expressed in four forms called alleles, two in group A (A_1 and A_2), and the B and O alleles. The possible phenotypes, and the corresponding genotypes, are shown in ►Tab. 1.1.

Tab. 1.1: ABO phenotypes and possible genotypes.

Phenotype	Possible genotype
A	A_1A_1, A_1A_2, A_1O, A_2O
B	BB, BO
O	OO
AB	AB

The O gene is amorphic, so it does not express a trait and it is phenotypically dominated by the expression of the antigens A_1, A_2 or B. As for the quantitative distribution of the antigens on the surface of the red cells, their prevalence is $A_1>A_2>O$, and this is why several genotypes may correspond to a given phenotype, and why a whole family needs to be studied to identify a genotype, or molecular biology techniques have to be used.

Whether a person belongs to a given ABO blood group depends on the presence of a specific gene located on chromosome 9, which encodes the synthesis of an enzyme capable of transferring a sugar on the precursor substance on the red cell's membrane (3). The ABO system antigens belong to the group of glycoproteins and the antigenic determinant is an oligosaccharide linked to a membrane sphingomyelin called *ceramide* or *paragloboside*: the difference between A and B specificity lies in the terminal monosaccharide, which is N-acetylgalactosamine for group A, and D-galactose for group B (►Fig 1.1).

The monosaccharide is bonded to the precursor oligosaccharide chain by a specific transferase enzyme; the O allele, located on chromosome 19, is not responsible for producing any enzymes, so if it is expressed in homozygosis it induces no changes in the precursor oligosaccharide chain, or substance H, which remains unaltered.

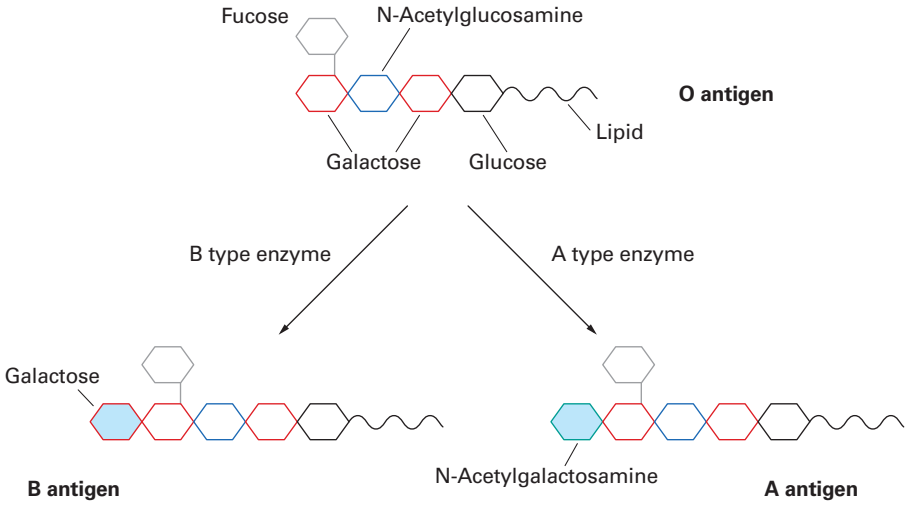

Fig. 1.1: A and B antigens: schematic representation.